ORIGINAL RESEARCH

Evidence-Based Nonpharmacologic Strategies for Comprehensive Pain Care: The Consortium Pain Task Force White Paper

Heather Tick, MD[1#] Arya Nielsen, PhD[2##] Kenneth R. Pelletier, PhD, MD[3] Robert Bonakdar, MD[4] Samantha Simmons, MPH[5] Ronald Glick, MD[6] Emily Ratner, MD[7] Russell L. Lemmon, MD[8] Peter Wayne, PhD[9] and Veronica Zador, BSc[10] The Pain Task Force of the Academic Consortium for Integrative Medicine and Health

ABSTRACT

Medical pain management is in crisis; from the pervasiveness of pain to inadequate pain treatment, from the escalation of prescription opioids to an epidemic in addiction, diversion and overdose deaths. The rising costs of pain care and managing adverse effects of that care have prompted action from state and federal agencies including the DOD, VHA, NIH, FDA and CDC.

There is pressure for pain medicine to shift away from reliance on opioids, ineffective procedures and surgeries toward comprehensive pain management that includes evidence-based nonpharmacologic options. This White Paper details the historical context and magnitude of the current pain problem including individual, social and economic impacts as well as the challenges of pain management for patients and a healthcare workforce engaging prevalent strategies not entirely based in current evidence. Detailed here is the evidence-base for nonpharmacologic therapies effective in postsurgical pain with opioid sparing, acute non-surgical pain, cancer pain and chronic pain. Therapies reviewed include acupuncture therapy, massage therapy, osteopathic and chiropractic manipulation, meditative movement therapies Tai chi and yoga, mind body behavioral interventions, dietary components and self-care/self-efficacy strategies.

Transforming the system of pain care to a responsive comprehensive model necessitates that options for treatment and collaborative care must be evidence-based and include effective nonpharmacologic strategies that have the advantage of reduced risks of adverse events and addiction liability.

The evidence demands a call to action to increase awareness of effective nonpharmacologic treatments for pain, to train healthcare practitioners and administrators in the evidence base of effective nonpharmacologic practice, to advocate for policy initiatives that remedy system and reimbursement barriers to evidence-informed comprehensive pain care, and to promote ongoing research and dissemination of the role of effective nonpharmacologic treatments in pain, focused on the short- and long-term therapeutic and economic impact of comprehensive care practices.

Keywords: Non Surgical Pain Management, Public Health, Evidence-Based Practice in Health Care System, Acute Pain Management, Integrative Medicine, Chronic Pain Management

(Explore 2018; 14:177-211 © 2018 The Authors. Published by Elsevier Inc. All rights reserved.)

1 Departments of Family Medicine, Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, WA
2 Department of Family Medicine & Community Health, Icahn School of Medicine at Mount Sinai, New York, NY
3 Department of Medicine, University of California School of Medicine, San Francisco, CA
4 Department of Pain Management, Scripps Center for Integrative Medicine, La Jolla, CA
5 Oregon Collaborative for Integrative Medicine, Portland, OR
6 Departments of Psychiatry and Physical Medicine and Rehabilitation, University of Pittsburgh School of Medicine, Pittsburgh, PA
7 MedStar Health, Institute for Innovation, Integrative Medicine Initiatives, MedStar Montgomery Medical Center, Washington, DC
8 Department of Family Medicine and Community Health, University of Wisconsin School of Medicine and Public Health, Madison, WI
9 Osher Center for Integrative Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
10 Beaumont Hospital Integrative Medicine, Oakland University William Beaumont School of Medicine, Rochester, MI

The authors would like to express their gratitude for the support and/or review of this document to Jane Ballantyne, MD; Margaret Chesney, PhD; Roni Evans, DC, PhD; Seth Gilbert, BA; Marsha J. Handel, MLS; John Loeser, MD; Robert B. Saper, MD; Rebecca Schultz, MS, ARNP; Rosanne Sheinberg MD; and Leonard A. Wisneski, MD.

The Academic Consortium for Integrative Medicine & Health (the Consortium) is an institutional member organization of 72 North American academic medical centers and health systems whose mission is to advance evidence-based integrative medicine and health in research, curricula, and sustainable models of clinical care.

[#] *Corresponding author*: Heather Tick, MD, Departments of Family Medicine, Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, WA.
[##] *Corresponding author*: Arya Nielsen, PhD, Department of Family Medicine & Community Health, Icahn School of Medicine at Mount Sinai, New York, NY.
E-mail: HTick@uw.edu (H. Tick), Arya.Nielsen@mountsinai.org (A. Nielsen).

ISSN 1550-8307

https://doi.org/10.1016/j.explore.2018.02.001

SECTION 1: THE PROBLEM

HISTORICAL CONTEXT FOR A CALL TO CHANGE

Pain care in America is in crisis. The prevalence of pain is high despite costly, well-intentioned medical responses, which rely mainly on pharmaceuticals and high-tech interventions. Pain and aspects of current pain management strategies are having enormous deleterious impacts on patients, the health system and society.[1,2] From the 1970s to the 1990s there was hope that new drugs, more liberal use of opioids, new technologies and a growing understanding about the mechanisms of pain would reduce the occurrence of uncontrolled pain. This was not the case. Growing rates and escalating costs of pain-related morbidity, mortality and disability have led to calls for culture change in pain medicine by The Office of the Army Surgeon General Pain Management Task Force (PMTF) Report,[3] Institute of Medicine (IOM) (now the National Academy of Medicine, NAM),[1,2] Interagency Pain Research Coordinating Committee's National Pain Strategy[4] and others. Government leaders have declared the opioid crisis a national emergency. The recommendations consistently promote a shift toward a more comprehensive, patient-centered and health-focused approach to pain patients. In this model, collaborative care is team-based, interdisciplinary, and involves both pharmacologic and nonpharmacologic approaches. The model affirms the essential role patients have in improving their own health and pain-related behaviors. There is a growing recognition that current conventional medical treatment may not be the best starting point and is often not sufficient. In addition to inadequately addressing pain there is increasing evidence that conventional treatment strategies are fueling the opioid crisis, according to a National Institute for Drug Abuse (NIDA) report citing one in three Americans used prescription opioids for pain in 2015.[5] Moreover, evidence-based nonpharmacologic approaches may be the more appropriate initial treatment for acute and chronic pain management.

Currently, there is no clear roadmap for a comprehensive approach to pain management that includes evidence-based nonpharmacologic strategies. The goal of this white paper is to outline the role of evidence-based nonpharmacologic strategies for the management of pain and how they can best be integrated with conventional approaches. This integrative pain management approach is in alignment with the stated goals of the reports from the Office of the Army Surgeon General PMTF, NAM, National Academies of Science, and the NIH National Pain Strategy. How pain is assessed, managed and taught to health professionals must be updated. A shift is essential to address the immense deleterious impact that pain and the current system of pain care, including opioid reliance, have on patients, the health system and society.

List of organizations and abbreviations.

ACP	American College of Physicians
ACT	Acceptance and Commitment Therapy
AHRQ	Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services
APAP	acetaminophen
APRN	nurse practitioners
AT	Alexander Technique
CBA	cost-benefit analyses
CBD	cannabidiol
CBT	Cognitive behavioral therapy
CDC	Centers for Disease Control and Prevention
CEA	cost-effectiveness analyses
CFO	Chief Financial Officer
CHD	coronary heart disease
cLBP	chronic low back pain
CMS	Centers for Medicare and Medicaid Services
CNCP	chronic noncancer pain
CUA	cost-utility analyses
ED	Emergency Department
eHealth	web-based health interventions
E-stim	electrical stimulation
FDA	Food and Drug Administration, U.S. Department of Health and Human Services
HVLA	high velocity, low amplitude thrust techniques (SMT, MT)
IBI	Integrated Benefits Institute
IOM	Institute of Medicine, now NAM
IV	intravenous
LVLA	low velocity, low amplitude thrust technique (SMT, MT)
MBSR	Mindfulness-Based Stress Reduction
MT	manipulative therapy, manual therapy including massage therapy
NAM	National Academy of Medicine
NAS	neonate abstinence syndrome
NCCIH	National Center for Complementary and Integrative Health, NIH
NHIS	National Health Interview Survey
NICE	UK National Institute for Health and Care Excellence
NIDA	National Institute for Drug Abuse
NIH	National Institutes of Health, US Department of Health and Human Services
NMDA	N-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
OHP	Oregon Health Plan, Oregon's Medicaid Program
OA	Osteoarthritis
PA	Physician's Assistant
PCP	Primary Care Practitioner, Physician
PCST	pain-coping skills training
PM&R	physical medicine and rehabilitation
PMTF	The Office of the Army Surgeon General Pain Management Task Force
PT	physical therapy
PTSD	post-traumatic stress disorder
PUFA	polyunsaturated fatty acids
QALY	quality adjusted year of life
QOL	quality of life
ROI	return on investment
S&P	Standard and Poor's 500 Index
SMT	spinal manipulation therapy
SUD	substance use disorder
TENS	transcutaneous electric nerve stimulation
THC	tetrahydrocannabinol
TJC	The Joint Commission

Magnitude of the Pain Problem

Societal impact

The morbidity, disability and economic costs of pain in America are enormous. Recent estimates for the cost of pain care fall in the vicinity of $560–635 billion annually.[1] This exceeds the annual expenditures for heart disease, cancer and diabetes combined, the nation's priority health conditions.[6] The IOM report estimated over 100 million American adults suffer from chronic pain. This figure is likely an underestimate of America's overall pain burden, as it does not include children, nursing home residents, active military, or those in prison.[1,2] The prevalence of chronic pain conditions in the general adult US population is estimated to range from 11–47% in large surveys.[1,6–11] Low back and neck pain, osteoarthritis (OA), and headache are the most common pain conditions in the US and are leading global causes of disability in 2015 in most countries.[12] Unfortunately, we can expect the chronic pain burden to escalate. A 2013 National Academy of Sciences report predicts pain prevalence will rise as chronic illnesses increase.[13] For example, neuropathic pain currently affects over six million Americans and is expected to rise dramatically due to the increasing prevalence of diabetes. Obesity is also increasing and is associated with risk of diabetes, neuropathy and orthopedic problems.[1] Inadequate postsurgical pain management strategies for the increasing numbers of ambulatory and outpatient surgeries have resulted in chronic pain. As surgical, anesthetic and pharmaceutical interventions save lives in cases of catastrophic injury and life threatening illness there is another growing cohort of people who are living with chronic pain.[1]

Although pediatric pain statistics are less well studied, a systematic review of the epidemiology of chronic pain in children and adolescents found that "persistent and recurrent chronic pain is overwhelmingly prevalent in children and adolescents and should be recognized as a major health concern in this population."[14] The most common pediatric chronic pain complaints include migraine, recurrent abdominal pain and general musculoskeletal pain, including limb pain and back pain.[15] Depending upon the population surveyed and time frame of the survey, prevalence estimates for pediatric chronic pain range from 4–89%: headache (8–83%), abdominal pain (4–53%), back pain (12–24%), musculoskeletal pain (4–40%), and "other" or general pains that included recurring earaches, throat pain.[14]

Impact of pain: individual, workplace and employer health costs

The impact of pain is felt at many levels ranging from the effects on the individual, families, the healthcare system, employers and the community at large. Chronic pain is a high-impact disruptor of lives and economies. It is complex—physically, neurologically, psychologically, socially, spiritually, economically and symbolically.[16] For the individual, there may be decreased physical functioning and increasing difficulties with simple daily and self-care activities.[17] These changes can have an effect on psychological health, with an increase in sadness, worry, anger, depression, suicidal thoughts and a reduced sense of self-worth with changes in abilities.[18] For children, there may be an impact on school performance, school attendance and interactions with peers.[14,19] For both adults and children, pain negatively effects social functioning and relationships. As a result of alterations in work capacity, people in pain have lower hourly wages and miss more time from work than those without pain.[6] In some cases pain leads to the need for work modifications or disability claims. Pain is associated with impairment in physical and psychological functioning,[12,20] lost work productivity[21] and lower socioeconomic status.[22] In addition to the costs and time needed for seeking care, people with pain conditions have significantly higher direct healthcare expenditures.[6]

Opioid abuse/dependence impact on health care costs

Among the distinctions of the current epidemic from earlier opioid abuse epidemics is that this crisis, having been based in medical prescribing, is disproportionately affecting white, middle-class people in nonurban settings, including those with private insurance.[23]

- 2007–2014 opioid dependence rose by 3,203% among patients privately insured.[23]
- 2011–2015 privately insured opioid abuse or dependence charges rose from $72 million to $722 million.[24]
- Allowed amounts for opioid abuse/dependence healthcare services grew more than 13-fold during the same period, from $32 million in 2011 to $446 million in 2015.
- In 2015 the average annual per-patient charges and estimated allowed amounts by insurance were more than five times higher for patients with diagnoses of opioid abuse or dependence than for those with any diagnosis.
- In 2015 private insurers and employers providing self-funded plans paid nearly $16,000 more per patient with a diagnosis of opioid abuse or dependence than for those with any diagnosis.[24]
- 2006–2010 emergency department (ED) visits related to prescription opioid poisoning increased to 259,093: over half were hospitalized resulting in over $4 billion in costs.[25]
- ED visits for pediatric opioid poisoning between 2006 and 2012 numbered 21,928 with over $81 million in total charges.[26]
- From 2007–2014 pregnancy drug dependence diagnosis (including prescription opioid) rose 511%.[23]
- From 2003–2012 neonate abstinence syndrome (NAS) admissions increased more than fourfold with annual costs growing from $61 million to nearly $316 million.[27]
- Hospital stay is 3.5 times longer for NAS neonates compared to non-NAS neonates, with a threefold increase in cost.[27]
- A sizable percentage of the driving public has detectable levels of opioids in their blood[28] with opioid impaired driving implicated in motor vehicle accidents.[29]

These costs and risks are substantial and yet fail to measure the costs to the health and wellbeing of society: communities, families, friendships and individuals.

Economic impact of pain

The US spent 17.8% of it's GDP on healthcare in 2015,[30] expected to increase to 20% or higher by 2025.[31] A significant portion of that is pain related since pain is the most common and compelling reason for seeking medical attention.[32,33] "The economic burden of prescription opioid overdose, abuse and dependency is estimated to be $78.5 billion each year in the United States".[34] Social Security Disability Insurance statistics suggest that worker disability from musculoskeletal and connective tissue disorders is rising, not falling. Work disability attributed to musculoskeletal and connective tissue disorders increased from 20.6% of beneficiaries in 1996 to 25.4% in 2005[35] to 31.7% in 2015.[36] In addition to worker disability there are direct and indirect workforce financial costs including both workplace absenteeism[2] and lost productivity from ill and injured workers while still working, called presenteeism.[37,38] There can be lost business opportunities and reduced customer goodwill due to work that goes undone and deadlines, meetings, appointments or engagements missed due to employee absence or reduced capacity. The Integrated Benefits Institute (IBI) conducted a landmark and ubiquitously cited survey in 2005: nearly all CFOs surveyed (343 senior finance executives) reported that they will focus on controlling health plan costs over the next two years because they believe that work time lost to employee illness including chronic pain is reaching critical levels and is affecting business performance.[39] A majority will seek to manage all health-related costs, including absenteeism and bottom-line effects as key impacts of employee ill health. IBI also found, however, that CFOs are ill-informed about health-related lost work time. Nearly half of survey respondents never receive reports about "incidence of absence," and less than a quarter receive reports on its financial impact. Far fewer know about presenteeism with nine in ten never receiving reports on the incidence or impact of presenteeism in the organization.

Cost savings from improving worker health requires new record keeping strategies. One of the most significant new research models is the extension of return on investment (ROI) analyses to include economic outcomes resulting from health interventions such as performance and productivity. For example, while very few newly approved pharmaceuticals actually save money, they can improve health at a reasonable cost. In pharmacy literature, net increases in spending that are up to $50,000 may be deemed acceptable or cost-effective if these dollars will save at least one quality-adjusted year of life (QALY). However, this widely accepted methodology has rarely been used when considering the value of health improvement programs.[40] By contrast, the more demanding objective of realizing net savings has generally been required in evaluations of health and productivity management programs.[41] Companies with successful wellness programs, with improved health-related and economic outcomes, encouraged wellness to improve employees' lives not only to reduce costs.[42] Furthermore, employers and payers need to realize that benefits of investments in health accrue over time, and there may be a lag between improvements in health and savings from improved productivity. Standard calculations of documenting ROI may need to become more sophisticated to capture net cost savings in the intermediate and long run.

The current workforce literature is inadequate to evaluate the specific role of pain as distinct from overall illness. The literature on work-related injuries such as back, neck and upper limb pain covers a subset of pain problems but does not capture data on such pain-related conditions as arthritis, autoimmune disorders, and diabetic and other neuropathies that are not work related. The current lack of clarity of clinical and especially cost implications remains to be resolved by future, more rigorous studies conducted at worksites over multiple years with adequate follow up times to determine both clinical and cost benefits.[43,44] Ongoing studies seek to develop best practice models for business analysis outcomes. Recent reviews confirm that companies that invest in worker health and well-being, including through health-promotion programs, have markedly improved stock price performance compared to the Standard and Poor's 500 Index (S&P).[45,46] Similar savings have also been observed through health promotion programs among individuals who are retired and on Medicare.[47]

Health disparities and pain: race/ethnicity, gender and age

Pain and pain care impact specific socioeconomic and demographic groups differently. Increased vulnerability to pain is associated with having English as a second language, race and ethnicity, lower income and education, sex and gender, age group, geographic location, military veterans, cognitive impairments, surgical patients, cancer patients and the end of life.[1] Many of these same groups are also vulnerable to pain treatment that is limited in access and scope.[1,2,48] In addition to factors such as age, race/ethnicity, socioeconomic status, gender and geography, education and health literacy also influence access to kinds of care and to care outcomes. For example, while back pain is common across all primary care populations, low-income, racially diverse individuals are impacted differently. African Americans have a lower likelihood than whites of receiving comprehensive pain assessment and management.[48] African Americans may also receive less intensive diagnostic and treatment approaches compared to white patients.[48] For occupation-related back pain, whites are more likely to be diagnosed with disc herniations and have surgery than blacks; yet a nonspecific diagnosis and lack of surgery uniquely predicts lower treatment expenditure and disability ratings for African Americans.[49] Perversely, it is possible that this disparity in care provides an advantage to those African Americans who might ostensibly be considered "undertreated": less treatment for back pain may be better treatment.[35]

This does not, however, erase the sting of discriminatory care. Episodes of major lifetime racial discriminatory events are the strongest predictors of back pain reported in African Americans, with perceived day-to-day discrimination being the strongest predictor of back pain for African American women.[50] Racial discrimination as a predictor of pain is consistent with the impact of social context and its interrelationship with chronic pain.[51] Older African Americans experience severe mismanagement of pain and potentially inappropriate or dangerous medication duplication or interactions, particularly those with comorbidity, multiple providers and limited access.[52] Patients of lower socioeconomic status and lower healthcare literacy are less likely to be able pursue effective healthcare options not typically covered by insurance. There is ongoing research to assess how disparities in health care and outcomes operate along ethnic and socioeconomic lines. A recent review of long-term survey data indicate that racial/ethnic disparities in pain may be in part accounted for by socioeconomic status and education level—both factors that interact with race and ethnicity.[11]

Hispanics are at higher risk for pain and pain undertreatment given the incidence of lower education, income levels, and lack of health insurance and/or access to care. These disadvantages are further compounded when there is limited English proficiency that impacts communication with healthcare providers.[1] American Indians and Alaska natives have markedly higher rates of pain symptoms compared to US general population,[53] with high rates of diseases and health conditions such as diabetes, arthritis and obesity that produce significant pain.[1] Despite this, American Indians report minimizing pain complaints and not readily asking for help, likely exacerbating disparities through underdiagnosis and undertreatment.[54] Asian Americans have overall lower pain prevalence than non-Hispanic whites. However, the variety of national origins, cultures, languages and ethnicities lead to variations within this group. Lower reports may be due to a general reluctance to report pain (perceived as a sign of weakness) and a fear of side effects of pain medication combined with the potential liability of lower English proficiency and the experience of cultural bias by health professionals.[1]

In every ethnic/racial category, women are more likely than men to report a wide range of chronic pain conditions[1,55,56] while pain prevalence varies for women by age and race/ethnicity.[57] Women experience disparities in pain care with misdiagnoses, delays in correct diagnoses, improper and uneven treatment, gender bias, stigma and neglect, and dismissal and discrimination from the healthcare system.[1,58] Women report greater severity, longer-lasting and more frequent pain than men, and also experience multiple pain problems. Women are prescribed opioids and benzodiazepine sedatives at higher rates than men.[59,60] While men are more likely than women to die from prescription opioid painkillers, the percentage increase in deaths since 1999 is over fivefold greater among women.[61] Between 1999 and 2010, about 18 women died every day in the US from a prescription opioid overdose. For every woman who died of an overdose, there were 30 who went to the emergency department for painkiller misuse or abuse.[61]

Chronic pain in children is often underrecognized[1] and even when recognized is still undertreated, with consequences that include behavioral changes and adverse effects on child development.[62] While both boys and girls are more at risk of chronic pain as they get older, girls report chronic pain more often than boys.[14,63] Undertreated pain is also common among hospitalized children.[64] There are many levels at which children may receive disadvantaged care.[65] Many pain medicines have not undergone clinical trials or been approved for pediatric use and consequently providers are more reluctant to administer them.

The prevalence of chronic pain among independent living older adults ranges from 18% to 57%, depending on the definition of chronic pain. More severe pain and pain that interferes with activities increases with age.[1] Additionally, there may be difficulty assessing pain in older adults with cognitive impairment. Side effects of drug treatment may further adversely affect their cognitive function and overall health.[66–68]

Easy access to opioids as the main pillar of pain care can be viewed as inadequate or "disadvantaged" care based on the lack of evidence for safety or effectiveness for chronic noncancer (CNCP) pain.[69,70] This is further reinforced by opioids' abuse liability. The successful marketing of opioid dose-escalation for CNCP has adversely affected those traditionally considered disadvantaged as well as those who are not.

The perfect storm of circumstances, with opioids for CNCP promoted by physicians[71] and pharma alike, opened the floodgates to single modality care with opioids creating an addiction crisis[72] with a staggering impact on, for example, unemployed and disabled workers in economically devastated industrial communities.[73] White, middle-class people in non-urban settings are disproportionately affected by the current opioid crisis. Between 2007 and 2014, opioid dependence rose by 3,203% among patients privately insured in these communities.[23] Effective pain care is not assured by economic access to care, for example, through private insurers.[13]

While the 2016 Centers for Disease Control and Prevention (CDC) guidelines confirm non-opioid therapy is preferred for chronic pain outside of active cancer, palliative and end-of-life care,[74] for these populations pain is often the dominant symptom.[1] There is substantial evidence that nonpharmacologic therapies can play a significant role in cancer pain, palliative and end of life pain care as well.[75–77]

Taking into account all health care disparities and the current US crisis in pain care, a case can be made that any patient no matter their ethnic or socioeconomic status, who is not informed or who is not offered effective nonpharmacologic options for pain is, in fact, inadequately served. One could argue that given the risks of standard care, failing to educate patients and recommend nonpharmacologic care should be considered unethical.

Complexity of pain categorization

There is tremendous variability in the categorization of pain states that can obscure the magnitude of the problem of pain management. Pain is commonly categorized into acute and chronic, according to timeline and connection to tissue injury. Acute pain typically lasts less than 3 months but may persist longer and usually has a clear connection to a physically identifiable nociceptive (pain generating) pathology or tissue damage.[78] Acute pain is expected to resolve as the tissue damage heals. Chronic pain is present for longer than 3 months and may or may not have a clear and current connection to an identifiable tissue-based cause, structural injury or defect. Cancer pain can be acute, whether it is post-surgical or due to ongoing nociception, or can be chronic. The timeline of a pain condition is increasingly being recognized as an artificial metric, as the distinguishing features of the mechanisms of acute and chronic pain are recognized. For chronic pain, the search for causative physical sources can be frustrated by many factors, including the lack of sensitivity of available imaging technology to detect soft issue and neuropathic causes, the complex structures that can be involved in the generation and modification of pain, and the limited training most doctors receive in the subtleties of physical examination for pain conditions.[79,80] Physicians report wanting more training and knowledge on evidence-based nonpharmacologic therapies and are not aware of evidence-based resources.[81] "Any meaningful effort to improve pain management will require a basic culture shift in the nation's approach to mandating pain-related education for all health professionals who provide care to people with pain."[82]

More recent discoveries about central and peripheral nervous system pain processing (central sensitization and peripheral sensitization) are being recognized as more actionable when classifying pain. Central sensitization involves neuronal and nonneuronal pathways (e.g., glial pathways) to and from the brain and spinal cord.[83] Peripheral sensitization involves peripheral structures such as muscle, nerve, fascia and others.[84,85] In both central and peripheral sensitization, decreased inhibitory signals meant to downregulate nociceptive transmission are themselves inhibited, leading to enhanced perception of pain. This presents clinically as hyperalgesia (experiencing a mildly painful stimulus as very painful) and allodynia (experiencing nonpainful stimuli as painful). The phenomena of peripheral sensitization are increasingly recognized in the medical community and well documented in basic science literature.[84,85] Another increasingly recognized neuroplastic process is the reorganization of the somatosensory cortex leading to altered and inefficient movement strategies, which can themselves cause fatigue and pain.[86,87] These changes in the nervous system currently inform our perceptions of chronic pain and are seen in many common chronic pain syndromes, including headache; back and neck pain; chronic abdominal pain; fibromyalgia and chronic fatigue; visceral pain; and the group of conditions called repetitive strain injuries such as cervical postural syndrome, most cases of thoracic outlet syndrome, carpal tunnel disorders, trigger fingers, and forearm and thumb tendonitis.

Pain can also be subcategorized according to anatomical sites where the pain is felt such as headache, neck and back pain. Pain can be named for the tissues involved such as musculoskeletal, visceral or neuropathic. It can be named for the pathological process such as cancer pain, osteoporotic pain, OA pain, repetitive strain injury or post-surgical pain. Many of these categories of pain can coexist and even overlap, making it important to understand the parameters and definitions used with studies evaluating pain statistics. Regardless of classification systems, the number of people in pain is high and increasing.[1,7–10] Moreover, chronic pain states have the highest economic and societal adverse impacts.

Comorbidities associated with pain

The definition of pain commonly used in hospice was proposed by Dame Cicely Saunders and includes the physical, psychological, social and spiritual domains.[88] This inclusive definition can be helpful in thinking about non-terminal cases involving pain since comorbidities spanning Saunders' domains are common in chronic pain patients and can complicate the evaluation and successful treatment of pain. There is a complex association between pain and psychiatric disorders. Adults with mental health disorders are significantly more likely to be prescribed opioids; 16% of Americans who have mental health disorders receive over half of all opioid prescriptions.[89] Patients with chronic pain are at increased risk of comorbid depression, anxiety and post-traumatic stress disorder.[32,90] Pain increases depression risk 3-5 fold.[91] Pain, rather than chronic disease, is associated with the recurrence of depressive and anxiety disorders;[20] 50–80% of chronic pain patients report insomnia of a severity that warrants clinical attention.[92] However, opioids generally exacerbate rather than improve these sleep and mental health comorbidities.[93]

There are many interconnections between social rejection or exclusion and pain; for example, both are experienced in the same parts of the brain.[51] Social isolation is a common condition among pain patients. Pain itself isolates the individuals since they may withdraw from family, work, school and social activities. Pain medications, however, can exacerbate rather than improve isolation by interfering with hormonal and neurotransmitter functions.[94] The endogenous opioid system is involved in the development and maintenance of human attachment. According to the brain opioid theory of social bonding,[95,96] beta endorphins attach to mu opioid receptors resulting in analgesia and feelings of well-being. These are closely related to the dopamine reward system and the oxytocin system affecting bonding, reinforcing the rewarding nature of close social interactions.[97–99] The disruption of these interconnected functions—human social bonding, parent-infant bonding, the endogenous reward system, which includes sexual response—by exogenous opioids is currently being studied extensively. Hypogonadism as a result of long-term opioids has long been recognized.[100] The measure of the social dysfunction seen with opioid use is far reaching and has not been adequately addressed in most clinical practice settings.[99]

As discussed above, substance use disorders (SUD) commonly occur and have increased as a result of the liberal use of prescription opioids. These may result from preexisting SUD or be iatrogenically induced dependence, tolerance and addiction to prescribed opioids. For a brief time, the term "pseudo addiction" was used to justify the prescribing of higher opioid doses while ignoring "red-flag" signs of addiction such as lost prescriptions, requests for early refills and nonadherence with prescribed doses.[101]

In studying the association of prolonged opioid use with psychiatric comorbidities, there is an "adverse selection" at play; people with serious psychiatric comorbidities are more likely to end up on high dose, long-term opioids.[102–105] This could be in part a result of the difficulty accessing behavioral health and addiction services as well as the need to present with physical symptoms to obtain care. Opioids are being used as a proxy treatment, a convenient but risky option for complex pathologies that are characterized and labeled as "pain" by patients and practitioners.[102] The social services needed to fully assess and treat them are often unavailable.

Pain interacts with overall health. Other comorbidities such as diabetes, cardiovascular disease and obesity are at once the cause of certain types of pain and exacerbated by pain.[1] Illnesses that are comorbid with pain can, in turn, be exacerbated by the use of opioids that are ineffective for chronic pain, produce illness behavior and carry a significant abuse liability.

Healthcare workforce considerations

Many factors contribute to the current trends in pain management. The majority of medical/healthcare visits are initiated because of pain[32–35] and as a result, primary care practitioners (PCPs), family medicine, general internal medicine, general pediatrics, combined medicine-pediatrics, general obstetrics and gynecology, osteopathy, and general surgery assisted by nurses, nurse practitioners (APRN) and physicians' assistants (PAs) care for the largest proportion of those with pain and prescribe the largest proportion of pain medications including opioids.[106–108] The current business model for most primary care settings encourages short appointments to increase the volume of patients seen. Pain patients, especially chronic pain patients, have complex medical histories and often have multiple overlapping causes of pain. These presentations place an intense time pressure on PCPs making it difficult for them to fully address the complexities of chronic pain and may encourage therapeutic choices that can be easily recommended within the time allotted, most commonly prescription drugs. In 2012 nearly 49% of all dispensed opioid prescriptions were accounted for by primary care specialists.[2]

Additionally, the education currently provided to PCPs is deficient in content related to pain in general and the full spectrum of evidence-based pain care approaches. Pain curricula in medical school education for both MDs and DOs in the US ranges from 1 to 31 hours during the 3–4 year curriculum, with a mean of 11.13 hours and a mode, or common length, of 4 hours.[109] Residency education is also insufficient to prepare primary care practitioners for competency in the treatment of common pain problems.[1,110] "A lack of knowledge and/or evidence of clinical effectiveness preclude the delivery of adequate care."[110] "Thus, the current training system has left primary care practitioners with inadequate tools with which to deal with some of their most frequent and challenging patients."[80] "Any meaningful effort to improve pain management will require a basic culture shift in the nation's approach to mandating pain-related education for all health professionals who provide care to people with pain."[82]

Other medical specialists also treat pain that is within the purview of their specialty on a regular basis. Examples of this are urologists treating kidney stones and their painful sequelae or orthopedic surgeons treating post-operative pain. Generally, these specialists will treat pain for a short term and then return the patient to primary care or specialty pain care. Other specialties such as rheumatology, sports medicine, and physical medicine and rehabilitation (PM&R) sometimes have long-term engagement with pain care for their patients, mainly with interventional and pharmacologic options.

The medical pain specialty grew out of the work of John J. Bonica who directed the Department of Anesthesiology and Pain Medicine at the University of Washington in the 1960s. Many, if not most, pain clinics are still housed in anesthesiology clinics, but fellowship pain training can now be pursued not only by anesthesiologists but other specialists in neurology/psychiatry, PM&R, and internal and family medicine. Physicians who receive fellowship training in pain care learn interventional pain strategies that originated in regional anesthesia and acute pain care. Acute pain interventions are an essential part of pain care. But the expansion of these strategies, which are the mainstay of anesthesiology and acute pain practices, to chronic pain care have had more modest success and only in carefully selected patient groups.[111] Additionally, there are licensed practitioners from evidence-based disciplines, as in acupuncture therapy, massage therapy, osteopathic therapy, chiropractic and others, providing pain care but whose work may currently be less accessible within most formalized health systems.

Another way to categorize the practitioners in the pain field is through insurance reimbursement. Some practitioners are typically insurance reimbursable such as physical therapists, psychologists, psychiatrists, social workers and dentists, and under certain circumstances, pharmacists. Practitioners licensed in fields such as acupuncture, massage, chiropractic and naturopathy provide care that is 60–70% less likely to be reimbursed.[112] Even when health coverage is available it is generally limited, such that patients will still have substantial out-of-pocket costs.[113] There are also studied approaches to pain care that are not regulated but are delivered by licensed practitioners "in place" such as nurses using guided imagery or progressive relaxation, for example. These services are generally not reimbursed.

The need for an informed strategy including all evidence-based comprehensive pain care is clearly demonstrated to be in patients' best interest, as reflected by their healthcare seeking and out-of-pocket expenditures for pain care. Reported in 1993 the number of visits to what were called "unconventional" providers exceeded visits to all US primary care physicians; 1990 expenditures were 13.7 billion, 10.3 billion of which was out of pocket.[114] Analysis of the 2012 National Health Interview Survey estimated the out-of-pocket expenditure at $30.2 billion.[115] Out-of-pocket expenditures for back pain alone was $8.7 billion.[113]

Coordination of care across disciplines and access to nonpharmacologic care have not been optimized in the current system in most states and territories. There are a few state Medicaid policy initiatives aimed at increasing access to effective nonpharmacologic therapies as a first line treatment for pain conditions. For example, the Oregon Health Plan (OHP—Oregon's Medicaid program) covers acupuncture therapy, chiropractic and osteopathic manipulation, physical therapy and cognitive behavioral therapy for all back conditions. In addition, yoga, intensive rehabilitation, massage and/or supervised exercise therapy are recommended to be included in the comprehensive treatment plans and will be provided where available as determined by each of Oregon's Coordinated Care Organizations.[116] Vermont's legislature is piloting a program where they will cover acupuncture therapy for back pain in a Medicaid population and monitor health outcomes and cost-effectiveness.[117] Private coverage of every category of licensed provider is mandated in the State of Washington, where the number of people using insurance benefits for care by these providers was similar to data by the National Health Interview Survey (NHIS); hence coverage did not lead to runaway utilization.[118] Musculoskeletal pain was the most common diagnosis for a visit. For insured patients with back pain, fibromyalgia and menopause symptoms, users of nonpharmacologic therapy providers had lower insurance expenditures than those who did not use them.[119]

Coverage for care is not current to the evidence-based detailed in Section 2 Solutions to the Problem below. Diversity of practice and engaging multiple evidence-based disciplines is enthusiastically embraced in pain medicine as a concept. Yet without a strategy on evidence-based pain care both in terms of effectiveness and cost-effectiveness, patients are not well guided in options and are often left to be the sole case managers for their own care as they navigate a system fragmented into silos.

Practitioners and patients are challenged by other barriers in access to nonpharmacologic options that are effective for pain. In addition to the socioeconomic, gender and racial/ethnic disparities already detailed, geographic disparities exist in the numbers and locations of practitioners using nonpharmacologic options leaving many regions and populations underserved.[120,121] As of the writing of this paper there are ongoing meetings regarding Medicare and Medicaid coverage for licensed practitioners working within their state-regulated scope of practice and utilizing therapies proven effective for pain. The Joint Commission (TJC), which has long recognized nonpharmacologic approaches to pain, has now mandated that it's accredited hospitals and facilities provide evidence-based nonpharmacologic options for pain, emphasizing the importance of options in comprehensive care. Strategies will be needed to facilitate both access and coverage to nonpharmacologic therapies.

Risk and lack of effectiveness of prevalent pain care strategies

Despite increased medical expenditures for pain and technological advances such as magnetic resonance imaging, new medications and surgical approaches, the prevalence and impact of chronic pain is worsening rather than improving. Many factors have contributed to the current situation. Both patients and medical practitioners labor under the mistaken idea that most pain problems can be fixed by the doctor or surgeon with a drug or procedure. Medical school and graduate courses still emphasize a search for appropriate dosing of opioid medications rather than considering other options. The business model of medicine, the cultural authority of projected and perceived certainty, and the disempowered position of patients in pain has promoted simplistic solutions—albeit well-intentioned—to complex problems. Patients are often regarded as passive participants with little emphasis placed on self-care, on pain prevention, or therapies that engage preventive and self-care strategies, despite demonstrated longitude of benefit.

The increasing need to respond to poorly addressed pain resulted in the numeric quantification of pain. As the notion of pain as the "fifth vital sign" took hold in the late 1990s, pain assessment became increasingly focused on a single dimension of patient status—the pain score on an 11-point, 0–10 rating scale; either a numeric rating scale with numbers marked on a 10cm line or the visual analogue scale like the Wong-Baker scale, usually a 10-cm line with faces expressing levels of pain and no numeric markings on it.[122] By taking eyes off the more complex goals of quality of life and overall functional ability, the system inadvertently contributed to reduced functioning and increased suffering of pain patients.[69] The pressure to manage pain scores rather than to treat patients themselves has contributed to overprescribing opioids, widespread drug diversion, which is engaging illegal sources for prescription drugs, the resurgence of heroin addiction, increasing disability from pain, and deaths from overdose.[1,2,35,123,124] Pain practitioners have long noted that pain scores do not deliver accurate information about the status of a patient. Scores vary inexplicably and alone do not inform tailored, comprehensive and effective solutions. Pain scores do not capture level of function or quality of life (QOL) intrinsic to an experience of well-being that can be present despite high pain scores. The reduction of a patient's pain experience to pain scores led to a narrowly defined goal of pain score reduction in response to interventions.[123]

Opioids and other drugs

The US prescribes 50 times more opioids than the rest of the world combined.[72] Between 1999 and 2010, opioid prescriptions in the US were enough to medicate every American adult with a standard pain treatment dose of 5 mg of hydrocodone every 4 hours for a month.[125] This indicates a public health crisis as prescription opioids contribute to substance use disorder (SUD) or addiction. Prescription opioids are now the most frequent gateway drug to heroin. Inadvertent overdose deaths associated with prescription opioids exceed overdose deaths from heroin and cocaine combined[125] and in many states now exceed deaths from motor vehicle accidents.[126,127] Societal and family disruption, violence and insufficient resources to treat SUD have resulted.

Complications attributable to the rapid rise of opioid use for chronic noncancer pain (CNCP) have led to an evidence-based re-evaluation of the practice of prescribing ever-increasing doses of opioids that have known risks and unproven benefits.[69,128] This has finally propagated recommendations for a shift away from opioids and toward comprehensive, multi-modal evidence-based care. While the government has increased access to naloxone for the treatment of acute opioid toxicity (respiratory arrest), it is important to note that this is not a preventative strategy for the deepening opioid crisis.

Acute pain care can impact the development of chronic pain and disability and the development of opioid dependence, tolerance, addiction and diversion. Patients often receive long-term opioid therapy after an acute problem such as dental procedure, surgery or injury. Alarming numbers of patients then transition to chronic use after starting opioids for the short-term treatment of post-operative pain (27%) or injury-related pain (27%).[129] Pain relievers are the medications reported most often prescribed at hospital emergency and outpatient department visits.[33] Per the CDC, the economic burden of prescription opioid overdose, abuse and dependence is estimated to be $78.5 billion each year in the US.[34,130] Moreover, misuse and abuse of prescription opioids costs the country an estimated $42 billion a year in lost productivity.[131] Workers' compensation data from Washington State indicates that injured workers who are on opioids for over three months are unlikely to return to work.[124]

The probability of long-term opioid use increases after as little as five days of prescribed opioids as the initial treatment of pain; the probability of patients remaining on opioids for the long-term is the highest when treatment is initiated with long acting opioids,[132] a strategy borrowed from cancer pain treatment[71] and not well studied in noncancer pain. Tolerance (requiring higher doses to achieve the same analgesic effect), dependence (suffering withdrawal symptoms if a dose is missed) and opioid induced hyperalgesia[133] (a heightened sensitivity to pain) can develop quickly. There is no clear way to ascertain what baseline pain is present and what pain is in response to withdrawal from the last dose of opioid or induced by the opioid itself.

Acetaminophen (APAP) has been found to be only modestly helpful for mild pain; it is ineffective for acute low back pain,[134] and it is uncertain if it has any effect in chronic low back pain (cLBP).[135] Although there are fewer adverse events with acetaminophen than other medications,[134] there are dose limitations due to hepatotoxicity.[68] *Nonsteroidal anti-inflammatory (NSAID)* medications may be helpful in decreasing pain from a variety of causes such as arthritis, headache and back pain. More recent trials, however, report "that NSAIDs had smaller benefits for cLBP than previously observed".[134] The benefit of NSAIDs for spinal pain compared to placebo were not clinically important.[136] NSAIDs are now recognized to interfere with healing[137,138] and cause significant morbidity and mortality. They are a well-recognized cause of rebound headaches. Rebound pain, chronic medication use, and discontinuation syndromes in other conditions have not been as widely studied but exist.[139] Many patients have difficulty tolerating NSAID medicines due to gastrointestinal (GI) side effects such as nausea and abdominal pain.[140] The FDA has issued new warnings on NSAIDs,[66] adding stroke and cardiac risk to the list of already well-known risks, which include delayed healing, renal failure and acute and chronic GI bleeding.[2,68] There are 16,500 deaths annually from NSAID associated GI complications among RA and OA patients alone.[67,140]

Corticosteroid medications are considered potent anti-inflammatories often prescribed orally or by injection for refractory neurologic and autoimmune related pain as in discogenic pain, rheumatoid arthritis and intractable headache. Recent studies challenge the usefulness of steroids for many indications including chronic pain.[134,141] One in five American adults in a commercially insured plan were given prescriptions for short-term use of oral corticosteroids during the three-year period from 2012 through 2014.[142] Even at relatively low doses, corticosteroids can be associated with insomnia, nervousness, behavioral changes, increased appetite, headache and joint pain.[143,144] There are increased risks of serious acute complications such as infection, venous thromboembolism, avascular necrosis and fracture. There are also risks of development and or exacerbation of chronic disease such as diabetes mellitus, hypertension, osteoporosis and other features of iatrogenic Cushing's syndrome.[142] Corticosteroids are one of the most common reasons for admission to hospital for drug related adverse events.[142] Yet corticosteroids do not appear to be effective for acute, radicular, or nonradicular low back pain.[134,141,145] Epidural steroid injections are associated with less improvement in patients with lumbar spine stenosis,[146] increased risk of spinal fractures,[147] and increased risk of infection if followed within three months by spinal fusion surgery.[148]

Skeletal muscle relaxants are prescribed for short-term pain relief in acute pain but are associated with central nervous system adverse effects, especially sedation.[134] Research is equivocal on significant benefit of some muscle relaxants for pain or muscle spasm.[149] Baclofen (oral, IV, or intrathecal) can be helpful for neurologically mediated spasticity as in multiple sclerosis, traumatic brain or spine injury but with risk of increase in mean fat body weight[150] and serious complications, even organ failure, with disruption in administration.[151] Carisoprodol (Soma) should be avoided as it metabolizes to meprobamate, which has been withdrawn from the market in many jurisdictions due to toxicity and respiratory suppression when combined with opioids. Benzodiazepines may provide some relief for nonradicular low back pain and muscle spasm.[134] However, common adverse effects include anticholinergic symptoms such as dry mouth, blurred vision, constipation, drowsiness, sedation and confusion. Adverse effects and risk of dependence are important limiting factors especially since there is a high prevalence of concurrent benzodiazepine and opioid use in patients with chronic pain.[152] Moreover, half of deaths from drug overdoses among veterans occurred when concurrently prescribed benzodiazepines and opioids.[153]

Anticonvulsant (antiepileptic) medications gabapentin and pregabalin are often used in neuropathic and neurological pain conditions such as diabetic neuropathy, postherpetic neuralgia and migraine and more recently in acute perioperative pain.[2] Topiramate and valproate/divalproex are commonly used for headache attenuation or prevention.[154,155] Though carbamazepine is commonly used in the treatment of trigeminal neuralgia, evidence for its effectiveness is not strong.[155,156] These medications provide mild to moderate benefit while being limited by neurological adverse effects including drowsiness and cognitive slowing.[157]

Antidepressants of various classes including tricyclic, serotonin and norepinephrine modulators are commonly used in pain conditions including neuropathic, migraine, and amplified pain disorders such as fibromyalgia and complex regional pain syndrome.[158] There is also a growing recognition that mood disorders, anxiety and other psychiatric comorbidities increase the suffering associated with pain, which has resulted in an increase in the use of non-opioid drugs such as antidepressants. Certain antidepressants have propensity to anticholinergic effects, vasomotor symptoms, weight gain, sexual dysfunction, emotional blunting and suicidality, and need to be chosen carefully based on risk and comorbidities.[159]

Breakthroughs in neuroscience regarding the roles of glial cells[160] and other pain modulating neuroplastic changes have led to the premature use of purported *modulators of glial function*, including ketamine, naltrexone, dextromethorphan, some tricyclics and other drugs, with variable results.[161,162] But an effective course of acupuncture applied to local points for carpal tunnel syndrome results in distinct neuroplastic changes[87,163] as do other nonpharmacologic interventions for chronic pain.[164] This trend to include the neuroplastic related aspects of chronic pain represents a significant contribution to pain care and is the focus of further research.

Topical medications from various categories including local and general anesthetics (e.g., lidocaine and ketamine), muscle relaxants (e.g., baclofen), capsaicin, anti-inflammatory drugs (e.g., ketoprofen and diclofenac) and antidepressants (e.g., amitriptyline) are used singularly or in combination for local pain management. Anti-inflammatories and capsaicin have been most studied and have the strongest evidence for benefit in musculoskeletal and neuropathic pain, respectively.[165,166] Local anesthetics have been used topically and as intralesional injections. More recently intravenous infusions have been used for neuropathic pain or generalized pain.[167]

Inhaled and topical medications containing *cannabinoids*, most commonly tetrahydrocannabinol (THC) and the less psychotropic cannabidiol (CBD), interact with cannabinoid receptors primarily in the brain to provide a broad range of effects.[168] In addition to reduction of nausea, recent evidence demonstrates that cannabinoids exhibit comparable effectiveness to opioids in models of acute pain and significant effectiveness in chronic neuropathic pain.[169,170] In a systematic review of RCTs of medical marijuana for CNCP, no serious adverse events were noted but “neurocognitive adverse effects related to learning, memory and psychomotor deficits were common even with low-dose, short-term use of medical marijuana though they appear well tolerated”.[171] Headaches, sedation, dysphoria and poor concentration were also noted. Long-term consequences of medical marijuana remain unknown and research is ongoing for benefit in non-neuropathic chronic pain.

Several classes of condition-based medications like *triptans* are prescribed for acute migraine[172] and “disease modifying agents” in autoimmune conditions have benefit in reducing pain related to these conditions, as in rheumatoid arthritis.[173] Cardiovascular and immunosuppressive adverse effects limit their use.

Imaging, procedures and surgery

In medical systems where a team approach to care is absent, a variety of specialists end up delivering a menu of very similar services, primarily medication, along with costly, invasive procedures and surgeries. A sometimes-premature response to or over-interpretation of imaging technology can result in higher rates of procedures and surgeries.

In the first decade of the 21st century, the use of high-cost imaging for spine and joint pain rose dramatically.[174] However, studies suggest that MRI findings do not correlate well with pain intensity or functional impairment, nor is advanced imaging associated with better outcomes.[175] Surgery rates are highest in areas of the country where imaging rates are highest,[176] yet imaging is not associated with an advantage in subsequent pain, function, quality of life or overall improvement.[35] While the process of imaging is not related to a high incidence of adverse events, part of the risk of imaging is the prompting of interventions that may result in increased risk with little gain. Moreover, common age-related, nonspecific MRI findings such as degenerative disc disease or anomalies of the spine may unnecessarily contribute to patient alarm and distress[35] that leads to reduced physical and work activity and a vicious cycle of disuse, distress and greater disability. The focus on imaging encourages patients to identify with their anatomical pathology often with little understanding of how that contributed to their pain or functional state.

Procedures for pain include injections of various kinds, nerve blocks, epidurals, tissue ablations, spinal cord stimulators and pain pumps. These procedures can significantly reduce suffering and allow salvage of damaged limbs and tissues in the case of acute tissue injury. Timely use of these techniques can reduce the development of post-traumatic stress disorder (PTSD).[177] In chronic pain these interventions can also be very helpful in carefully selected patients.[178,179] Unfortunately, for many procedures there are no practice guidelines that are universally followed. Expensive interventional procedures for chronic pain, such as epidural and joint steroid injections increased by 228% from 2000 to 2011,[180] and surgical center utilization increased by 300%.[181] The overuse of these strategies raises risk for patients and costs to the system. Moreover, their lack of effectiveness can be demoralizing for patients.[182,183]

As the long-term outcomes of surgical procedures are assessed, it is more evident that surgery performed to alleviate pain often does not achieve its goal. In geographic regions, the best spinal surgery outcomes occurred where surgery rates were the lowest; the worst results occurred in areas where rates were the highest.[35] Structural pathology of the knee, rated during meniscal surgery, for example, does not correlate with patient reported pain and function.[184] There is equivocal evidence for many common surgeries intended to remedy chronic pain; knee arthroscopies[185] and meniscectomies, for example.[186–188] Surgery is found effective in the short but not in the long term for most patients with cervical radiculopathy and facet arthropathy neck pain.[189] When long-term follow-up for lumbar spine stenosis surgery is done, non-operative groups fare as well as the operative groups,[190] except the operative groups experience an increased rate of side effects.

The cost of a laminectomy can range from $50,000 to $90,000 without insurance and up to $2000 in copayments with insurance coverage. A spinal fusion can cost between $80,000–$150,000.[191] "Despite no specific concurrent reports of clarified indications or improved efficacy, there was a 220% increase in the rate of lumbar spine fusion surgery from 1990 to 2001 in the US".[35] Yet there are no clear benefits observed with surgical vs. non-surgical treatment.[190] Conservative treatment including physical therapy has been associated with positive long-term outcome and a reduced likelihood of cross-over to surgery after one year.[192]

Increased costs and lack of evidence of efficacy is not to condemn surgery as an option, but to question practice that engages surgery before or instead of more conservative, evidence-based therapeutic care. Decisions are complicated by a business model of medicine that continues to value costly interventions not necessarily supported by evidence, particularly in the case of chronic pain and despite the fact that many patients who submit to surgery do not have resolution of their chronic pain.

While more research is needed to understand the progression from acute to chronic pain, it is clear that the limited, siloed strategies of the prevalent pain management system have not addressed the scope of pain in America. The NIH National Pain Strategy,[4] NAM,[82] the CDC opioid guidelines,[193] the updated pain mandate from The Joint Commission,[194] the FDA,[195] and the American College of Physicians (ACP) Clinical Practice Guideline[141] recommend evidence-informed, comprehensive pain care while conceding that past strategies generally, and the use of opioid medications specifically, have not remedied but rather exacerbated chronic pain, abuse, addiction, illness behavior and disability. Rapidly emerging science continues to inform our understanding of pain states and potential responses. Emerging science about the impact on pain states by the microbiome,[196–198] mitochondria,[199] fascia,[200–202] glia[160] and neuroplasticity,[87,163] and movement disorders secondary to pain[86] will likely inform future pain treatments.

The national pain strategies are shifting from a model of pain care, well-intentioned but delivered in specialty silos, favoring expensive solutions that have equivocal evidence of benefit to multimodal evidence-informed options, fitted to a patient's whole experience of pain and therapeutic goals.

Evidence-informed practice is based in evaluation and dissemination of current research including biological, medical and behavioral science. Thirty seven US State Attorneys General have submitted a letter to America's Health Insurance Plans (AHIP) asking them to include and incentivize evidence-based non-opioid treatments for pain.[203] Nonpharmacologic therapies for pain are now recommended by the American College of Physicians (ACP) for acute, subacute and chronic... and chronic low back pain. As of January 1, 2018, the largest hospital accreditation organization, the Joint Commission, will require hospitals provide nonpharmacologic modalities for pain.[203] The current evidence for nonpharmacologic therapies for acute and chronic pain is detailed next.

SECTION 2: SOLUTIONS TO THE PROBLEM EVIDENCE-BASED NONPHARMACOLOGIC PAIN CARE (NPPC)

Nonpharmacologic therapies are best considered within the context of all evidence-based medical treatment. The terms "complementary and alternative" stratify care by considerations other than evidence of effectiveness and risk. Evidence-based nonpharmacologic therapies are safe and effective components in comprehensive pain care that can also be opioid sparing, that is, reduce the need for opioids to manage severe, acute pain and consequently reduce the need for chronic opioids. Nonpharmacologic therapies can be standalone interventions or work in combination with medicine, procedures or surgery. An often underrecognized feature of nonpharmacologic therapies is their ability to confer additional benefits: a treatment to reduce pain can also reduce anxiety and depression, nausea and vomiting; facilitate restful sleep; and increase a patient's sense of well-being and desire to participate in their own recovery.

Policy decisions for strategies on pain care must be informed by research and evidence for all practices in medicine. The assumption that conventional care is proven care has been challenged by reviews: the US Office of Technology Assessment in 1978 estimated that only 10–20% of all procedures then used in medical practice were shown to be efficacious by controlled trial.[204] Estimates reported in the early 1990s determined 10–15% of medical interventions were based on results from randomized controlled trials; by 2003 that figure improved: approximately 50% of conventional care was found to be evidence-based.[205] Comprehensive, research-informed care should follow the evidence and include all evidence-based disciplines in a multimodal approach to pain care, particularly therapies that have evidence not only in the short term but have been evaluated for impact longitudinally, that is, care that registers improvement months and years following a course of treatment.[206,207]

There are effective nonpharmacologic therapies available from licensed and regulated professionals such as acupuncture therapy, massage therapy, osteopathic manual medicine, chiropractic, physical therapy and psychology. There are instructors trained in evidence-based, directed or self-engaged movement and meditative movement therapies as in yoga and Tai chi. Lifestyle or behavioral approaches, such as stress management, cognitive behavioral therapy, meditation/mindfulness and meditative movement therapies are also recommended as nonpharmacologic strategies. Other lifestyle approaches including diet and sleep hygiene have been shown to benefit health. These are low risk, low cost, well accepted by patients and many have been used successfully for thousands of years.

There is an additional benefit to many of NPPC strategies; unlike drugs and surgery, they involve patient participation and a commitment to self-care. Increased self-efficacy in managing pain often accompanies NPPC and correlates with improved mood and predicts improved outcomes in many chronic conditions, including pain.[208] For example, the military has studied "active self-care therapies" as a category of pain management that may be of value in an integrated, multimodal approach.[209]

Evidence-Based Nonpharmacologic Therapies for Acute Pain

Over 50% of chronic opioid use begins in the acute care setting, after surgery, or for treatment of acute injury related pain.[129] Nonpharmacologic therapies have demonstrated benefit for acute pain with opioid sparing in hospital settings for inpatient post-operative pain and for acute pain not related to surgery. The largest hospital accreditation organization in the US, The Joint Commission (TJC), has revised it's pain mandate, originally introduced in 2000. Effective January 1, 2018, TJC will require that it's accredited hospitals and facilities provide nonpharmacologic therapies for pain as a scorable element of performance.[194] Per TJC clarification statement of 2015, these include but are not limited to, physical modalities such as acupuncture therapy, chiropractic therapy, osteopathic manipulative treatment, massage therapy, physical therapy (PT), relaxation therapy and cognitive behavioral therapy (CBT).[210] While CBT, PT, exercise[2] and electrical stimulation (E-Stim) have shown benefit for chronic pain,[211,212] they are not covered in detail in this evidence review as they are currently recognized and part of covered conventional care options, albeit underutilized in some systems. CBT, PT, exercise and E-Stim are effective nonpharmacologic therapies for pain and are included in our recommendations.

Nonpharmacologic Therapies for Acute Inpatient Pain with Opioid Sparing

Acupuncture therapy post-operative pain

Acupuncture is understood as the insertion and manipulation of fine solid core needles at specified points or combination of points on the body. "Acupuncture therapy" derives from the traditional East Asian paradigm recognizing the interrelationship of organs and body points and channels as well as associated symptoms, disease and dysfunction. Depending on a state's scope of practice, acupuncture often includes treating by means of mechanical, thermal or electrical stimulation; by insertion of needles, or by application of heat, pressure or other forms of stimulation. In practice, acupuncture needling is often done in combination with other therapies such as palpation, Tui na, Gua sha, cupping, moxibustion, E-Stim, auricular treatment, herbal medicine and recommendations on diet, exercise, self-reflection and meditative movement like Tai chi. Acupuncture therapy, therefore includes acupuncture needling, accompanying therapies and recommendations that engage a patient in self-care, particularly in the treatment of chronic pain.

In multiple systematic reviews with meta-analyses, acupuncture was effective in reducing post-surgical pain compared to sham acupuncture, controls and usual care with reduction in opioid need (21% opioid reduction at 8 hours, 23% at 24 hours and 29% at 72 hours post-surgery) with lowered incidence of opioid-related side effects such as nausea, dizziness, sedation, pruritus and urinary retention.[213–215] A systematic review with meta-analysis found acupuncture after total knee arthroplasty reduced pain and was associated with delayed opioid use.[216] In a systematic review and meta-analysis, peri-operative auricular acupuncture reduced postoperative pain and need for analgesic use compared to sham or standard-of-care controls.[217] Pain benefit at 48 hours was equivalent to analgesics with fewer side effects. These findings have potential for reduction of hospital readmission due to uncontrolled pain.[218]

Intraoperative electrical stimulation of acupuncture points reduced intraoperative opioid requirements, post-operative pain and duration of stay in the post-anesthesia care unit.[219] Acupuncture was effective, safe and well tolerated for post-tonsillectomy pain in children with no significant side effects.[220] The American Pain Society's guidelines on post-operative pain management neither "recommend nor discourage" acupuncture therapy as part of recommended multimodal post-operative pain based on the literature available at the time of it's guideline writing.[221] A subsequent systematic review with meta-analysis cited above supports the use of acupuncture as adjuvant therapy in treating post-operative pain and reducing opioid use.[214]

Acupuncture therapy acute non-surgical pain

For acute and subacute low back pain, a systematic review with meta-analysis[222] led the American College of Physicians (ACP) to recommend acupuncture as a first-line treatment.[141] Acupuncture is also effective for acute migraine.[223] In an RCT enrolling 300 patients with acute pain presenting to an emergency department, acupuncture was superior to parenteral morphine for pain relief and onset of action with fewer adverse effects.[224] A retrospective study of emergency department acute pain patients found acupuncture decreased pain comparable to analgesics with additional benefit of reduction in anxiety.[225] A trial of 1,964 patients found acupuncture benefit comparable to pharmacotherapy for emergency department patients presenting with acute low back pain and ankle sprain.[226] A systematic review with meta-analysis of acupuncture analgesia in the emergency setting found acupuncture "provided statistically significant, clinically meaningful, and improved levels of patient satisfaction with respect to pain relief in the emergency setting".[227] The authors found evidence of lower cost and low adverse effects profile. In an observational study of 1,008 patients including children, acupuncture given as first aid immediately after, optimally within 48 hours, of a burn injury reduced pain, reddening, pigmentation, scarring and PTSD that commonly follows traumatic burns.[228]

Acupuncture therapy safety

Acupuncture has a low risk of adverse events. The NIH Consensus Statement on Acupuncture published in 1998 found that "the incidence of adverse effects is substantially lower than that of many drugs or other accepted procedures for the same conditions".[229] Systematic reviews and surveys have clarified that acupuncture is safe when performed by appropriately trained practitioners[230–237] with infrequent minor side effects such as feeling relaxed, elated, tired or having sensation or itching at point of insertion.[234] Rare serious complications such as infection or pneumothorax are directly related to insufficient training.[235,236,238] Safe use of acupuncture has also been established in pediatrics[230,239–241] and for women who are pregnant.[242–244]

Massage therapy post-operative pain

Massage therapy involves manipulation of soft tissue structures of the body to prevent or alleviate pain, spasm, tension or stress and to promote health and wellness. A systematic review with meta-analysis of 10 trials showed a single dose of massage therapy provided significant improvement in post-operative pain.[245] In a systematic review of 16 trials, massage therapy was effective for treating pain and anxiety compared to active comparators in surgical pain populations.[246] In a randomized trial of veterans undergoing major surgery, massage was effective and a safe adjuvant therapy for the relief of acute post-operative pain.[247] Massage is effective for pain reduction in post-cesarean section patients,[248] cardiac[249] and thoracic surgery patients.[250]

Massage therapy safety

Therapeutic massage is considered safe. Studies in adults and children with cancer[251–253] and in the post-operative period[247] have found rare serious adverse events[254–256] and low rates of minor complaints such as muscle soreness.[141]

Mind body[1] directed therapies post-operative and acute pain

Music therapy post-operative acute pain

A systematic review with meta-analysis of research found music therapy reduced pain in burn patients[257] and in pediatric post-operative pain.[258] A meta-analysis of 97 studies evaluating music therapies for pain from a variety of causes (acute and procedural pain, and cancer/chronic pain) demonstrated statistically significant decreases in pain intensity, emotional distress and analgesic use, both opioid and non-opioid intake.[259] A trial of music therapy for post-cesarean section pain found decreased pain in the 24 hours following surgery and decreased analgesic consumption in the first four hours.[260]

Suggestive techniques and guided imagery post-operative and acute pain

A meta-analysis of trials found suggestive techniques such as hypnosis may be useful tools to alleviate post-operative pain, especially in minor surgeries.[261] A systematic review and meta-analysis of the efficacy of audio recorded therapeutic suggestions given while under general anesthesia found no effect on pain and small but significant effects on medication use and recovery.[262] Listening to a guided imagery CD 2 weeks before and 3 weeks after total knee replacement resulted in reduced pain that persisted at 3 weeks.[263]

[1] The term "mind body" represents an attempt to accommodate the bidirectional or circular impact that interventions have on symptoms typically categorized as either mental/psychological/spiritual or "discretely physical." However, this is an artificial bifurcation since all body systems use identical communication molecules and mechanisms and since there is never a physical condition that does not register a psychological component. We use the term here as it has been utilized in the current literature but acknowledge a certain limitation shared by terms such as "behavioral" or "relaxation" therapies.

Virtual reality assisted distraction

Virtual reality (VR) technology enables people to become immersed in a computer-simulated, three-dimensional environment as a distraction to pain.[264] Coupled with standard analgesia, VR has been found beneficial in reduction of burn-induced pain and burn wound care in adults and children.[264,265] VR assisted burn and nonburn wound care reduced opioid need by 39% compared to no VR, while levels of pain and anxiety were similar.[266] VR has shown potential in inpatient cancer procedure-related pain.[267]

Mind body directed therapies safety

Music therapy, suggestive techniques and guided imagery are not associated with significant adverse effects and are safe options to improve post-operative recovery.[260–262] VR has potential risk of nausea and increased potential for collisions with objects in the real world.[268] The latter is controlled by creating "safe areas" to use VR and with in-person "spotting" supervision. Debriefing post-VR experience may benefit especially young children and those vulnerable to effects of immersive reality experience.

Multimodal Approach to Acute Pain Care

Multimodal pain care is now recognized as the optimal inclusive and responsive approach to patients experiencing pain: inclusive of all evidence-based therapies including effective nonpharmacologic options and responsive to patients' diverse and evolving needs. Evidence-based nonpharmacologic therapies are recommended in comprehensive pediatric and adult pain care.[82,194,269] Multimodal pain care is recommended by the American Pain Society in it's guidelines to post-operative pain management.[221] Effective nonpharmacologic options are recommended by the ACP in it's guidelines for acute low back pain.[141]

Frequency, Dosage and Timing of Nonpharmacologic Interventions for Inpatient and Acute Pain Care

Therapies that are delivered by a single licensed independent practitioner, such as an acupuncturist, massage therapist or therapist providing an engaged or guided mind body intervention, are generally given as daily treatment for the term of the inpatient stay with referral for outpatient care follow-up. Care such as music therapy or virtual guided imagery are not single practitioner dependent. Access can be continuous or timed if provided by recordings that can be self-administered by patients. A session of inpatient acupuncture or massage therapy care can last from 20-45 minutes. There is evidence-based data on dosage and frequency of nonpharmacologic therapies, but more research is needed to determine the optimal frequency, dosage and timing of interventions: length of a session, or for the case of acupuncture therapy, what constitutes an optimal intervention in terms of session time, number of points palpated, needled, point retention time, and with what additional hands-on therapies.

Evidence-Based Nonpharmacologic Therapies for Cancer Pain

Acupuncture therapy cancer pain

The American Society of Clinical Oncology Clinical Practice Guidelines found acupuncture was effective in improving pain. The reviewers categorized these findings as "evidence-based, benefits outweigh harms, evidence quality: low, and strength of recommendation: weak".[270] A more recent systematic review with meta-analysis of 29 RCTs found acupuncture effective for cancer-related pain, particularly malignancy-related and surgery-induced pain.[75] Acupuncture alleviates side effects of radiation treatment, including pain associated dysphagia,[271] as was found in a systematic review of acupuncture treatment for dysphagia following stroke.[272] Cancer patients receiving inpatient acupuncture at a major cancer center experienced significant improvement in pain, sleep disturbance, anxiety, drowsiness, nausea and fatigue.[273] In a systematic review with meta-analysis acupuncture relieved joint pain associated with breast cancer treatment induced menopause.[274] A review on the management of peripheral neuropathy induced by chemotherapy found acupuncture to be among therapies that may be useful.[275]

Massage therapy cancer pain

Massage therapy was found in systematic reviews with meta-analyses to be effective for pain in cancer patients compared to active comparators[276] or usual care.[76] Massage therapy was also effective for metastatic bone pain,[277] for pain in children with cancer[278] and those undergoing stem cell transplantation.[278,279]

Mind body directed therapy cancer pain

Mindfulness-based courses including web-based mindfulness interventions (eHealth)[280] are supportive for cancer patients' symptom burden. In systematic reviews with meta-analyses mindfulness-based stress reduction (MBSR) had a beneficial psychological impact for breast cancer patients,[281,282] and on quality of life, mood and distress in cancer patients.[283] A recent trial of MBSR for metastatic breast cancer patients demonstrated a positive impact on distress with a mild effect of improving average pain.[284]

In a large systematic review with meta-analysis, music therapy showed statistically significant improvements in cancer pain, emotional distress from pain and a small but significant effect on anesthetic use, opioid and non-opioid intake.[259] Music therapy in a palliative care setting produced significant improvement in pain, anxiety, depression, shortness of breath and mood.[77]

Evidence-Based Nonpharmacologic Therapies for Chronic Pain

Nonpharmacologic therapies are well studied and effective for chronic pain. A Clinical Practice Guideline from the American College of Physicians (ACP) states nonpharmacologic interventions should be considered as first-line options in chronic low back pain, noting that fewer harms are associated with these effective therapies than with pharmacologic options. The ACP emphasizes therapies be administered by practitioners with appropriate training.[141]

Acupuncture therapy chronic pain

Acupuncture has accrued extremely strong evidence in the treatment of chronic pain. An individual patient data meta-analysis of 29 randomized trials involving 17,922 patients using acupuncture therapy for chronic musculoskeletal pain related to the neck and low back, knee OA, headache and migraine found acupuncture was significantly better than both sham acupuncture and usual care for all conditions.[285,286] In a systematic review with meta-analysis, acupuncture was associated with greater immediate relief of chronic pain compared to sham acupuncture or analgesic injection.[287] In a meta-analysis on long-term impact, the effects of a course of acupuncture treatment for patients with chronic pain persisted significantly following care; 90% of acupuncture benefit persisted at 12 months in trials using wait list or usual care controls. Trials comparing acupuncture to sham found 50% persistence of benefit at 12 months for the verum groups.[207]

An updated individual patient meta-analysis of acupuncture for chronic nonspecific back pain, neck pain, shoulder pain, chronic headache or osteoarthritis included an additional 7 years of trials evaluating 39 trials (20,827 patients).[288] Acupuncture was superior to both sham and no acupuncture controls for each pain condition. The effects of acupuncture were found to persist over time with only a small decrease, approximately 15%, in treatment effect at one year after randomization or 9–10 months after the completion of treatment. A new finding was additional confirmation of benefit for acupuncture over sham on upper body musculoskeletal pain, neck and shoulder pain.

In a systematic review with meta-analysis, acupuncture showed benefit over controls in the treatment of peripheral neuropathy related to diabetes, HIV, Bell's palsy and carpal tunnel syndrome.[289] Simple pressure sustained by seeds or small magnets taped to ear points, a form of auricular treatment, showed benefit in acute and chronic pain in systematic reviews with meta-analyses.[217,290]

In a large multicenter trial of 14,161 patients with chronic neck pain, acupuncture (15 sessions over 3 months) added to routine care was associated with improvements in neck pain and disability maintained through six months compared to routine care alone.[291] Although acupuncture care increased cost of treatment, the health benefits lasted well beyond the three-month study duration; per international cost-effectiveness threshold values, acupuncture was determined to be a cost-effective treatment strategy.[292] In a cost-effectiveness review of nonpharmacologic interventions for low back pain (LBP), acupuncture was found to be a cost-effective option.[211] Meta-analyses demonstrate acupuncture is effective and cost-effective for knee OA.[293,294] A systematic review and meta-analysis of manual acupuncture for myofascial pain syndrome found treatment of myofascial trigger points reduced pain and improved pain threshold in studies using a single treatment or a course of eight treatments.[295] Further research is needed to clarify the longitudinal impact of myofascial trigger point treatments as single or multiple sessions. A network meta-analysis demonstrated that acupuncture needling alone and combined with Gua sha, moxibustion, or e-stim are effective in decreasing pain and in improving physical function in myofascial pain syndrome.[296]

In systematic reviews[297,298] and meta-analyses,[299] acupuncture was found effective for frequent episodic or chronic tension headaches and for episodic migraine. Acupuncture has also been shown to be effective for chronic shoulder pain,[285,300] pain related to OA of the hip,[301] and temporomandibular disorder myofascial pain.[302,303] In a military population, acupuncture treatment given at least four times within a year was associated with improved symptoms, ability to function and sense of well-being as well as reductions in opioid prescriptions (45%) muscle relaxants (34%), NSAIDs (42%) and benzodiazepines (14%).[304]

In a systematic review and meta-analysis, acupuncture therapies with prokinetics were more effective than prokinetics alone for functional dyspepsia.[305] Acupuncture therapy is recommended for functional dyspepsia in patients contraindicated for prokinetics.

A systematic review and meta-analysis of trials comparing acupoint stimulation to NSAIDs for primary dysmenorrhea found advantages in acupoint stimulation in alleviation of dysmenorrhea symptoms with fewer side effects and potential use for patients with NSAID contraindication.[306]

Based on a systematic review, the American College of Physicians (ACP) Clinical Practice Guideline recommends acupuncture for acute, subacute and chronic low back pain (cLBP).[141,222] The US Department of Health and Human Services Agency for Healthcare Research and Quality (AHRQ) concluded that acupuncture therapy is effective for cLBP compared to placebo, sham, no treatment, usual care or wait list controls.[145] The NIH also recommends acupuncture for low back pain and for knee OA.[307] The *FDA Education Blueprint For Health Care Providers Involved In The Management or Support of Patients with Pain* suggests acupuncture among a range of available therapies as part of a multidisciplinary approach to pain management.[195]

As stated above, acupuncture therapy has a low risk of adverse events when provided by qualified trained practitioners.

Massage therapy chronic pain

Based on it's systematic review, the ACP Clinical Practice Guideline recommends massage for acute, subacute and chronic low back pain (cLBP).[141,222] AHRQ found massage effective for cLBP compared to placebo, sham, no treatment, usual care, or wait list controls.[145] The NIH also recommends massage for neck pain.[307]

Sixty high quality and seven low quality studies included in a systematic review with meta-analysis on pain and function across all pain populations found massage therapy effectively treats pain compared to sham, no treatment and active comparators.[308] A systematic review for upper and lower extremity conditions found soft tissue therapy effective for the management of heel pain and lateral epicondylitis.[309] A trial of massage therapy for knee OA found the optimal dose at 8 weekly one-hour sessions with benefits persisting for at least 8 weeks beyond treatment.[310] A systematic review with meta-analysis found manual therapy including massage was effective for pain, stiffness and physical function in knee OA with a call for more study with extended follow-up.[311] Stiffness and physical function showed significant improvement with treatment duration of more than 4 weeks.

As indicated above, massage therapy has a low risk of adverse events when provided by a trained practitioner.

Spinal manipulation therapy and manipulative therapy chronic pain

Spinal manipulative therapy (SMT) involves treatment of the spine and pelvic related joints; manipulative therapy (MT) refers to the treatment of other joints in the body including upper and lower extremities. SMT and MT are often associated with high velocity, low amplitude (HVLA) thrust techniques, as well as low velocity, low amplitude (LVLA) or joint mobilization techniques. SMT, MT, HVLA and LVLA are techniques commonly used to improve pain and function, primarily by osteopathic physicians and chiropractors.

A systematic review with meta-analysis showed SMT improves low back pain with benefits maintained for up to six weeks.[312] SMT was also shown to be cost-effective for low back pain.[211] Based on it's systematic review, the ACP Clinical Practice Guideline recommends spinal manipulation for acute, subacute and chronic low back pain (cLBP).[141,222] AHRQ found SMT as effective as other active interventions for cLBP.[145] Systematic reviews found SMT beneficial for neck pain,[313] cervicogenic headache,[314] and prophylaxis of migraine.[315]

Systematic reviews and a meta-analyses found manual therapy beneficial for knee OA[311,316] as well as OA of the hip, patellofemoral syndrome, ankle inversion sprain, plantar fasciitis,[317] and common shoulder disorders.[318] A systematic review also found evidence that MT is effective when combined with exercise and/or multimodal therapy for lateral epicondylitis, carpal tunnel syndrome and temporomandibular disorders.[319] A systematic review found for adults with “whiplash-associated disorders” and “neck pain associated disorders,” nonpharmacologic therapies including manual therapy are cost-effective.[320] For improving low back and shoulder pain, MT may be more cost-effective than usual care that included exercise, stabilization and/or advice about activity.[321]

Manipulation therapy safety

Adverse events associated with spinal manipulation include muscle soreness or transient increases in pain.[141] Rare serious adverse events include cervical artery dissection, stroke and neck injury.[322] The most recent review of systematic reviews found that though rare, there is some risk of significant adverse events with spinal manipulation.[323]

Mind body directed therapies for chronic pain

Mindfulness, meditation and relaxation therapies chronic pain

Mindfulness and meditation-based therapies focus training on moment to moment awareness of breathing and attention without judgment to transform perception and relationships to pain and the larger environment.

Mindfulness-based stress reduction (MBSR) is a training that has had considerable study for chronic pain. A systematic review and meta-analysis found MBSR for low back pain was associated with short-term improvements in pain intensity and physical functioning compared to usual care.[324] In a trial for patients with chronic low back pain, comparing MBSR to CBT or usual care found both MBSR and CBT to be cost-effective and MBSR to be cost-saving.[212] CBT is recognized as a moderately effective approach to chronic pain, for example, low back pain;[141] however, we do not include an in-depth review of CBT as it is currently part of covered conventional care options, albeit underutilized. Based on it's systematic review, the American College of Physicians (ACP) Clinical Practice Guideline recommends both CBT and MBSR for chronic low back pain.[141,222]

Mindfulness and relaxation-based eHealth interventions have evidence of positive effects on health outcomes for patients with chronic pain including headache, fibromyalgia and irritable bowel syndrome.[280] Internet-delivered pain-coping skills training (PCST) with physiotherapist-prescribed home exercise for persons with chronic knee pain provided clinically meaningful improvements in pain and function that are sustained for at least six months.[325] PCST is an approach based on CBT principles that target psychological factors such as low self-efficacy, poor pain coping, and pain catastrophizing, common in persons with chronic pain. PCST has been shown to be effective for osteoarthritis or rheumatoid arthritis pain[326] and specifically knee OA.[327]

MBSR has also shown benefit in pain in adolescents[328,329] and in adult patients with chronic headache.[330,331] A review of patients with arthritis, chronic back or neck pain, or two or more comorbid pain conditions experienced the largest average improvement from a mindfulness program in pain severity and functional limitations.[332] Greater home meditation practice was significantly associated with greater improvements in psychological distress and self-rated general health. Benefit for pain and high continued compliance have been consistently associated with MBSR from its earliest study.[333]

Relaxation therapies use physiologic techniques (e.g., slow diaphragmatic breathing or progressive muscle relaxation) to regulate the sympathetic/parasympathetic balance and reduce symptoms of sympathetic arousal often seen in chronic pain including situational stress, muscle tension and shallow breathing. They also include other directed therapies like guided imagery (use of words depicting calming images and music to evoke positive imaginative scenarios), hypnosis and suggestion (induction of a relaxed but focused state of consciousness receptive to positive suggestion), acceptance and commitment therapy (strategies of mindful awareness and acceptance) and music therapy.

In a large meta-analysis, music therapy showed a reduction of chronic pain, emotional distress due to pain and a small but statistically significant reduction in opioid and non-opioid intake.[259] Based on it's systematic review, the ACP Clinical Practice Guideline recommends progressive relaxation for chronic low back pain.[141,222] The NIH also recommends relaxation, "autonomic regulatory" approaches for fibromyalgia.[307]

In a meta-analysis of trials, acceptance and commitment therapy (ACT) and mindfulness-based interventions were shown to be comparable to cognitive behavioral therapy (CBT) in managing chronic pain.[334] ACT was comparable to CBT but with higher patient satisfaction in one trial on chronic pain;[335] older adults with chronic pain were more likely to respond to ACT in another RCT.[336]

Systematic reviews of guided imagery were found encouraging but inconclusive for musculoskeletal and non-musculoskeletal pain.[337,338] A more recent systematic review of guided imagery in fibromyalgia, arthritis and rheumatologic disorders found statistically significant improvement in pain and function, with several trials demonstrating reduction in medication use.[339]

Mindfulness, meditation and relaxation therapy safety

The body of research evidence has shown mindfulness-based practices, hypnosis, suggestive therapies, guided imagery, CBT, ACT and progressive relaxation techniques are utilized across diverse patient populations. These approaches are safe, with rare adverse reactions in psychiatric patients, people with epilepsy or those who have suffered abuse or trauma where relaxation may trigger a rare paradoxical reaction.[141,324,339,340]

Biofeedback chronic pain

Biofeedback utilizes techniques in which a signal generated by a device trains the patient to manipulate an aspect of their physiology not typically directed (e.g., heart rate variability and muscle tension) and provides a self-care tool for physiologic modulation. A meta-analysis of biofeedback for chronic low back pain (cLBP) found pain reduction, reduced depression, disability, and muscle tension and improved coping.[341] Based on another systematic review, the ACP Clinical Practice Guideline recommends electromyography biofeedback for cLBP.[141,222]

A meta-analysis of trials also found biofeedback effective for tension headache with stable benefit over an average follow-up phase of 15 months. Biofeedback with relaxation therapy was most effective for children and adolescents with headache.[342] A meta-analysis of biofeedback for fibromyalgia found significant reduction of pain,[343] with less effect established in another systematic review due to variability of measures across trials.[344]

Biofeedback safety

In a systematic review of trials for fatigue and cognition, neurofeedback (EEG biofeedback) and biofeedback were shown to be well-tolerated without major adverse effects.[345] Biofeedback has low risk of harms with rare side effects of headache, fatigue or sleep problems.[343] No adverse events are reported in a meta-analysis of biofeedback for chronic back pain.[341]

Movement therapies for chronic pain

Yoga chronic pain

Therapeutic yoga is the use of yoga to help people with health problems manage their health conditions and reduce their symptoms. Yoga originated in ancient India and has been adapted in the West. Yoga practice combines attention and meditation (dhyana), breathing (pranayama) and physical postures (asanas).

A Cochrane review of yoga for chronic nonspecific back pain found moderate supporting evidence that yoga compared to non-exercise controls resulted in small-to-moderate improvements in back-related function at three and six months and was comparable to exercise for chronic low back pain (cLBP).[346] Early intervention with "medical yoga"—group sessions of guided Kundalini yoga individualized to each medically screened patient with low back pain—was found to be cost-effective.[211,347] Based on it's systematic review, the American College of Physicians (ACP) Clinical Practice Guideline recommends yoga for cLBP.[141,222] AHRQ found yoga effective for cLBP compared to placebo, sham, no treatment, usual care or wait list.[145] NIH recommends yoga (hatha, Iyengar and viniyoga) for cLBP.[307]

In a systematic review and summary of reviews,[348,349] yoga was found to have beneficial effects in patients with pain. In addition to low back pain, systematic reviews with meta-analyses found yoga beneficial for osteoarthritis, rheumatoid arthritis, kyphosis and fibromyalgia.[350] Additional systematic reviews found yoga to have positive effects on pain and function in patients with knee OA[351] and neck pain.[352] A meta-analysis found yoga, even as a short-term intervention, could be effective for pain and associated disability.[353] A large systematic review (306 trials) identified 52 different yoga styles and techniques with the most common being hatha, Iyengar, Pranayama and integrated approaches to yoga therapy. There was no advantage to a particular style of yoga. The reviewers recommended the choice of yoga style be based on personal preference and availability.[354] In a systematic review with meta-analysis on efficacy and safety of meditative movement therapies (Qi gong, Tai chi and yoga) for fibromyalgia syndrome, yoga yielded significant effects on pain, fatigue, sleep, depression and health-related quality of life at final treatment, while Tai chi showed benefit for sleep.[355] In an access-to-care innovation for veterans, a clinical yoga program via telehealth real-time interactive video conferencing, provided comparable satisfaction and health improvements to in-person yoga, including benefit for pain.[356]

Yoga therapy safety

Reported harms associated with yoga for cLBP were mild to moderate;[141,357] self-limiting joint and back pain comparable to physical therapy (PT).[358] A systematic review and meta-analysis of RCTs found yoga to be as safe as usual care and exercise.[359] No association between yoga practice and joint problems was found in a large survey of women aged 62–67.[360] A review of published adverse event cases associated with yoga recommends patients with medical preconditions such as glaucoma or compromised bone health work with their physician and a qualified yoga teacher to adapt postures.[361]

Tai chi chronic pain

Tai chi is a low-impact, mind body exercise originating in China that has become increasingly popular in the West as an effective exercise for rehabilitation related to multiple medical conditions. Tai chi consists of slow prescribed movements with attention to breathing and meditative concentration.

In systematic reviews with meta-analyses, Tai chi was effective for chronic pain associated with OA.[362,363] An evidence map of 107 systematic reviews on health outcomes confirmed its potential benefit for chronic pain syndromes and OA.[364] Based on it's systematic review, the American College of Physicians (ACP) Clinical Practice Guideline recommends Tai chi for chronic low back pain (cLBP).[141,222] The US Department of Health and Human Services AHRQ found Tai chi effective for cLBP compared to placebo, sham, no treatment, usual care or wait list controls.[145] The NIH also recommends Tai chi for knee OA and fibromyalgia.[307] In a RCT of 12 weeks of Tai chi with heart failure patients, decreased pain was among the physical benefits reported.[365]

Tai chi safety

In a review of 153 trials, adverse events related to Tai chi were not regularly monitored or reported. When reported, Tai chi did not result in any serious adverse events but was associated with minor musculoskeletal aches and pains not unlike other forms of therapeutic movment.[366]

Other movement therapies chronic pain: Alexander technique, Pilates and Feldenkrais

Alexander technique (AT), Pilates and Feldenkrais are therapies developed by Frederick Alexander, Joseph Pilates and Moshe Feldenkrais, respectively. They share features of touch, directed exercise, strengthening, and awareness of posture and muscle utilization in the treatment of pain and postural problems. While there are fewer studies and reviews of these therapies, there is preliminary evidence of benefit for chronic pain.

A systematic review supported the effectiveness of AT lessons in chronic back pain.[367] A large three-arm randomized trial compared usual care, usual care plus acupuncture therapy (10 sessions), and usual care plus AT (14 sessions) for chronic neck pain (median duration 6 years). The acupuncture and AT groups both led to significant reductions in pain and associated disability compared with usual care, with benefit persisting at 12 months following the intervention period.[368]

In systematic reviews of Pilates for chronic nonspecific low back pain, significant improvement in pain relief and functional enhancement was demonstrated.[369] Pilates exercise offered greater improvements in pain and functional ability compared to usual care and physical activity in the short term and improvements equivalent to massage therapy and other forms of exercise for chronic low back pain (cLBP) in the short or long term.[370] A trial of post-menopausal women with cLBP compared six weeks of Pilates plus physiotherapy to physiotherapy alone and found improvement in pain management and functional status with benefits persisting after one year.[371]

Feldenkrais has demonstrated benefit in chronic pain trials for neck and scapular pain in people who are visually impaired.[372]

Alexander technique, Pilates and Feldenkrais safety

Adverse events related to movement therapies are low with minor events of transient pain and muscle soreness.[368,373–375]

Frequency, Dosage and Timing of Nonpharmacologic Interventions for Chronic Pain

A recommended course of acupuncture treatment for chronic pain will depend on the patient and the term and severity of the condition. In a large meta-analysis of RCTs of acupuncture for chronic pain of the head, neck, shoulder, low back and knee, where benefit persisted significantly (12 months) following a course of treatment, patients received on average 8–15 treatments over 10–12 weeks.[207] In the Cochrane reviews recommending acupuncture for tension headache[297] and migraine,[298] a minimum of six sessions was required for review. Weekly treatment was common; no trials gave acupuncture more than twice per week.[376]

In a large meta-analysis that identified characteristics of acupuncture treatment associated with outcome, where average session time was recorded in a trial, the length of session averaged 16–45 min.[376] Average needle insertion sites were 6–20. Increased number of needle sites treated and more sessions were associated with better outcomes.[376] Therefore, referral for acupuncture therapy is recommended for at least 8 sessions, and preferably 8–15 weekly sessions of care. For a severe or acute ambulatory pain event, initial treatment frequency may be more than once per week.

Acupuncture therapy delivered in a group setting is being studied as an option for underserved populations,[377] in line with research on group medical visits.[378] Costs are reduced for patients and session times approximate individual practitioner-patient encounters. Patients' arrivals are staggered with care overlapping in a shared treatment space.

In a systematic review and meta-analysis of massage therapy for pain, treatment dosage ranged from a single session of 1.5 minutes to daily 40–60 minutes sessions for 20 weeks.[308] In chronic ambulatory pain conditions, massage is usually given once per week, more frequently for a severe or acute ambulatory event. Sessions are typically 45–60 minutes, longer if elected. Number of sessions recommended is not established in the literature.

Chiropractic and osteopathic spinal manipulation reviews evaluate varied session frequency including single sessions trials, trials of 4-7 sessions over 2 weeks to 5 months, and up to 12 sessions or more a month with or without subsequent maintenance.[145] Once a week sessions for 4-6 weeks was slightly superior to back school or physical therapy for chronic low back pain.[379]

The most studied mindfulness intervention is MBSR, which is structured as eight weekly group sessions.[222,324,380]

Movement therapies like Tai chi and yoga are typically given in group sessions, and have been studied in a term of intervention from 1-5 sessions per week for 6 weeks to a year for Tai chi[362,366] and as 12 weekly sessions of 75 minutes for yoga.[358]

Lifestyle Behaviors and Self-Efficacy Chronic Pain

Self-efficacy is a psychological construct based on social cognitive theory, which describes the interaction between behavioral, personal and environmental factors in health and chronic disease. The theory proposes that patients' confidence in their ability to perform specific health behaviors influences their engagement in and actual performance of those behaviors, which in turn influences health outcomes.[365]

The evidence for the impact of healthy lifestyle choices—what we eat, drink, think, feel and do—on our health outcomes has become a major focus of current research. We are all born with a genome, a set of genes we inherit from our parents. Epigenetic changes happen when genes within our genome are turned on and off by environmental factors before and after conception. Epigenetic changes have been shown to be passed from generation to generation. Altered gene expression rather than genetic code accounts for the majority of risks to health outcomes. The NIH cites the following environmental factors as causes of epigenetic changes: exercise, diet, nicotine, alcohol, chemical exposures, medications and stress.[381] Though pain specific studies are scarce,[382] there are many studies that document the relationship of healthy behaviors to improved overall health and a reduction of diseases such as diabetes, atherosclerosis and obesity,[383] which are associated with pain conditions.[384,385] The relationships are complex, multifactorial and have reciprocal influence on each other. For example, obesity is associated with inflammation[386] and musculoskeletal disorders involving connective tissue structures, including bones, joints and soft tissues of the musculoskeletal system.[387,388] At the same time, persistent or severe pain impedes weight loss in patients enrolled in weight management programs compared to none-to-moderate pain.[389] Poor blood sugar control in type II diabetes leads to delayed healing, neuropathic pain and vascular complications all of which increase the difficulties that patients have with exercise that can benefit diabetic control. Optimal lifestyle choices can improve health and pain and are tantamount to healthy outcomes.

Studies have shown that healthy life choices, such as dietary changes, self-engaged stress management, smoking cessation, exercise, and supportive relationships with others can impact depression, hypertension, heart disease, cholesterol, obesity, diabetes and prediabetes, and cancer.[390,391] Success with healthy lifestyle choices improves patient self-efficacy and is also found to improve the length of leukocyte telomeres[392] associated with healthy aging and longevity.[393,394]

A large scale multiyear study, *The European Prospective Investigation into Cancer and Nutrition–Potsdam Study* (EPIC), studied 23,000 people for 7.8 years to evaluate the impact of four lifestyle factors on health—never smoking, a BMI under 30, physical activity for at least 3.5 hours a week, and eating a healthy diet that includes vegetables, fruit, whole grain bread and low meat consumption.[395] Subjects with all four factors at baseline had reduced their risk of diabetes by 93%, myocardial infarction by 81%, strokes by 50%, and cancer by 36%, and had a 78% lower overall risk of developing a chronic disease. All of these diseases impact pain and healing. Lifestyle behaviors can affect biology as well as self-efficacy and therefore can be viewed as a key factor impacting pain.

Nutrition and pain

Nutrition science is not new and though it has long been recognized that nutritional status can either promote or reduce body-wide inflammation[396,397] and can promote healing or inhibit it, most medical encounters for pain do not address diet in a meaningful way. As there is a growing awareness of the impact of nutritional status on overall health, there are more studies of nutrition and pain.[398–400]

An anti-inflammatory diet is one that is high in non-starchy vegetables, fruits, legumes, nuts and seeds, healthy oils and whole grains with low levels of animal protein consumption. This type of diet balances tissue pH levels for optimal mitochondrial enzyme functioning and has been shown to have health benefits.[401] Mitochondrial dysfunction in turn is being recognized as a root cause of many illnesses including pain related conditions.[402–404] Dietary antioxidants are essential for optimal mitochondrial health[405] and the basic science literature has thousands of articles on “targeting antioxidants to mitochondria” within the last 10 years alone.[406]

Turmeric, its derivative curcumin, and ginger, a related tuber, are extensively studied in both food and supplement form for pain patients. Turmeric is used for a wide variety of painful and inflammatory conditions including peri-operative pain[407] with opioid and NSAID sparing; joint pain[408–410] and musculoskeletal pain,[411] and inflammatory bowel disease.[412,413] Ginger is studied for its effect on nausea[414,415] but also for pain,[416–418] including joint pain[419] and primary dysmenorrhea.[420] Though ginger and turmeric combine the actions of plant-based antioxidants and COX inhibition they are very well tolerated. Whereas pharmaceutical nonsteroidal anti-inflammatories (NSAIDs) cause very significant morbidity[421,422] and mortality,[67] ginger and turmeric do not show the same side effects profile.[408,418,423] This is likely, at least in part, because NSAIDs have been shown to inhibit the initial step in healing which is an inflammatory one.[424] A recent systematic review of curcuminoids for musculoskeletal pain found that in the studies comparing curcuminoids to nonspecific NSAIDs, the evidence was moderate to high for noninferiority of the curcuminoid intervention.[411] Curcuminoids were equal to NSAIDs in terms of pain improvement without the long-term risks related to the morbidity and mortality of NSAIDs, situating curcuminoids as a viable oral pain medication option.

Micronutrient deficiency is prevalent in the United States,[425] associated with the extensive consumption of highly processed foods. Although consumption of meals from fast food restaurants is decreasing, there has been a compensatory increase in retail purchase of highly processed foods.[426] Symptoms associated with deficiencies, especially when sub-clinical, are nonspecific and include fatigue, irritability, aches and pains, decreased immune function and heart palpitations.[425] Supplementation of deficient nutrients helps overall health and is being studied for its effects on pain. The following is by no means a comprehensive listing but touches on some of the most prevalent deficiencies.

Vitamin D is one of the best studied micronutrient deficiencies associated with pain and delayed healing. Skin pigmentation, obesity, northern latitudes and other yet unidentified factors lead to Vitamin D deficiencies. Deficiency of Vitamin D is often found in chronic pain sufferers, and is correlated with muscle fatigue risk factors.[427] While no definitive mechanism for how Vitamin D influences chronic pain development is known, supplementation of Vitamin D may benefit chronic pain.[428] It poses a low health risk, is well accepted, inexpensive and offers numerous health benefits.[429] A rapid dose of Vitamin D_3 attenuates inflammation, epidermal structure damage, and redness from acute sunburn.[430]

Magnesium is also seen as a common micronutrient deficiency, which is being studied for its relationship to muscle spasm, systemic inflammation, insulin resistance and diabetes, hypertension and neuropathic pain. There have been positive trials using magnesium infusions for migraine and many emergency rooms employ this intervention.[431,432] Magnesium has also been studied as an NMDA (N-methyl-D-aspartate) receptor blocker in the treatment of neuropathic pain.[433,434] A review of the concomitant use of magnesium with opioids in animals suggests that magnesium may potentiate opioid analgesia while also mitigating some of the adverse effects of opioids including the development of hyperalgesia, improving outcomes in neuropathic pain.[435]

Fish oils high in omega-3 fatty acids, also called polyunsaturated fatty acids (PUFAs), are associated with reduced pro-inflammatory prostaglandins.[436] A 2012 meta-analysis concluded that PUFAs at doses over 2.7 g/day for over three months reduced NSAID consumption in rheumatoid arthritis patients.[437] The North American diet is high in omega-6 fatty acids which are proinflammatory.

Vitamin B12 (cobalamin) deficiency has long been recognized as a cause of neurological disorders including pain. At present, we are only able to measure serum B12 which may or may not reflect B12 levels in the tissues where it is active. There are over 20 recognized genetic abnormalities affecting the cobalamin transport proteins required for intracellular delivery of B12 to tissue targets including mitochondria. Some are severe, leading to early failure to thrive and death and others are states where B12 is insufficient for cellular function despite normal serum levels.[438]

Other lifestyle factors

Many medications have an adverse effect on micronutrient levels and the health of the microbiome, the mass of micro-organisms mainly housed in the gut. Elie Metchnikoff, Nobel Laureate in 1908 for the discovery of cellular immunity, also identified the microbiome as a major determinant of health. Its role in protecting optimal intestinal permeability, modulation of body-wide inflammation, nutrient absorption, and abdominal pain in inflammatory bowel diseases is being widely studied.[196] Poor nutrition and many drugs can adversely affect the microbiome. Proton pump inhibitors (PPIs) deserve special mention in this regard since they are widely used for prolonged periods and their negative effects on nutritional status has long been unrecognized. The FDA has issued warnings of profound deficiencies in magnesium and calcium, B12 and protein absorption with the use of PPIs. PPIs also disrupt the microbiome and increase the risk of pathologic dysbiosis and enteric infection such as food poisoning and Clostridium difficile.[439] Long-term use of PPI medication increases risk of death.[440]

Important behavioral factors such as physical activity level, sleep and stress management can have direct and indirect impact on the experience of pain. Physical activity can be practitioner or instructor directed as in physical therapy, acupuncture therapy, chiropractic, osteopathy, yoga, Tai chi, or other movement systems, or it can be and often is self-directed. Physical activity has been shown to increase strength, balance and coordination, reduce pain and improve motor function and mood for patients with hip and knee OA.[441–443] Sleep disorders are commonly seen in pain patients. The disorders may follow or precede the onset of pain.[444] Sleeplessness has been shown experimentally to induce a generalized state of hyperalgesia, a "fibromyalgia-like syndrome".[445] Both pain and pain medications can cause sleep disorders. Sleep apnea is a risk factor for many conditions such as diabetes and hypertension and can be aggravated by medications that are often prescribed for pain patients. Improved sleep leads to improved resilience for pain. Stress has long been reported by patients to be an aggravator of pain.

> In the year 2000, the number of deaths related to poor diet and physical inactivity were 15–16% of total deaths in the United States, while continuing to increase.[446]

Economic Benefits of Nonpharmacologic Therapies in the Treatment of Pain

Full economic evaluations, reported as cost-effectiveness analyses (CEA), cost-utility analyses (CUA), and cost-benefit analyses (CBA), often compare costs and health effects between two or more therapies.[447] Low back pain, knee OA and headache are among the most common and costly chronic pain conditions responsible for a significant economic burden on the healthcare system.

There have been extensive economic evaluations of acupuncture therapies for pain conditions. Acupuncture has been shown to be cost-effective in the treatment of chronic, persistent low back pain.[28,206,211,448–450] A cost-effectiveness analysis of nonpharmacologic treatments for knee OA found acupuncture to be one of the more clinically and cost-effective therapies using the UK National Institute for Health and Care Excellence (NICE) QALY (quality adjusted life years) thresholds[294] when done alone or together with exercise-based PT.[451] In a large trial, acupuncture was not only effective in the treatment of neck pain but benefits lasted beyond the three-month study duration, per international cost-effectiveness threshold values, showing acupuncture to be a cost-effective treatment strategy.[292] And while using acupuncture (12 treatments over three months) for migraine and chronic headache increased cost to the UK NHS health service, there was improved health-related quality of life over the year that patients were followed that was favorably cost-effective compared to other NHS provided therapies.[452]

Similarly, the longevity of benefit for acupuncture in chronic pain was evaluated in a meta-analysis of 20 trials and over 6,000 patients and showed that clinical benefits of acupuncture were sustained at 12 months after a single course of treatment. Improvements in pain were 90% sustained at 12 months in trials compared to usual care and 50% sustained in trials that compared to sham,[286] with implications for reduction in health care utilization over that period. An update to that meta-analysis of 7 additional years of trials (39 trials and 20,827 patients) confirmed previous findings.[288]

A curious and compelling finding in a large trial performing a one to one propensity score match (a statistical matching technique that attempts to estimate the effects of a treatment by accounting for the covariates that predict receiving the treatment) of 58,899 patients who received acupuncture for fibromyalgia to 58,899 who did not have acupuncture found the cumulative incidence of coronary heart disease (CHD) was significantly lower in the acupuncture cohort independent of age, sex, comorbidities or statins used.[453]

Systematic reviews have shown manual therapy is a cost-effective treatment for adults with whiplash-associated and neck pain-associated disorders[320] and is also more cost-effective for improving low back and shoulder pain than general practice care that included exercise, stabilization and/or advice.[321]

An inclusive review of effective nonpharmacologic therapies for chronic low back pain (33 studies) found cost-effectiveness for combined physical and psychological treatments, medical yoga, information and education programs, acupuncture therapy and spinal manipulation.[211] An earlier review of 26 studies found cost-effectiveness for treatments consistent with the ACP guideline of interdisciplinary rehabilitation, exercise, acupuncture therapy, spinal manipulation and cognitive behavioral therapy for sub-acute and chronic LBP.[454] Group acceptance and commitment therapy (ACT) was found cost-effective for fibromyalgia when compared to medication in a six month RCT.[455]

There may be a common perception that nonpharmacologic therapies are an "add on" expense; however, an analysis of the scope of economic benefits changes this perception. There is evidence of cost-effectiveness and cost savings through avoided high tech conventional care, lower future healthcare utilization, and reduction of productive loss for employers.[447] A study by the State of Washington found that even with a substantial number of people using insurance benefits for nonpharmacologic therapies, the effect on insurance expenditures was modest.[118] In a follow-up study of Washington state insured patients with back pain, fibromyalgia and menopause symptoms, users of nonpharmacologic therapy providers had lower insurance expenditures than those who did not use them.[119]

Finally, a cost-analysis of an interdisciplinary pediatric pain clinic found interdisciplinary treatment that included acupuncture, biofeedback, psychotherapy and massage with medication management reduced inpatient and emergency department visits and resulted in hospital cost savings of $36,228/patient/year and in insurance cost savings of $11,482/patient/year.[456] The findings of the current cost analysis support that over the course of just one year, participation in an outpatient individually tailored interdisciplinary pain clinic can significantly reduce costs by more than the cost of the intervention itself.

Course of treatment and cost for inpatient acute care

Inpatient acute pain care using nonpharmacologic pain modalities can engage a course of as little as one to several treatments, or daily treatment over the course of a hospital stay. Inpatient acupuncture sessions can be given at a patient's bedside and sessions can last from 20 to 45 minutes or longer and is recommended in the 24 hours before surgery, after surgery, and daily as requested by inpatients or their caregivers. An integrative medicine approach using yoga therapy, holistic nursing techniques and a "healing environment" used in inpatient oncology had an immediate term cost benefit from reduced use of antiemetic, anxiolytic and hypnotic medication costs in the amount of $156/day/patient. If extrapolated to the number of patients, beds and days of operation for the unit studied this would result in a savings of nearly one million dollars a year.[457]

Course of treatment and costs for outpatient chronic pain

Projections of costs for a course of treatment of an evidence-based nonpharmacologic therapy will vary depending on the geographic area, health system, and access to care options. First, a course of care recommendation would be based on studies as well as systematic reviews and meta-analyses of effectiveness trials. Second, a recommended course of treatment for chronic pain will depend on the patient and the term and severity of the condition.

In a large meta-analysis of RCTs of acupuncture for chronic pain of the head, neck, shoulder, low back and knee, where benefit persisted significantly (12 months) following a course of treatment, patients received on average 8–15 treatments over 10–12 weeks.[207] In the Cochrane Reviews recommending acupuncture for tension headache[297] and migraine,[298] a minimum of six sessions was required for inclusions in the review. Weekly treatment was common; no trials gave acupuncture more than twice per week.[376] Based on these studies, referral for acupuncture therapy is recommended for at least 8 sessions, and preferably 8–15 weekly sessions of care. For a severe or acute ambulatory pain event, initial treatment frequency may be more than once per week. Acupuncture therapy cost per session varies from $60–120[458] or more, with the initial session longer and higher in cost. A course of ambulatory care of 10 sessions then can range from $700.00 to $1300 or more.

Acupuncture therapy delivered in a group setting is being studied as an option for underserved populations,[377] in line with research on group medical visits,[378] and group-style self-management interventions.[459] Costs are reduced, with care overlapping in a shared treatment space. Group sessions can be less than half the cost of an individual session.

Chiropractic and osteopathic manipulation sessions are structured as individual care with additional costs of techniques like ultrasound that may be applied by an assistant. Sessions can be more than once a week to once a week for maintenance. Costs of sessions vary from $35 to $106[460] or more for 30 minutes with averages $65–$70 depending on the region of the country. Charges may increase with a-la-carte fees for interventions in addition to manipulations, such as applications of heat or cold, for example.

Massage therapy is generally offered in weekly sessions with costs varying from $60 to $90 or more for a 60-minute session, less for shorter sessions, more for longer sessions. Fees also depend on the site, whether a clinic, gym, spa, hotel or practitioner's office.

Movement therapies like Tai chi and yoga are typically given in group sessions, and have been studied in a term of intervention from 1-5 sessions per week for 6 weeks to a year for Tai chi[362,366] and as 12 weekly sessions of 75 minutes for yoga.[358] Session fees can range from $10–$20, with prices reduced with purchases of multiple sessions or more if private or semi-private sessions. Similarly, sessions for Pilates, Feldenkrais or Alexander technique are paid as individual sessions or reduced if bought as a package for multiple sessions. Pilates costs anywhere from $15–$55 for 45-minute group mat classes, $35–$85 for group classes using equipment, and private sessions costing upwards of $50–$150 per one-hour session.[461] Feldenkrais is offered as private, semi-private or group sessions with costs varying from $50–$90 for private and $10–$25 for classes.[462] Alexander technique sessions vary in cost depending on country or region but are generally on par with massage therapy costs if given in private sessions, less if given in a group setting.

MBSR has been shown to be cost-effective and cost-saving for patients with low back pain.[212] An eight-week course of MBSR ranges from $500–$600 or more depending on the area of the country.

In general, the costs of evidence-based nonpharmacologic options are nominal compared to medical costs of treating chronic pain with risk mitigation and greater potential for engaging patients in ongoing self-care.

Recommendations

Education, Treatment, and Research

Many in medicine and policy decision-making acknowledge the crisis in pain and pain care detailed in this paper and seek evidence-based solutions for successful comprehensive pain management. Currently, most of the nonpharmacologic strategies reviewed here are underutilized due to lack of evidence dissemination, education and reimbursement. It is time for civilian medicine to join the call to action of military medicine outlined by Schoomaker and Buckenmaier in "If not now, when? If not you, who?" urging the immediate incorporation of effective nonpharmacologic modalities and active self-care because of their safety, effectiveness and acceptance by patients.[463] The goal in these recommendations and the call to action that follows is to increase awareness, access and utilization of safe, effective nonpharmacologic treatments through education of practitioners and patients; dissemination of and reimbursement for evidence-based treatment options; and to promote ongoing research focused on the therapeutic and economic impact, in the short and long term, of comprehensive care practices.

Education

The training of physicians and healthcare providers must include current pain mechanisms and all evidence-based treatment options for pain including effective nonpharmacologic options as stand-alone first line of care and as part of individualized comprehensive pain care. This includes individualized pain care that is patient-centered and evidence-informed, and which assumes the following:

(1) Patient-centered care focuses on each person's unique healthcare needs and experiences by asking
   a. How do you manage pain now and in the past?
   b. What nonpharmacologic strategies have you used?
   c. What are you interested in exploring?
(2) Practitioners should become familiar with nonpharmacologic modalities and licensed independent practitioners in their system and or area of practice.

Treatment: nonpharmacologic therapy frequency, dosage and timing

While physicians are familiar with dosage of medications, evidence-informed frequency, "dosage" and timing of nonpharmacologic therapies is less well disseminated. For inpatient care daily care is recommended, or every other day when staggered with another available nonpharmacologic intervention. In acute extreme pain that is not well managed, a second same or different treatment may be needed in a single day.

Evidence-based nonpharmacologic options for inpatient acute pain care include:

(1) Acupuncture therapy, massage therapy, mind body interventions and transcutaneous electric nerve stimulation (TENS).
(2) Daily inpatient access to effective nonpharmacologic care is recommended.

Evidence-based nonpharmacologic options for chronic pain include:

(1) Acupuncture therapy, chiropractic and osteopathic care, massage therapy, physical therapy, mind body and movement therapies and cognitive behavioral therapy.
(2) Referral to a course of effective nonpharmacologic care is recommended.

Recommendations and referral must take into account a patient's unique presentation and circumstances in terms of access and coverage. Even when not covered by insurance, a course of nonpharmacologic treatment may have a longitude of benefit that exceeds short-term benefit of medications that are accompanied by adverse events and addiction liability.

Research

The call for research includes further study on the timing, dosage, frequency, longitude and combinations of care in the development of a comprehensive pain care model for both the inpatient and outpatient setting.

SECTION 3: CALL TO ACTION

As detailed in this paper, documented in the literature and accepted by health professionals and researchers, the crisis in pain care and aspects of current pain management strategies are having enormous detrimental impacts on patients, the health system and society.[1,2] In response to the grim statistics about pain care and the opioid epidemic, health care professionals, policy makers, researchers and multiple major health organizations and government agencies are moving in the right direction. The IOM,[1] NAM,[2] NIH,[4] the CDC,[193] The Joint Commission,[194] the military,[463] the FDA,[195] the ACP,[141] and the former US Surgeon General[464] concede that past strategies and the use of opioid medications have not remedied but rather exacerbated chronic pain, abuse, addiction, illness behavior and disability and call for evidence-based, comprehensive pain care, to include nonpharmacologic therapies.

While there is consensus that pain care must drastically improve and prioritize evidence-based nonpharmacologic treatments, there is a need for an informed strategy that includes all evidence-based and comprehensive pain care. Currently, most of the nonpharmacologic strategies outlined in the preceding review are underutilized due to inadequate dissemination of evidence, professional and public education and inadequate reimbursement.

The Consortium Pain Task Force Goals in a Call to Action Are To.

- increase awareness of effective nonpharmacologic treatments for pain
- train healthcare practitioners and administrators in the evidence base of effective nonpharmacologic practice
- advocate for policy initiatives that remedy system and reimbursement barriers to evidence-informed compre- hensive pain care and
- promote ongoing research and dissemination of the role of effective nonpharmacologic treatments in pain, focused on the short and long term therapeutic and economic impact of comprehensive care practices.

This paper is a call to action for policy makers, hospitals and health systems, insurers, primary care providers and other licensed health practitioners and health care educators to lead in effecting this change.

POLICY: Federal and State policy should increase access to and reimbursement for evidence-based nonpharmacologic therapies

Based on the literature, stakeholders must petition and support evidence-based policy guidelines to increase access to and coverage for nonpharmacologic options as an essential part of comprehensive pain care.

Federal policy Currently, there is evidence of effectiveness, cost-effectiveness, cost-savings and risk mitigation for evidence-based nonpharmacologic options. Nonpharmacologic therapies for pain are now recommended by the NIH, FDA, TJC, CDC and ACP. Federal reimbursement policy needs to be based on current evidence of effectiveness, cost-effectiveness and risk mitigation, and include nonpharmacologic care.

State policy States need to adopt policies of coverage and plans for access to pain care based on current evidence of effectiveness, cost-effectiveness, cost-savings and risk mitigation that includes effective nonpharmacologic therapies. Policy should require private insurers to cover evidence-based nonpharmacologic therapies for acute and chronic pain.

BEST PRACTICES: Identify and develop clinical models that integrate evidence-based nonpharmacologic therapies for pain

Develop, optimize, incentivize and coordinate care across disciplines with nondiscriminatory access to evidence-based nonpharmacologic therapies, as stand-alone first line of care and as essential part of comprehensive care.

EDUCATION: Deliver evidence-based training to learners and graduates of the healthcare system in all disciplines on pain and effective nonpharmacologic treatments for pain

As recommended by the National Academy of Medicine (NAM), pain-related education for all health professionals who provide care to people with pain must become a national mandate.[82] Academic healthcare education should train students and health practitioners on the evolving understanding of pain and its complexities, including physical and psychiatric comorbidities and substance use disorder (SUD) as well as evidence-based frequency, "dosage" and timing of effective nonpharmacologic therapies. Healthcare practitioners require education and practical changes in practice models to enable them to be responsible to inform and educate patients on evidence-based comprehensive models of pain care including self-efficacy, patient responsibility, self-care and lifestyle choices.

RESEARCH: Identify and fund research to evaluate health outcomes and economic impact of comprehensive pain care that includes effective nonpharmacologic therapies

The call for research includes studies on the timing, dosage, frequency, longitude of benefit, and combinations of care in the development of a comprehensive pain care model for both the inpatient and outpatient setting. NIH, NCCIH, AHRQ, CMS, and other agencies and foundations should seek to fund investigation of comprehensive models of pain care and their impact on health outcomes, potential opioid sparing and reduction of opioid liability overuse and dependency.

DISSEMINATION: Stakeholder groups need to engage the media and foster public awareness of comprehensive pain care options that include evidence-based nonpharmacologic therapies

Academic organizations, pain societies, medical societies, patient advocacy groups, insurance carriers and the media have important roles in the dissemination and education of their members and the public regarding the benefits of nonpharmacologic options of pain care. Dissemination facilitates general and individual patient–practitioner conversations on options for personal comprehensive pain care.

APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.explore.2018.02.001.

REFERENCES

1. Institute of Medicine, Committee on Advancing Pain Research, Care and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington (DC): National Academies Press (US); 2011.
2. National Academies of Sciences Engineering and Medicine. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use (2017)*. Washington, DC: The National Academies Press. 2017. http://dx.doi.org/10.17226/24781.
3. Office of the Army Surgeon General. Pain Management Task Force Final Report May 2010. ⟨http://armymedicine.mil/Documents/Pain-Management-Task-Force.pdf; 2010⟩. Accessed May 24, 2017.
4. National Institutes of Health. *National Pain Strategy, a Comprehensive Population Health-Level Strategy for Pain*. 2016. ⟨https://iprcc.nih.gov/National_Pain_Strategy/NPS_Main.htm⟩. Accessed June 7, 2017.
5. National Institutes of Health, National Institute on Drug Abuse. *Pain Relief Most Reported Reason for Misuse of Opioid Pain Relievers*. 2017. Available at: ⟨https://www.drugabuse.gov/news-events/news-releases/2017/07/pain-relief-most-reported-reason-misuse-opioid-pain-relievers⟩. Accessed August 11, 2017.
6. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain*. 2012;13(8):715–724.
7. Kennedy J, Roll JM, Schraudner T, Murphy S, McPherson S. Prevalence of persistent pain in the US adult population: new data from the 2010 National Health Interview Survey. *J Pain*. 2014;15(10):979–984.
8. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for US adults: National Health Interview Survey, 2012. National Center for Health Statistics. *Vital Health Stat*. 2014;10(260). Available at: ⟨https://www.cdc.gov/nchs/data/series/sr_10/sr10_260.pdf⟩. Accessed January 14, 2017.
9. Reyes-Gibby CC, Aday L, Cleeland C. Impact of pain on self-rated health in the community-dwelling older adults. *Pain*. 2002;95(1-2):75–82.
10. Brown A. Chronic pain rates shoot up until Americans reach late 50s. *Gallup Healthways* 2012. Available at: ⟨http://www.gallup.com/poll/154169/Chronic-Pain-Rates-Shoot-Until-Americans-Reach-Late-50s.aspx?ref=image⟩. Accessed May 6, 2017.
11. Grol-Prokopczyk H. Sociodemographic disparities in chronic pain, based on 12-year longitudinal data. *Pain*. 2017;158(2):313–322.
12. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1545–1602.
13. Institute of Medicine and National Research Council. *US Health in International Perspective: Shorter Lives, Poorer Health (2013)*. Washington DC: National Academies Press (US); http://dx.doi.org/10.17226/13497.

14. King S, Chambers CT, Huguet A, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. *Pain*. 2011;152(12):2729–2738.
15. Odell S, Logan DE. Pediatric pain management: the multidisciplinary approach. *J Pain Res*. 2013;6:785–790.
16. Cassel EJ. The nature of suffering and the goals of medicine. *N Engl J Med*. 1982;306(11):639–645.
17. Duenas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. *J Pain Res*. 2016;9:457–467.
18. Bushnell MC, Case LK, Ceko M, et al. Effect of environment on the long-term consequences of chronic pain. *Pain*. 2015;156 (suppl 1):S42–S49.
19. Agoston AM, Gray LS, Logan DE. Pain in school: patterns of pain-related school impairment among adolescents with primary pain conditions, juvenile idiopathic arthritis pain, and pain-free peers. *Children (Basel)*. 2016;3(4) P. II: E39.
20. Gerrits MM, van Oppen P, Leone SS, van Marwijk HW, van der Horst HE, Penninx BW. Pain, not chronic disease, is associated with the recurrence of depressive and anxiety disorders. *BMC Psychiatry*. 2014;14:187.
21. Goetzel RZ, Hawkins K, Ozminkowski RJ, Wang S. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large US employers in 1999. *J Occup Environ Med*. 2003;45(1):5–14.
22. Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an Internet-based survey. *J Pain*. 2010;11(11):1230–1239.
23. FAIR Health. *The Opioid Crisis Among the Privately Insured; the Opioid Abuse Epidemic as Documented in Private Claims Data (July 2016)*. 2016. ⟨https://www.fairhealth.org/publications/whitepapers⟩. Accessed June 6, 2017
24. FAIR Health. *The Impact of the Opioid Crisis on the Healthcare System: A Study of Privately Billed Services (September 2016)* 2016 Available at: ⟨https://www.fairhealth.org/publications/whitepapers⟩. Accessed June 6, 2017.
25. Tadros A, Layman SM, Davis SM, Davidov DM, Cimino S. Emergency visits for prescription opioid poisonings. *J Emerg Med*. 2015;49(6):871–877.
26. Tadros A, Layman SM, Davis SM, Bozeman R, Davidov DM. Emergency department visits by pediatric patients for poisoning by prescription opioids. *Am J Drug Alcohol Abuse*. 2016;42(5):550–555.
27. Corr TE, Hollenbeak CS. The economic burden of neonatal abstinence syndrome in the United States. *Addiction*. 2017;112(9):1590–1599.
28. Wilhelmi BG, Cohen SP. A framework for "driving under the influence of drugs" policy for the opioid using driver. *Pain Physician*. 2012;15(suppl 3):Es215–Es230.
29. Rudisill TM, Zhu M, Kelley GA, Pilkerton C, Rudisill BR. Medication use and the risk of motor vehicle collisions among licensed drivers: a systematic review. *Accid Anal Prev*. 2016;96:255–270.
30. Centers for Medicare and Medicaid Services. *National Health Expenditures 2015 Highlights*. Baltimore, MD: U.S Centers for Medicare & Medicaid Services; 2016.
31. Keehan SP, Stone DA, Poisal JA, et al. National health expenditure projections, 2016-2025: price increases, aging push sector to 20 percent of economy. *Health Aff (Millwood)*. 2017;36 (3):553–563.
32. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. *J Am Med Assoc*. 1998;280(2):147–151.
33. Raofi S, Schappert SM. Medication therapy in ambulatory medical care: United States, 2003-04. *Vital Health Stat*. 2006;13 (163):1–40.
34. Guy GP Jr., Zhang K, Bohm MK, et al. Vital signs: changes in opioid prescribing in the United States, 2006-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(26):697–704.
35. Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: time to back off? *J Am Board Fam Med*. 2009;22(1):62–68.
36. Social Security Admininistration Office of Retirement and Disablity Policy, Office of Research, Evaluation, and Statistics, 2016. Annual Statistical Report on the Social Security Disability Insurance Program, 2015. SSA Publication No. 13-11826. 2016; SSA Publication No. 13-11826. Available at: ⟨https://www.ssa.gov/policy/docs/statcomps/di_asr/2015/di_asr15.pdf⟩. Accessed September 11, 2017.
37. Goetzel RZ, Long SR, Ozminkowski RJ, Hawkins K, Wang S, Lynch W. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting US employers. *J Occup Environ Med*. 2004;46 (4):398–412.
38. Koopman C, Pelletier KR, Murray JF, et al. Stanford presenteeism scale: health status and employee productivity. *J Occup Environ Med*. 2002;44(1):14–20.
39. Parry TP JK, Molmen W, Lu Y. Integrated Benefits Institute. *The business value of health, linking CFOs to health and productivity*. 2006. Available at: ⟨http://www.acoem.org/uploadedFiles/Career_Development/Tools_for_Occ_Health_Professional/Health_and_Productivity/Bus%20Value%20of%20Health%20for%20web.pdf⟩. Accessed June 7, 2017.
40. Serxner SA, Gold DB, Grossmeier JJ, Anderson DR. The relationship between health promotion program participation and medical costs: a dose response. *J Occup Environ Med*. 2003;45(11):1196–1200.
41. Liu H, Harris KM, Weinberger S, Serxner S, Mattke S, Exum E. Effect of an employer-sponsored health and wellness program on medical cost and utilization. *Popul Health Manag*. 2013;16(1):1–6.
42. Kaspin LC, Gorman KM, Miller RM. Systematic review of employer-sponsored wellness strategies and their economic and health-related outcomes. *Popul Health Manag*. 2013;16(1):14–21.
43. Goetzel RZ, Guindon AM, Turshen IJ, Ozminkowski RJ. Health and productivity management: establishing key performance measures, benchmarks, and best practices. *J Occup Environ Med*. 2001;43(1):10–17.
44. O'Donnell M. Studying workplace health. *CMAJ*. 1998;158 (11):1434–1435.
45. Goetzel RZ, Fabius R, Fabius D, et al. The stock performance of C. Everett Koop award winners compared with the Standard & Poor's 500 Index. *J Occup Environ Med*. 2016;58(1):9–15.
46. Grossmeier J, Fabius R, Flynn JP, et al. Linking workplace health promotion best practices and organizational financial performance: tracking market performance of companies with highest scores on the HERO Scorecard. *J Occup Environ Med*. 2016;58(1):16–23.
47. Goetzel RZ, Shechter D, Ozminkowski RJ, et al. Can health promotion programs save Medicare money? *Clin Interv Aging*. 2007;2(1):117–122.
48. Institute of Medicine. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care (With CD)*. Washington, DC: The National Academies Press; 2003.
49. Chibnall JT, Tait RC, Andresen EM, Hadler NM. Race differences in diagnosis and surgery for occupational low back injuries. *Spine (Phila Pa 1976)*. 2006;31(11):1272–1275.
50. Edwards RR. The association of perceived discrimination with low back pain. *J Behav Med*. 2008;31(5):379.
51. Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An fMRI study of social exclusion. *Science*. 2003;302 (5643):290–292.

52. Yazdanshenas H, Bazargan M, Smith J, Martins D, Motahari H, Orum G. Pain treatment of underserved older African Americans. *J Am Geriatr Soc*. 2016;64(10):2116–2121.
53. Jimenez N, Garroutte E, Kundu A, Morales L, Buchwald D. A review of the experience, epidemiology, and management of pain among American Indian, Alaska Native, and Aboriginal Canadian Peoples. *J Pain*. 2011;12(5):511–522.
54. Kramer BJ, Harker JO, Wong AL. Arthritis beliefs and self-care in an urban American Indian population. *Arthritis Rheum*. 2002;47(6):588–594.
55. Hardt J, Jacobsen C, Goldberg J, Nickel R, Buchwald D. Prevalence of chronic pain in a representative sample in the United States. *Pain Med*. 2008;9(7):803–812.
56. Unruh AM. Gender variations in clinical pain experience. *Pain*. 1996;65(2-3):123–167.
57. Plesh O, Adams SH, Gansky SA. Racial/ethnic and gender prevalences in reported common pains in a national sample. *J Orofac Pain*. 2011;25(1):25–31.
58. Campaign to End Chronic Pain in Women. *Chronic Pain in Women: Neglect, Dismissal and Discrimination*. 2010. Available at: ⟨http://www.endwomenspain.org/⟩. Accessed June 19, 2017.
59. Campbell CI, Weisner C, Leresche L, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. *Am J Public Health*. 2010;100(12):2541–2547.
60. Paulozzi LJ, Strickler GK, Kreiner PW, Koris CM. Controlled substance prescribing patterns—prescription behavior surveillance system, eight states, 2013. *MMWR Surveill Summ*. 2015;64(9):1–14.
61. Vital signs: overdoses of prescription opioid pain relievers and other drugs among women—United States, 1999-2010. *MMWR Morb Mortal Wkly Rep*. 2013;62(26):537–542.
62. Howard RF. Current status of pain management in children. *J Am Med Assoc*. 2003;290(18):2464–2469.
63. Huguet A, Miro J. The severity of chronic pediatric pain: an epidemiological study. *J Pain*. 2008;9(3):226–236.
64. Kozlowski LJ, Kost-Byerly S, Colantuoni E, et al. Pain prevalence, intensity, assessment and management in a hospitalized pediatric population. *Pain Manag Nurs*. 2014;15(1):22–35.
65. Mathews L. Pain in children: neglected, unaddressed and mismanaged. *Indian J Palliat Care*. 2011;17(suppl):S70–S73.
66. US Food and Drug Administration. *Drug Safety Communication: FDA Strengthens Warning That Non-Aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) can Cause Heart Attacks or Strokes*. 2015. ⟨https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm⟩. Accessed June 2, 2017.
67. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol Suppl*. 1999;56:18–24.
68. Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*. 2017;20(2S):S3–S92.
69. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349(20):1943–1953.
70. Ballantyne JC. Avoiding opioid analgesics for treatment of chronic low back pain. *J Am Med Assoc*. 2016;315(22):2459–2460.
71. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25(2):171–186.
72. Manchikanti L, Helm S 2nd, Fellows B, et al. Opioid epidemic in the United States. *Pain Physician*. 2012;15(suppl 3):ES9–ES38.
73. McLean K. "There's nothing here": deindustrialization as risk environment for overdose. *Int J Drug Policy*. 2016;29:19–26.
74. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *J Am Med Assoc*. 2016;315(15):1624–1645.
75. Chiu HY, Hsieh YJ, Tsai PS. Systematic review and meta-analysis of acupuncture to reduce cancer-related pain. *Eur J Cancer Care (Engl)*. 2017;26(2).
76. Lee SH, Kim JY, Yeo S, Kim SH, Lim S. Meta-analysis of massage therapy on cancer pain. *Integr Cancer Ther*. 2015;14(4):297–304.
77. Gallagher LM, Lagman R, Rybicki L. Outcomes of music therapy interventions on symptom management in palliative medicine patients. *Am J Hosp Palliat Care*. 2018;35(2):250–257.
78. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain*. 2015;156(6):1003–1007.
79. Loeser JD. Five crises in pain management. *International Association for the Study of Pain; Pain Clinical Updates*. 2012;XX(1):1–4.
80. Tick H, Chauvin SW, Brown M, Haramati A. Core competencies in integrative pain care for entry-level primary care physicians. *Pain Med*. 2015;16(11):2090–2097.
81. Patel SJ, Kemper KJ, Kitzmiller JP. Physician perspectives on education, training, and implementation of complementary and alternative medicine. *Adv Med Educ Pract*. 2017;8:499–503.
82. National Academies of Sciences Engineering and Medicine. *Consensus Study Report Highlights. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*. 2017. ⟨https://www.nap.edu/resource/24781/Highlights_071317_Opioids.pdf⟩. Accessed September 11, 2017.
83. Rygh LJ, Svendsen F, Fiska A, Haugan F, Hole K, Tjolsen A. Long-term potentiation in spinal nociceptive systems—how acute pain may become chronic. *Psychoneuroendocrinology*. 2005;30(10):959–964.
84. Stanos S, Brodsky M, Argoff C, et al. Rethinking chronic pain in a primary care setting. *Postgrad Med*. 2016;128(5):502–515.
85. Mense S. Muscle pain: mechanisms and clinical significance. *Dtsch Arztebl Int*. 2008;105(12):214–219.
86. Coq JO, Barr AE, Strata F, et al. Peripheral and central changes combine to induce motor behavioral deficits in a moderate repetition task. *Exp Neurol*. 2009;220(2):234–245.
87. Napadow V, Kettner N, Ryan A, Kwong KK, Audette J, Hui KK. Somatosensory cortical plasticity in carpal tunnel syndrome—a cross-sectional fMRI evaluation. *Neuroimage*. 2006;31(2):520–530.
88. Saunders C. The symptomatic treatment of incurable malignant disease. *Prescribers J*. 1964;4(4):68–73.
89. Davis MA, Lin LA, Liu H, Sites BD. Prescription opioid use among adults with mental health disorders in the United States. *J Am Bd Fam Med*. 2017;30(4):407–417.
90. Von Korff M, Crane P, Lane M, et al. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. *Pain*. 2005;113(3):331–339.
91. Von Korff M, Dworkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints. *Pain*. 1988;32(2):173–183.
92. Tang NK, Lereya ST, Boulton H, Miller MA, Wolke D, Cappuccio FP. Nonpharmacological treatments of insomnia for long-term painful conditions: a systematic review and

meta-analysis of patient-reported outcomes in randomized controlled trials. *Sleep*. 2015;38(11):1751–1764.
93. Scherrer JF, Salas J, Sullivan MD, et al. The influence of prescription opioid use duration and dose on development of treatment resistant depression. *Prev Med*. 2016;91:110–116.
94. Katz N, Mazer NA. The impact of opioids on the endocrine system. *Clin J Pain*. 2009;25(2):170–175.
95. Akil H, Watson SJ, Young E, Lewis ME, Khachaturian H, Walker JM. Endogenous opioids: biology and function. *Annu Rev Neurosci*. 1984;7:223–255.
96. Panksepp J, Oxford University P. *Affective Neuroscience: the Foundations of Human and Animal Emotions*. Oxford: Oxford University Press; 2014.
97. Trezza V, Damsteegt R, Achterberg EJ, Vanderschuren LJ. Nucleus accumbens mu-opioid receptors mediate social reward. *J Neurosci*. 2011;31(17):6362–6370.
98. Loseth GE, Ellingsen DM, Leknes S. State-dependent mu-opioid modulation of social motivation. *Front Behav Neurosci*. 2014;8:430.
99. Fields HL, Margolis EB. Understanding opioid reward. *Trends Neurosci*. 2015;38(4):217–225.
100. Demarest SP, Gill RS, Adler RA. Opioid endocrinopathy. *Endocr Pract*. 2015;21(2):190–198.
101. Brady KT, McCauley JL, Back SE. Prescription opioid misuse, abuse, and treatment in the United States: an update. *Am J Psychiatry*. 2016;173(1):18–26.
102. Sullivan MD, Ballantyne JC. What are we treating with long-term opioid therapy? *Arch Intern Med*. 2012;172(5):433–434.
103. Sullivan MD. Who gets high-dose opioid therapy for chronic non-cancer pain? *Pain*. 2010;151(3):567–568.
104. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006;166(19):2087–2093.
105. Sullivan MD, Edlund MJ, Steffick D, Unutzer J. Regular use of prescribed opioids: association with common psychiatric disorders. *Pain*. 2005;119(1-3):95–103.
106. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. *J Am Med Assoc*. 2011;305(13):1299–1301.
107. Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of opioids by different types of Medicare prescribers. *JAMA Intern Med*. 2016;176(2):259–261.
108. Wilson FA, Licciardone JC, Kearns CM, Akuoko M. Analysis of provider specialties in the treatment of patients with clinically diagnosed back and joint problems. *J Eval Clin Pract*. 2015;21(5):952–957.
109. Mezei L, Murinson BB. Pain education in North American medical schools. *J Pain*. 2011;12(12):1199–1208.
110. Lippe PM, Brock C, David J, Crossno R, Gitlow S. The First National Pain Medicine Summit—final summary report. *Pain Med*. 2010;11(10):1447–1468.
111. Ballantyne JC. Opioid therapy in chronic pain. *Phys Med Rehabil Clin N Am*. 2015;26(2):201–218.
112. Whedon J, Tosteson TD, Kizhakkeveettil A, Kimura MN. Insurance reimbursement for complementary healthcare services. *J Altern Complement Med*. 2017;23(4):264–267.
113. Nahin RL, Stussman BJ, Herman PM. Out-of-pocket expenditures on complementary health approaches associated with painful health conditions in a nationally representative adult sample. *J Pain*. 2015;16(11):1147–1162.
114. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med*. 1993;328(4):246–252.
115. Nahin RL, Barnes PM, Stussman BJ. Expenditures on complementary health approaches: United States, 2012. *Natl Health Stat Rep* 2016(95):1–11.
116. Oregon Health Authority, Office of Clinical Services Improvement. *Back Policy Changes Fact Sheet* 2016 Available at: ⟨http://www.oregon.gov/OHA/HPA/CSI-HERC/FactSheets/Back-policy-changes-fact-sheet.pdf⟩. Accessed August 17, 2017.
117. Davis R. Vermont policy makers assess the effectiveness of acupuncture treatment for chronic pain in medicaid enrollees. *J Altern Complement Med*. 2017;23(7):499–501.
118. Lafferty WE, Tyree PT, Bellas AS, et al. Insurance coverage and subsequent utilization of complementary and alternative medicine providers. *Am J Manag Care*. 2006;12(7):397–404.
119. Lind BK, Lafferty WE, Tyree PT, Diehr PK. Comparison of health care expenditures among insured users and nonusers of complementary and alternative medicine in Washington State: a cost minimization analysis. *J Altern Complement Med*. 2010;16(4):411–417.
120. Priester MA, Browne T, Iachini A, Clone S, DeHart D, Seay KD. Treatment access barriers and disparities among individuals with co-occurring mental health and substance use disorders: an integrative literature review. *J Subst Abuse Treat*. 2016;61:47–59.
121. Becker WC, Dorflinger L, Edmond SN, Islam L, Heapy AA, Fraenkel L. Barriers and facilitators to use of non-pharmacological treatments in chronic pain. *BMC Fam Pract*. 2017;18(1):41.
122. Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Pediatr Nurs*. 1988;14(1):9–17.
123. Ballantyne JC, Sullivan MD. Intensity of chronic pain—the wrong metric? *N Engl J Med*. 2015;373(22):2098–2099.
124. Mai J, Franklin G, Tauben D. Guideline for prescribing opioids to treat pain in injured workers. *Phys Med Rehabil Clin N Am*. 2015;26(3):453–465.
125. Vital signs: overdoses of prescription opioid pain relievers—United States, 1999-2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487–1492.
126. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000-2014. *MMWR Morb Mortal Wkly Rep*. 2016;64(50-51):1378–1382.
127. Alexander GC, Kruszewski SP, Webster DW. Rethinking opioid prescribing to protect patient safety and public health. *J Am Med Assoc*. 2012;308(18):1865–1866.
128. Von Korff M, Deyo RA. Potent opioids for chronic musculoskeletal pain: flying blind? *Pain*. 2004;109(3):207–209.
129. Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The initiation of chronic opioids: a survey of chronic pain patients. *J Pain*. 2016;18(4):360–365.
130. Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. *Med Care*. 2016;54(10):901–906.
131. Trust for America's Health. *Prescription Drug Abuse: Strategies to Stop the Epidemic*. 2013. ⟨http://healthyamericans.org/reports/drugabuse2013/⟩. Accessed June 27, 2017
132. Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use—United States, 2006-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(10):265–269.
133. Manchikanti L. Opioid-induced hyperalgesia method is a clinically relevant issue. *Ann Palliat Med*. 2012;1(1):2–3.
134. Chou R, Deyo R, Friedly J, et al. Systemic pharmacologic therapies for low back pain: a systematic review for an American College of Physicians clinical practice guideline. *Ann Intern Med*. 2017;166(7):480–492.

135. Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel Shaheed C, Maher CG. Paracetamol for low back pain. *Cochrane Database Syst Rev*. 2016(6):Cd012230.
136. Machado GC, Maher CG, Ferreira PH, Day RO, Pinheiro MB, Ferreira ML. Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis. *Ann Rheum Dis*. 2017;76(7):1269–1278.
137. Su B, O'Connor JP. NSAID therapy effects on healing of bone, tendon, and the enthesis. *J Appl Physiol (1985)*. 2013;115(6):892–899.
138. Wang Z, Bhattacharyya T. Trends of non-union and prescriptions for non-steroidal anti-inflammatory drugs in the United States, 1993-2012. *Acta Orthop*. 2015;86(5):632–637.
139. Doux JD, Bazar KA, Lee PY, Yun AJ. Can chronic use of anti-inflammatory agents paradoxically promote chronic inflammation through compensatory host response? *Med Hypotheses*. 2005;65(2):389–391.
140. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med*. 1996;156 (14):1530–1536.
141. Qaseem A, Wilt TJ, McLean RM, Forciea M. Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2017;166(7):514–530.
142. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *Br Med J*. 2017;357: j1415.
143. Goldberg H, Firtch W, Tyburski M, et al. Oral steroids for acute radiculopathy due to a herniated lumbar disk: a randomized clinical trial. *J Am Med Assoc*. 2015;313(19):1915–1923.
144. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. *Arch Dis Child*. 2016;101(4):365–370.
145. Chou R, Deyo R, Friedly J, et al. Noninvasive treatments for low back pain. *Agency for Healthcare Research and Quality (US) (AHRQ) Comparative Effectiveness Reviews*. 2016 Number 169 (Report No.: 16-EHC004-EF).
146. Radcliff K, Kepler C, Hilibrand A, et al. Epidural steroid injections are associated with less improvement in patients with lumbar spinal stenosis: a subgroup analysis of the Spine Patient Outcomes Research Trial. *Spine (Phila Pa 1976)*. 2013;38 (4):279–291.
147. Mandel S, Schilling J, Peterson E, Rao DS, Sanders W. A retrospective analysis of vertebral body fractures following epidural steroid injections. *J Bone Joint Surg Am*. 2013;95(11):961–964.
148. Singla A, Yang S, Werner BC, et al. The impact of preoperative epidural injections on postoperative infection in lumbar fusion surgery. *J Neurosurg Spine*. 2017;26(5):645–649.
149. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. *J Pain Symptom Manage*. 2004;28(2):140–175.
150. Skogberg O, Samuelsson K, Ertzgaard P, Levi R. Changes in body composition after spasticity treatment with intrathecal baclofen. *J Rehabil Med*. 2017;49(1):36–39.
151. Perez-Arredondo A, Cazares-Ramirez E, Carrillo-Mora P, et al. Baclofen in the therapeutic of sequele of traumatic brain injury; spasticity. *Clin Neuropharmacol*. 2016;39(6):311–319.
152. Cunningham JL, Craner JR, Evans MM, Hooten WM. Benzodiazepine use in patients with chronic pain in an interdisciplinary pain rehabilitation program. *J Pain Res*. 2017;10:311–317.
153. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *Br Med J*. 2015;350:h2698.
154. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: an updated Cochrane review. *Cephalalgia*. 2015;35(1):51–62.
155. Wang QP, Bai M. Topiramate versus carbamazepine for the treatment of classical trigeminal neuralgia: a meta-analysis. *CNS Drugs*. 2011;25(10):847–857.
156. Martin WJ, Forouzanfar T. The efficacy of anticonvulsants on orofacial pain: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;111(5):627–633.
157. Moulin DE, Clark AJ, Gordon A, et al. Long-term outcome of the management of chronic neuropathic pain: a prospective observational study. *J Pain*. 2015;16(9):852–861.
158. Tauben D. *Nonopioid Medications for Pain, Vol 26*. Philadelphia: W.B. Saunders; 2015.
159. Bet PM, Hugtenburg JG, Penninx BW, Hoogendijk WJ. Side effects of antidepressants during long-term use in a naturalistic setting. *Eur Neuropsychopharmacol*. 2013;23(11):1443–1451.
160. Watkins LR, Hutchinson MR, Rice KC, Maier SF. The "toll" of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. *Trends Pharmacol Sci*. 2009;30(11):581–591.
161. Dodds KN, Beckett EA, Evans SF, Grace PM, Watkins LR, Hutchinson MR. Glial contributions to visceral pain: implications for disease etiology and the female predominance of persistent pain. *Transl Psychiatry*. 2016;6(9):e888.
162. Amat J, Dolzani SD, Tilden S, et al. Previous ketamine produces an enduring blockade of neurochemical and behavioral effects of uncontrollable stress. *J Neurosci*. 2016;36(1):153–161.
163. Maeda Y, Kim H, Kettner N, et al. Rewiring the primary somatosensory cortex in carpal tunnel syndrome with acupuncture. *Brain*. 2017;140(4):914–927.
164. Tajerian M, Clark JD. Nonpharmacological interventions in targeting pain-related brain plasticity. *Neural Plast*. 2017;2017: 2038573.
165. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;5:Cd008609.
166. Casale R, Symeonidou Z, Bartolo M. Topical treatments for localized neuropathic pain. *Curr Pain Headache Rep*. 2017;21(3):15.
167. Kandil E, Melikman E, Adinoff B. Lidocaine infusion: a promising therapeutic approach for chronic pain. *J Anesth Clin Res*. 2017;8(1) pii: 697.
168. Zogopoulos P, Vasileiou I, Patsouris E, Theocharis SE. The role of endocannabinoids in pain modulation. *Fundam Clin Pharmacol*. 2013;27(1):64–80.
169. Andreae MH, Carter GM, Shaparin N, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. *J Pain*. 2015;16(12):1221–1232.
170. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *J Am Med Assoc*. 2015;313(24):2474–2483.
171. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: systematic review of randomized controlled trials. *Can Fam Physician*. 2015;61(8):e372–e381.
172. Cameron C, Kelly S, Hsieh SC, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. *Headache*. 2015;55(suppl 4):S221–S235.
173. Donahue K, Jonas DE, Hansen RA, et al. *Drug Therapy for Rheumatoid Arthritis in Adults: an Update. Comparative Effectiveness Review No. 55. (Prepared by RTI-UNC Evidence-based*

Practice Center under Contract No. 290-02-0016-I). Rockville, MD: Agency for Healthcare Research and Quality; 2012. Available at: ⟨www.effectivehealthcare.ahrq.govreports/final.cfm⟩. Accessed June 5, 2017.
174. Mitchell JM. Utilization trends for advanced imaging procedures: evidence from individuals with private insurance coverage in California. *Med Care*. 2008;46(5):460–466.
175. Cheng F, You J, Rampersaud YR. Relationship between spinal magnetic resonance imaging findings and candidacy for spinal surgery. *Can Fam Physician*. 2010;56(9):e323–e330.
176. Lurie JD, Birkmeyer NJ, Weinstein JN. Rates of advanced spinal imaging and spine surgery. *Spine (Phila Pa 1976)*. 2003;28(6): 616–620.
177. Kearns MC, Ressler KJ, Zatzick D, Rothbaum BO. Early interventions for PTSD: a review. *Depress Anxiety*. 2012;29 (10):833–842.
178. Kennedy DJ, Engel A, Kreiner DS, Nampiaparampil D, Duszynski B, MacVicar J. Fluoroscopically guided diagnostic and therapeutic intra-articular sacroiliac joint injections: a systematic review. *Pain Med*. 2015;16(8):1500–1518.
179. King W, Ahmed SU, Baisden J, et al. Diagnosis and treatment of posterior sacroiliac complex pain: a systematic review with comprehensive analysis of the published data. *Pain Med*. 2015;16(2):257–265.
180. Manchikanti L, Falco FJ, Singh V, et al. Utilization of interventional techniques in managing chronic pain in the Medicare population: analysis of growth patterns from 2000 to 2011. *Pain Physician*. 2012;15(6):E969–E982.
181. Manchikanti L, Parr AT, Singh V, Fellows B. Ambulatory surgery centers and interventional techniques: a look at long-term survival. *Pain Physician*. 2011;14(2):E177–E215.
182. Nguyen C, Boutron I, Baron G, et al. Intradiscal glucocorticoid injection for patients with chronic low back pain associated with active discopathy: a randomized trial. *Ann Intern Med*. 2017;166 (8):547–556.
183. Nguyen C, Boutron I, Baron G, et al. Steroid injections for patients with low back pain. *Ann Intern Med*. 2017;166(8).
184. Tornbjerg SM, Nissen N, Englund M, et al. Structural pathology is not related to patient-reported pain and function in patients undergoing meniscal surgery. *Br J Sports Med*. 2017;51(6):525–530.
185. Evidence Development and Standards Branch, Health Quality Ontario. Arthroscopic debridement of the knee: an evidence update. *Ont Health Technol Assess Ser*. 2014;14(13):1–43.
186. Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. *Br Med J*. 2016;354:i3740.
187. Lamplot JD, Brophy RH. The role for arthroscopic partial meniscectomy in knees with degenerative changes: a systematic review. *Bone Joint J*. 2016;98-b(7):934–938.
188. Thorlund JB, Englund M, Christensen R, et al. Patient reported outcomes in patients undergoing arthroscopic partial meniscectomy for traumatic or degenerative meniscal tears: comparative prospective cohort study. *Br Med J*. 2017;356:j356.
189. Cohen SP, Hooten WM. Advances in the diagnosis and management of neck pain. *Br Med J*. 2017;358:j3221.
190. Zaina F, Tomkins-Lane C, Carragee E, Negrini S. Surgical versus non-surgical treatment for lumbar spinal stenosis. *Cochrane Database Syst Rev*. 2016(1):Cd010264.
191. Costhelper health. How Much Does Back Surgery Cost? 2017; ⟨http://health.costhelper.com/back-surgery.html⟩. Accessed July 13, 2017.
192. Fritz JM, Lurie JD, Zhao W, et al. Associations between physical therapy and long-term outcomes for individuals with lumbar spinal stenosis in the SPORT study. *Spine J*. 2014;14(8): 1611–1621.
193. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep*. 2016;65(1):1–49.
194. The Joint Commission. *Joint Commission Enhances Pain Assessment and Management Requirements for Accredited Hospitals*. 2017. Available at: ⟨https://www.jointcommission.org/assets/1/18/Joint_Commission_Enhances_Pain_Assessment_and_Management_Requirements_for_Accredited_Hospitals1.PDF⟩. Accessed November 27, 2017.
195. US Food and Drug Administration. *FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients With Pain (May 2017)* 2017 Available at: ⟨https://www.fda.gov/downloads/Drugs/NewsEvents/UCM557071.pdf⟩. Accessed May 22, 2017.
196. Kabouridis PS, Pachnis V. Emerging roles of gut microbiota and the immune system in the development of the enteric nervous system. *J Clin Invest*. 2015;125(3):956–964.
197. Gilbert JA, Quinn RA, Debelius J, et al. Microbiome-wide association studies link dynamic microbial consortia to disease. *Nature*. 2016;535(7610):94–103.
198. Blaser MJ. *Missing Microbes: How the Overuse of Antibiotics is Fueling Our Modern Plagues*. New York: Picador; 2015.
199. Myhill S, Booth NE, McLaren-Howard J. Targeting mitochondrial dysfunction in the treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)—a clinical audit. *Int J Clin Exp Med*. 2013;6(1):1–15.
200. Langevin HM. Connective tissue: a body-wide signaling network? *Med Hypotheses*. 2006;66(6):1074–1077.
201. Langevin HM, Churchill DL, Wu J, et al. Evidence of connective tissue involvement in acupuncture. *FASEB J*. 2002;16(8):872–874.
202. Langevin HM, Nedergaard M, Howe AK. Cellular control of connective tissue matrix tension. *J Cell Biochem*. 2013;114 (8):1714–1719.
203. National Association of Attorneys General. *Letter to the President and CEO of the America's Health Insurance Plans Regarding the Prescription Opioid Epidemic. [Letter]*. 2017. ⟨https://ag.ny.gov/sites/default/files/final_naag_opioid_letter_to_ahip.pdf⟩. Accessed September 24, 2017
204. United States Congress Office of Technology Assessment. *Assessing the Efficacy and Safety of Medical Technologies*. Washington, DC: Congress of the United States, Office of Technology Assessment; 1978.
205. Matzen P. How evidence-based is medicine? A systematic literature review. *Ugeskr Laeger*. 2003;165(14):1431–1435.
206. Thomas KJ, MacPherson H, Ratcliffe J, et al. Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain. *Health Technol Assess*. 2005;9(32):1–109, iii-iv, ix-x.
207. MacPherson H, Vertosick EA, Foster NE, et al. The persistence of the effects of acupuncture after a course of treatment: a meta-analysis of patients with chronic pain. *Pain*. 2017;158(5): 784–793.
208. Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part II). *Health Promot Pract*. 2005;6(2):148–156.
209. Buckenmaier C 3rd, Schoomaker E. Patients' use of active self-care complementary and integrative medicine in their

management of chronic pain symptoms. *Pain Med*. 2014;15 (suppl 1):S7–S8.
210. The Joint Commission. Clarification of the pain management standard. 2015; https://www.jointcommission.org/assets/1/18/Clarification_of_the_Pain_Management__Standard.pdf. [Accessed July 15, 2017].
211. Andronis L, Kinghorn P, Qiao S, Whitehurst DG, Durrell S, McLeod H. Cost-effectiveness of non-invasive and non-pharmacological interventions for low back pain: a systematic literature review. *Appl Health Econ Health Policy*. 2017;15 (2):173–201.
212. Herman PM, Anderson ML, Sherman KJ, Balderson BH, Turner JA, Cherkin DC. Cost-effectiveness of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care among adults with chronic low-back pain. *Spine (Phila Pa 1976)*. 2017;42(20):1511–1520.
213. Liu XL, Tan JY, Molassiotis A, Suen LK, Shi Y. Acupuncture-point stimulation for postoperative pain control: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med*. 2015;2015:657809. http://dx.doi.org/10.1155/2015/657809.
214. Wu MS, Chen KH, Chen IF, et al. The efficacy of acupuncture in post-operative pain management: a systematic review and meta-analysis. *PLoS One*. 2016;11(3):e0150367.
215. Sun Y, Gan TJ, Dubose JW, Habib AS. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. *Br J Anaesth*. 2008;101(2): 151–160.
216. Tedesco D, Gori D, Desai KR, et al. Drug-free interventions to reduce pain or opioid consumption after total knee arthroplasty: a systematic review and meta-analysis. *JAMA Surg*. 2017: e172872.
217. Asher GN, Jonas DE, Coeytaux RR, et al. Auriculotherapy for pain management: a systematic review and meta-analysis of randomized controlled trials. *J Altern Complement Med*. 2010;16 (10):1097–1108.
218. Murakami M, Fox L, Dijkers MP. Ear acupuncture for immediate pain relief-a systematic review and meta-analysis of randomized controlled trials. *Pain Med*. 2017;18(3):551–564.
219. Huang S, Peng W, Tian X, et al. Effects of transcutaneous electrical acupoint stimulation at different frequencies on perioperative anesthetic dosage, recovery, complications, and prognosis in video-assisted thoracic surgical lobectomy: a randomized, double-blinded, placebo-controlled trial. *J Anesth*. 2017;31(1):58–65.
220. Dingemann J, Plewig B, Baumann I, Plinkert PK, Sertel S. Acupuncture in posttonsillectomy pain: a prospective, double-blinded, randomized, controlled trial. *HNO*. 2017;65(suppl 1): 73–79.
221. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016;17 (2):131–157.
222. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians clinical practice guideline. *Ann Intern Med*. 2017;166(7):493–505.
223. Li Y, Liang F, Yang X, et al. Acupuncture for treating acute attacks of migraine: a randomized controlled trial. *Headache*. 2009;49(6):805–816.
224. Grissa MH, Baccouche H, Boubaker H, et al. Acupuncture vs intravenous morphine in the management of acute pain in the ED. *Am J Emerg Med*. 2016;34(11):2112–2116.
225. Reinstein AS, Erickson LO, Griffin KH, et al. Acceptability, adaptation, and clinical outcomes of acupuncture provided in the emergency department: a retrospective pilot study. *Pain Med*. 2017;18(1):169–178.
226. Cohen MM, Parker SJ, Xue CC, et al. Acupuncture for analgesia in the emergency department: a multicentre, randomised, equivalence and non-inferiority trial. *Med J Aust*. 2017;206(11):494–499.
227. Jan AL, Aldridge ES, Rogers IR, Visser EJ, Bulsara MK, Niemtzow RC. Review article: does acupuncture have a role in providing analgesia in the emergency setting? A systematic review and meta-analysis. *Emerg Med Australas*. 2017;29(5):490–498.
228. Loskotova A, Loskotova J. The use of acupuncture in first aid of burns—Clinical report. *Burns*. 2017;43(8):1782–1791.
229. NIH Consensus Conference. Acupuncture. *J Am Med Assoc*. 1998;280(17):1518–1524.
230. Adams D, Cheng F, Jou H, Aung S, Yasui Y, Vohra S. The safety of pediatric acupuncture: a systematic review. *Pediatrics*. 2011;128(6):1575–1587.
231. Bergqvist D. Vascular injuries caused by acupuncture. A systematic review. *Int Angiol*. 2013;32(1):1–8.
232. Ernst E, White AR. Prospective studies of the safety of acupuncture: a systematic review. *Am J Med*. 2001;110(6): 481–485.
233. MacPherson H, Thomas K, Walters S, Fitter M. A prospective survey of adverse events and treatment reactions following 34,000 consultations with professional acupuncturists. *Acupunct Med*. 2001;19(2):93–102.
234. MacPherson H, Thomas K. Short term reactions to acupuncture —a cross-sectional survey of patient reports. *Acupunct Med*. 2005;23(3):112–120.
235. White A. A cumulative review of the range and incidence of significant adverse events associated with acupuncture. *Acupunct Med*. 2004;22(3):122–133.
236. Yamashita H, Tsukayama H, White AR, Tanno Y, Sugishita C, Ernst E. Systematic review of adverse events following acupuncture: the Japanese literature. *Complement Ther Med*. 2001;9 (2):98–104.
237. Zhao XF, Du Y, Liu PG, Wang S. Acupuncture for stroke: evidence of effectiveness, safety, and cost from systematic reviews. *Top Stroke Rehabil*. 2012;19(3):226–233.
238. Yamashita H, Tsukayama H. Safety of acupuncture practice in Japan: patient reactions, therapist negligence and error reduction strategies. *Evid Based Complement Alternat Med*. 2007;5 (4):391–398.
239. Jindal V, Ge A, Mansky PJ. Safety and efficacy of acupuncture in children: a review of the evidence. *J Pediatr Hematol Oncol*. 2008;30(6):431–442.
240. Ladas EJ, Rooney D, Taromina K, Ndao DH, Kelly KM. The safety of acupuncture in children and adolescents with cancer therapy-related thrombocytopenia. *Support Care Cancer*. 2010;18 (11):1487–1490.
241. Wu S, Sapru A, Stewart MA, et al. Using acupuncture for acute pain in hospitalized children. *Pediatr Crit Care Med*. 2009;10 (3):291–296.
242. Elden H, Ostgaard HC, Fagevik-Olsen M, Ladfors L, Hagberg H. Treatments of pelvic girdle pain in pregnant women: adverse effects of standard treatment, acupuncture and stabilising exercises on the pregnancy, mother, delivery and the fetus/ neonate. *BMC Complement Altern Med*. 2008;8:34.

243. Smith CA, Crowther CA, Grant SJ. Acupuncture for induction of labour. *Cochrane Database Syst Rev*. 2013(8)): Cd002962.
244. van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJ, Kamperman AM. Interventions to treat mental disorders during pregnancy: a systematic review and multiple treatment meta-analysis. *PLoS One*. 2017;12(3):e0173397.
245. Kukimoto Y, Ooe N, Ideguchi N. The effects of massage therapy on pain and anxiety after surgery: a systematic review and meta-analysis. *Pain Manag Nurs*. 2017;18(6):378–390.
246. Boyd C, Crawford C, Paat CF, Price A, Xenakis L, Zhang W. The impact of massage therapy on function in pain populations—a systematic review and meta-analysis of randomized controlled trials: part III, surgical pain populations. *Pain Med*. 2016;17(9):1757–1772.
247. Mitchinson AR, Kim HM, Rosenberg JM, et al. Acute postoperative pain management using massage as an adjuvant therapy: a randomized trial. *Arch Surg*. 2007;142(12): 1158–1167 discussion 1167.
248. Saatsaz S, Rezaei R, Alipour A, Beheshti Z. Massage as adjuvant therapy in the management of post-cesarean pain and anxiety: a randomized clinical trial. *Complement Ther Clin Pract*. 2016;24:92–98.
249. Braun LA, Stanguts C, Casanelia L, et al. Massage therapy for cardiac surgery patients–a randomized trial. *J Thorac Cardiovasc Surg*. 2012;144(6):1453–1459 1459.e1451.
250. Dion L, Rodgers N, Cutshall SM, et al. Effect of massage on pain management for thoracic surgery patients. *Int J Ther Massage Bodywork*. 2011;4(2):2–6.
251. Corbin L. Safety and efficacy of massage therapy for patients with cancer. *Cancer Control*. 2005;12(3):158–164.
252. Hughes D, Ladas E, Rooney D, Kelly K. Massage therapy as a supportive care intervention for children with cancer. *Oncol Nurs Forum*. 2008;35(3):431–442.
253. Mitchinson A, Fletcher CE, Kim HM, Montagnini M, Hinshaw DB. Integrating massage therapy within the palliative care of veterans with advanced illnesses: an outcome study. *Am J Hosp Palliat Care*. 2014;31(1):6–12.
254. Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG. A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. *Ann Intern Med*. 2003;138(11):898–906.
255. Ernst E. The safety of massage therapy. *Rheumatology (Oxford)*. 2003;42(9):1101–1106.
256. Yin P, Gao N, Wu J, Litscher G, Xu S. Adverse events of massage therapy in pain-related conditions: a systematic review. *Evid Based Complement Alternat Med*. 2014;2014:480956.
257. Li J, Zhou L, Wang Y. The effects of music intervention on burn patients during treatment procedures: a systematic review and meta-analysis of randomized controlled trials. *BMC Complement Altern Med*. 2017;17(1):158.
258. van der Heijden MJ, Oliai Araghi S, van Dijk M, Jeekel J, Hunink MG. The effects of perioperative music interventions in pediatric surgery: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2015;10(8):e0133608.
259. Lee JH. The effects of music on pain: a meta-analysis. *J Music Ther*. 2016;53(4):430–477.
260. Sen H, Yanarates O, Sizlan A, Kilic E, Ozkan S, Dagli G. The efficiency and duration of the analgesic effects of musical therapy on postoperative pain. *Agri*. 2010;22(4):145–150.
261. Kekecs Z, Nagy T, Varga K. The effectiveness of suggestive techniques in reducing postoperative side effects: a meta-analysis of randomized controlled trials. *Anesth Analg*. 2014;119(6):1407–1419.
262. Rosendahl J, Koranyi S, Jacob D, Zech N, Hansen E. Efficacy of therapeutic suggestions under general anesthesia: a systematic review and meta-analysis of randomized controlled trials. *BMC Anesthesiol*. 2016;16(1):125.
263. Jacobson AF, Umberger WA, Palmieri PA, et al. Guided imagery for total knee replacement: a randomized, placebo-controlled pilot study. *J Altern Complement Med*. 2016;22(7):563–575.
264. Li L, Yu F, Shi D, et al. Application of virtual reality technology in clinical medicine. *Am J Transl Res*. 2017;9(9):3867–3880.
265. Hoffman HG, Chambers GT, Meyer WJ 3rd, et al. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures. *Ann Behav Med*. 2011;41 (2):183–191.
266. McSherry T, Atterbury M, Gartner S, Helmold E, Searles DM, Schulman C. Randomized, crossover study of immersive Virtual Reality to decrease opioid use during painful wound care procedures in adults. *J Burn Care Res*. 2018;39(2):278–285.
267. Chirico A, Lucidi F, De Laurentiis M, Milanese C, Napoli A, Giordano A. Virtual Reality in health system: beyond entertainment. A mini-review on the efficacy of VR during cancer treatment. *J Cell Physiol*. 2016;231(2):275–287.
268. Won AS, Bailey J, Bailenson J, Tataru C, Yoon IA, Golianu B. Immersive Virtual Reality for pediatric pain. *children (Basel)*. 2017;4(7) pii. E52.
269. Dancel R, Liles EA, Fiore D. Acute pain management in hospitalized children. *Rev Recent Clin Trials*. 2017;12(4):277–283.
270. Paice JA, Portenoy R, Lacchetti C, et al. Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34 (27):3325–3345.
271. Asadpour R, Meng Z, Kessel KA, Combs SE. Use of acupuncture to alleviate side effects in radiation oncology: current evidence and future directions. *Adv Radiat Oncol*. 2016;1(4):344–350.
272. Ye Q, Xie Y, Shi J, Xu Z, Ou A, Xu N. Systematic review on acupuncture for treatment of dysphagia after stroke. *Evid Based Complement Alternat Med*. 2017;2017:6421852.
273. Garcia MK, Cohen L, Spano M, et al. Inpatient acupuncture at a major cancer center. *Integr Cancer Ther*. 2016;17(1):148–152.
274. Chien TJ, Hsu CH, Liu CY, Fang CJ. Effect of acupuncture on hot flush and menopause symptoms in breast cancer—a systematic review and meta-analysis. *PLoS One*. 2017;12(8):e0180918.
275. Al-Atiyyat N, Obaid A. Management of peripheral neuropathy induced by chemotherapy in adults with cancer: a review. *Int J Palliat Nurs*. 2017;23(1):13–17.
276. Boyd C, Crawford C, Paat CF, Price A, Xenakis L, Zhang W. The impact of massage therapy on function in pain populations—a systematic review and meta-analysis of randomized controlled trials: part II, cancer pain populations. *Pain Med*. 2016;17(8):1553–1568.
277. Jane SW, Chen SL, Wilkie DJ, et al. Effects of massage on pain, mood status, relaxation, and sleep in Taiwanese patients with metastatic bone pain: a randomized clinical trial. *Pain*. 2011;152(10):2432–2442.
278. Haun JN, Graham-Pole J, Shortley B. Children with cancer and blood diseases experience positive physical and psychological effects from massage therapy. *Int J Ther Massage Bodywork*. 2009;2(2):7–14.
279. Ackerman SL, Lown EA, Dvorak CC, et al. Massage for children undergoing hematopoietic cell transplantation: a qualitative report. *Evid Based Complement Alternat Med*. 2012;2012:792042.
280. Mikolasek M, Berg J, Witt CM, Barth J. Effectiveness of mindfulness- and relaxation-based ehealth interventions for patients with medical conditions: a systematic review and synthesis. *Int J Behav Med*. 2018;25(1):1–16.

281. Cramer H, Lauche R, Paul A, Dobos G. Mindfulness-based stress reduction for breast cancer—a systematic review and meta-analysis. *Curr Oncol*. 2012;19(5):e343–e352.
282. Haller H, Winkler MM, Klose P, Dobos G, Kummel S, Cramer H. Mindfulness-based interventions for women with breast cancer: an updated systematic review and meta-analysis. *Acta Oncol*. 2017;56(12):1665–1676.
283. Musial F, Büssing A, Heusser P, Choi KE, Ostermann T. Mindfulness-based stress reduction for integrative cancer care—a summary of evidence. *Complementary Med Res*. 2011;18(4):192–202.
284. Lee CE, Kim S, Kim S, Joo HM, Lee S. Effects of a mindfulness-based stress reduction program on the physical and psychological status and quality of life in patients with metastatic breast cancer. *Holist Nurs Pract*. 2017;31(4):260–269.
285. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med*. 2012;172(19):1444–1453.
286. MacPherson H, Vickers A, Bland M, et al. Acupuncture for chronic pain and depression in primary care: a programme of research. *Programme Grants Appl Res*. 2017;5(3).
287. Xiang A, Cheng K, Shen X, Xu P, Liu S. The immediate analgesic effect of acupuncture for pain: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2017;2017:3837194.
288. Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for chronic pain: update of an individual patient data meta-analysis. *J Pain* 2017. http://dx.doi.org/10.1016/j.jpain.2017.11.005.
289. Dimitrova A, Murchison C, Oken B. Acupuncture for the treatment of peripheral neuropathy: a systematic review and meta-analysis. *J Altern Complement Med*. 2017;23(3):164–179.
290. Yeh CH, Chiang YC, Hoffman SL, et al. Efficacy of auricular therapy for pain management: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2014;2014:934670.
291. Witt CM, Jena S, Brinkhaus B, Liecker B, Wegscheider K, Willich SN. Acupuncture for patients with chronic neck pain. *Pain*. 2006;125(1-2):98–106.
292. Willich SN, Reinhold T, Selim D, Jena S, Brinkhaus B, Witt CM. Cost-effectiveness of acupuncture treatment in patients with chronic neck pain. *Pain*. 2006;125(1-2):107–113.
293. Lin X, Huang K, Zhu G, Huang Z, Qin A, Fan S. The effects of acupuncture on chronic knee pain due to osteoarthritis: a meta-analysis. *J Bone Joint Surg Am*. 2016;98(18):1578–1585.
294. Woods B, Manca A, Weatherly H, et al. Cost-effectiveness of adjunct non-pharmacological interventions for osteoarthritis of the knee. *PLoS One*. 2017;12(3):e0172749.
295. Wang R, Li X, Zhou S, Zhang X, Yang K, Li X. Manual acupuncture for myofascial pain syndrome: a systematic review and meta-analysis. *Acupunct Med*. 2017;35(4):241–250.
296. Li X, Wang R, Xing X, et al. Acupuncture for myofascial pain syndrome: a network meta-analysis of 33 randomized controlled trials. *Pain Physician*. 2017;20(6):E883–e902.
297. Linde K, Allais G, Brinkhaus B, et al. Acupuncture for the prevention of tension-type headache. *Cochrane Database Syst Rev*. 2016;2016(4)Art.No.: CD007587.
298. Linde K, Allais G, Brinkhaus B, et al. Acupuncture for the prevention of episodic migraine. *Cochrane Database Syst Rev*. 2016;2016(6)Art.No.:CD001218.
299. Coeytaux RR, Befus D. Role of acupuncture in the treatment or prevention of migraine, tension-type headache, or chronic headache disorders. *Headache*. 2016;56(7):1238–1240.
300. Lee SH, Lim SM. Acupuncture for poststroke shoulder pain: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2016;2016:3549878.
301. Witt CM, Jena S, Brinkhaus B, Liecker B, Wegscheider K, Willich SN. Acupuncture in patients with osteoarthritis of the knee or hip: a randomized, controlled trial with an additional nonrandomized arm. *Arthritis Rheum*. 2006;54(11):3485–3493.
302. Wu JY, Zhang C, Xu YP, et al. Acupuncture therapy in the management of the clinical outcomes for temporomandibular disorders: a PRISMA-compliant meta-analysis. *Medicine (Baltimore)*. 2017;96(9):e6064.
303. Fernandes AC, Duarte Moura DM, Da Silva LGD, De Almeida EO, Barbosa GAS. Acupuncture in temporomandibular disorder myofascial pain treatment: a systematic review. *J Oral Facial Pain Headache*. 2017;31(3):225–232.
304. Crawford P, Penzien DB, Coeytaux R. Reduction in pain medication prescriptions and self-reported outcomes associated with acupuncture in a military patient population. *Med Acupunct*. 2017;29(4):229–231.
305. Ho RST, Chung VCH, Wong CHL, Wu JCY, Wong SYS, Wu IXY. Acupuncture and related therapies used as add-on or alternative to prokinetics for functional dyspepsia: overview of systematic reviews and network meta-analysis. *Sci Rep*. 2017;7(1):10320.
306. Xu Y, Zhao W, Li T, et al. Effects of acupoint-stimulation for the treatment of primary dysmenorrhoea compared with NSAIDs: a systematic review and meta-analysis of 19 RCTs. *BMC Complement Altern Med*. 2017;17(1):436.
307. Nahin RL, Boineau R, Khalsa PS, Stussman BJ, Weber WJ. Evidence-based evaluation of complementary health approaches for pain management in the United States. *Mayo Clin Proc*. 2016;91(9):1292–1306.
308. Crawford C, Boyd C, Paat CF, et al. The impact of massage therapy on function in pain populations-a systematic review and meta-analysis of randomized controlled trials: part I, patients experiencing pain in the general population. *Pain Med*. 2016;17:1353–1375.
309. Piper S, Shearer HM, Côté P, et al. The effectiveness of soft-tissue therapy for the management of musculoskeletal disorders and injuries of the upper and lower extremities: a systematic review by the Ontario Protocol for Traffic Injury management (OPTIMa) collaboration. *Man Ther*. 2016;21:18–34.
310. Perlman AI, Ali A, Njike VY, et al. Massage therapy for osteoarthritis of the knee: a randomized dose-finding trial. *PLoS One*. 2012;7(2):e30248.
311. Xu Q, Chen B, Wang Y, et al. The effectiveness of manual therapy for relieving pain, stiffness, and dysfunction in knee osteoarthritis: a systematic review and meta-analysis. *Pain Physician*. 2017;20(4):229–243.
312. Paige NM, Miake-Lye IM, Booth MS, et al. Association of spinal manipulative therapy with clinical benefit and harm for acute low back pain: systematic review and meta-analysis. *J Am Med Assoc*. 2017;317(14):1451–1460.
313. Gross A, Langevin P, Burnie SJ, et al. Manipulation and mobilisation for neck pain contrasted against an inactive control or another active treatment. *Cochrane Database Syst Rev*. 2015;2015(9) Art No.: CD004249.
314. Chaibi A, Russell MB. Manual therapies for cervicogenic headache: a systematic review. *J Headache Pain*. 2012;13(5):351–359.
315. Chaibi A, Tuchin PJ, Russell MB. Manual therapies for migraine: a systematic review. *J Headache Pain*. 2011;12(2):127–133.
316. Salamh P, Cook C, Reiman MP, Sheets C. Treatment effectiveness and fidelity of manual therapy to the knee: a systematic review and meta-analysis. *Musculoskeletal Care*. 2017;15(3):238–248.
317. Brantingham JW, Bonnefin D, Perle SM, et al. Manipulative therapy for lower extremity conditions: update of a literature review. *J Manipulative Physiol Ther*. 2012;35(2):127–166.

318. Brantingham JW, Cassa TK, Bonnefin D, et al. Manipulative therapy for shoulder pain and disorders: expansion of a systematic review. *J Manipulative Physiol Ther*. 2011;34(5):314–346.
319. Brantingham JW, Cassa TK, Bonnefin D, et al. Manipulative and multimodal therapy for upper extremity and temporomandibular disorders: a systematic review. *J Manipulative Physiol Ther*. 2013;36(3):143–201.
320. van der Velde G, Yu H, Paulden M, et al. Which interventions are cost-effective for the management of whiplash-associated and neck pain-associated disorders? A systematic review of the health economic literature by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *Spine J*. 2016;16(12):1582–1597.
321. Tsertsvadze A, Clar C, Court R, Clarke A, Mistry H, Sutcliffe P. Cost-effectiveness of manual therapy for the management of musculoskeletal conditions: a systematic review and narrative synthesis of evidence from randomized controlled trials. *J Manipulative Physiol Ther*. 2014;37(6):343–362.
322. Kranenburg HA, Schmitt MA, Puentedura EJ, Luijckx GJ, van der Schans CP. Adverse events associated with the use of cervical spine manipulation or mobilization and patient characteristics: a systematic review. *Musculoskelet Sci Pract*. 2017;28(2017):32–38.
323. Nielsen SM, Tarp S, Christensen R, Bliddal H, Klokker L, Henriksen M. The risk associated with spinal manipulation: an overview of reviews. *Syst Rev*. 2017;6(1):64.
324. Anheyer D, Haller H, Barth J, Lauche R, Dobos G, Cramer H. Mindfulness-based stress reduction for treating low back pain: a systematic review and meta-analysis. *Ann Intern Med*. 2017;166(11):799–807.
325. Bennell KL, Nelligan R, Dobson F, et al. Effectiveness of an Internet-delivered exercise and pain-coping skills training intervention for persons with chronic knee pain: a randomized trial. *Ann Intern Med*. 2017;166(7):453–462.
326. Dixon KE, Keefe FJ, Scipio CD, Perri LM, Abernethy AP. Psychological interventions for arthritis pain management in adults: a meta-analysis. *Health Psychol*. 2007;26(3):241–250.
327. Rini C, Porter LS, Somers TJ, et al. Automated internet-based pain coping skills training to manage osteoarthritis pain: a randomized controlled trial. *Pain*. 2015;156(5):837–848.
328. Ali A, Weiss TR, Dutton A, et al. Mindfulness-based stress reduction for adolescents with functional somatic syndromes: a pilot cohort study. *J Pediatr*. 2017;183:184–190.
329. Ruskin DA, Gagnon MM, Kohut SA, Stinson JN, Walker KS. A mindfulness program adapted for adolescents with chronic pain: feasibility, acceptability, and initial outcomes. *Clin J Pain*. 2017;33(11):1019–1029.
330. Bakhshani NM, Amirani A, Amirifard H, Shahrakipoor M. The effectiveness of mindfulness-based stress reduction on perceived pain intensity and quality of life in patients with chronic headache. *Glob J Health Sci*. 2015;8(4):142–151.
331. Hesse T, Holmes LG, Kennedy-Overfelt V, Kerr LM, Giles LL. Mindfulness-based intervention for adolescents with recurrent headaches: a pilot feasibility study. *Evid Based Complement Alternat Med*. 2015;2015:Art. ID.: 508958.
332. Rosenzweig S, Greeson JM, Reibel DK, Green JS, Jasser SA, Beasley D. Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice. *J Psychosom Res*. 2010;68(1):29–36.
333. Kabat-Zinn J, Lipworth L, Burney R. The clinical use of mindfulness meditation for the self-regulation of chronic pain. *J Behav Med*. 1985;8(2):163–190.
334. Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther*. 2016;45(1):5–31.
335. Wetherell JL, Afari N, Rutledge T, et al. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain*. 2011;152(9):2098–2107.
336. Wetherell JL, Petkus AJ, Alonso-Fernandez M, Bower ES, Steiner AR, Afari N. Age moderates response to acceptance and commitment therapy vs. cognitive behavioral therapy for chronic pain. *Int J Geriatr Psychiatry*. 2016;31(3):302–308.
337. Posadzki P, Ernst E. Guided imagery for musculoskeletal pain: a systematic review. *Clin J Pain*. 2011;27(7):648–653.
338. Posadzki P, Lewandowski W, Terry R, Ernst E, Stearns A. Guided imagery for non-musculoskeletal pain: a systematic review of randomized clinical trials. *J Pain Symptom Manage*. 2012;44(1):95–104.
339. Giacobbi PR Jr., Stabler ME, Stewart J, Jaeschke AM, Siebert JL, Kelley GA. Guided imagery for arthritis and other rheumatic diseases: a systematic review of randomized controlled trials. *Pain Manag Nurs*. 2015;16(5):792–803.
340. Zech N, Hansen E, Bernardy K, Hauser W. Efficacy, acceptability and safety of guided imagery/hypnosis in fibromyalgia—a systematic review and meta-analysis of randomized controlled trials. *Eur J Pain*. 2017;21(2):217–227.
341. Sielski R, Rief W, Glombiewski JA. Efficacy of biofeedback in chronic back pain: a meta-analysis. *Int J Behav Med*. 2017;24(1):25–41.
342. Nestoriuc Y, Rief W, Martin A. Meta-analysis of biofeedback for tension-type headache: efficacy, specificity, and treatment moderators. *J Consult Clin Psychol*. 2008;76(3):379–396.
343. Glombiewski JA, Bernardy K, Hauser W. Efficacy of EMG- and EEG-Biofeedback in fibromyalgia syndrome: a meta-analysis and a systematic review of randomized controlled trials. *Evid Based Complement Alternat Med*. 2013;2013:962741.
344. Theadom A, Cropley M, Smith HE, Feigin VL, McPherson K. Mind and body therapy for fibromyalgia. *Cochrane Database Syst Rev*. 2015;2015(4):Art. No.: CD001980.
345. Luctkar-Flude M, Groll D. A systematic review of the safety and effect of neurofeedback on fatigue and cognition. *Integr Cancer Ther*. 2015;14(4):318–340.
346. Wieland LS, Skoetz N, Pilkington K, Vempati R, D'Adamo CR, Berman BM. Yoga treatment for chronic non-specific low back pain. *Cochrane Database Syst Rev*. 2017;2017(1):Art. No.: CD010671.
347. Aboagye E, Karlsson ML, Hagberg J, Jensen I. Cost-effectiveness of early interventions for non-specific low back pain: a randomized controlled study investigating medical yoga, exercise therapy and self-care advice. *J Rehabil Med*. 2015;47(2):167–173.
348. Posadzki P, Ernst E, Terry R, Lee MS. Is yoga effective for pain? A systematic review of randomized clinical trials. *Complement Ther Med*. 2011;19(5):281–287.
349. Büssing A, Michalsen A, Khalsa SBS, Telles S, Sherman KJ. Effects of yoga on mental and physical health: a short summary of reviews. *Evid Based Complement Alternat Med*. 2012;2012(Art. ID.: 165410.).
350. Ward L, Stebbings S, Cherkin D, Baxter GD. Yoga for functional ability, pain and psychosocial outcomes in musculoskeletal conditions: a systematic review and meta-analysis. *Musculoskeletal Care*. 2013;11(4):203–217.
351. Kan L, Zhang J, Yang Y, Wang P. The effects of yoga on pain, mobility, and quality of life in patients with knee osteoarthritis: a systematic review. *Evid Based Complement Alternat Med*. 2016;2016:6016532.

352. Kim SD. Effects of yoga on chronic neck pain: a systematic review of randomized controlled trials. *J Phys Ther Sci*. 2016;28(7):2171–2174.
353. Bussing A, Ostermann T, Ludtke R, Michalsen A. Effects of yoga interventions on pain and pain-associated disability: a meta-analysis. *J Pain*. 2012;13(1):1–9.
354. Cramer H, Lauche R, Langhorst J, Dobos G. Is one yoga style better than another? A systematic review of associations of yoga style and conclusions in randomized yoga trials. *Complement Ther Med*. 2016;25:178–187.
355. Langhorst J, Klose P, Dobos GJ, Bernardy K, Hauser W. Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. *Rheumatol Int*. 2013;33(1):193–207.
356. Schulz-Heik RJ, Meyer H, Mahoney L, et al. Results from a clinical yoga program for veterans: yoga via telehealth provides comparable satisfaction and health improvements to in-person yoga. *BMC Complement Altern Med*. 2017;17(1):198.
357. Cramer H, Lauche R, Haller H, Dobos G. A systematic review and meta-analysis of yoga for low back pain. *Clin J Pain*. 2013;29(5):450–460.
358. Saper RB, Lemaster C, Delitto A, et al. Yoga, physical therapy, or education for chronic low back pain: a randomized noninferiority trial. *Ann Intern Med*. 2017;167(2):85–94.
359. Cramer H, Ward L, Saper R, Fishbein D, Dobos G, Lauche R. The safety of yoga: a systematic review and meta-analysis of randomized controlled trials. *Am J Epidemiol*. 2015;182(4):281–293.
360. Lauche R, Schumann D, Sibbritt D, Adams J, Cramer H. Associations between yoga practice and joint problems: a cross-sectional survey among 9151 Australian women. *Rheumatol Int*. 2017;37(7):1145–1148.
361. Cramer H, Krucoff C, Dobos G. Adverse events associated with yoga: a systematic review of published case reports and case series. *PLoS One*. 2013;8(10):e75515.
362. Kong LJ, Lauche R, Klose P, et al. Tai chi for chronic pain conditions: a systematic review and meta-analysis of randomized controlled trials. *Sci Rep*. 2016;6:25325.
363. Hall A, Copsey B, Richmond H, et al. Effectiveness of Tai chi for chronic musculoskeletal pain conditions: updated systematic review and meta-analysis. *Phys Ther*. 2016;97(2):227–238.
364. Solloway MR, Taylor SL, Shekelle PG, et al. An evidence map of the effect of Tai chi on health outcomes. *Syst Rev*. 2016;5(1):126.
365. Yeh GY, Chan CW, Wayne PM, Conboy L. The impact of Tai chi exercise on self-efficacy, social support, and empowerment in heart failure: insights from a qualitative sub-study from a randomized controlled trial. *PLoS One*. 2016;11(5):e0154678.
366. Wayne PM, Berkowitz DL, Litrownik DE, Buring JE, Yeh GY. What do we really know about the safety of Tai chi?: a systematic review of adverse event reports in randomized trials. *Arch Phys Med Rehabil*. 2014;95(12):2470–2483.
367. Woodman JP, Moore NR. Evidence for the effectiveness of Alexander technique lessons in medical and health-related conditions: a systematic review. *Int J Clin Pract*. 2012;66(1):98–112.
368. MacPherson H, Tilbrook H, Richmond S, et al. Alexander technique lessons or acupuncture sessions for persons with chronic neck pain: a randomized trial. *Ann Intern Med*. 2015;163(9):653–662.
369. Lin HT, Hung WC, Hung JL, Wu PS, Liaw LJ, Chang JH. Effects of Pilates on patients with chronic non-specific low back pain: a systematic review. *J Phys Ther Sci*. 2016;28(10):2961–2969.
370. Wells C, Kolt GS, Marshall P, Hill B, Bialocerkowski A. The effectiveness of Pilates exercise in people with chronic low back pain: a systematic review. *PLoS One*. 2014;9(7):e100402.
371. Cruz-Diaz D, Martinez-Amat A, Osuna-Perez MC, De la Torre-Cruz MJ, Hita-Contreras F. Short- and long-term effects of a six-week clinical Pilates program in addition to physical therapy on postmenopausal women with chronic low back pain: a randomized controlled trial. *Disabil Rehabil*. 2016;38(13):1300–1308.
372. Lundqvist LO, Zetterlund C, Richter HO. Effects of Feldenkrais method on chronic neck/scapular pain in people with visual impairment: a randomized controlled trial with one-year follow-up. *Arch Phys Med Rehabil*. 2014;95(9):1656–1661.
373. Yamato TP, Maher CG, Saragiotto BT, et al. Pilates for low back pain. *Sao Paulo Med J*. 2016;134(4):366–367.
374. Yamato TP, Maher CG, Saragiotto BT, et al. Pilates for low back pain. *Cochrane Database Syst Rev*. 2015;2015(7) Art. No.: CD010265.
375. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;2017(4):Art. No.: CD011279.
376. MacPherson H, Maschino AC, Lewith G, et al. Characteristics of acupuncture treatment associated with outcome: an individual patient meta-analysis of 17,922 patients with chronic pain in randomised controlled trials. *PLoS One*. 2013;8(10):e77438.
377. Kligler B, Nielsen A, Kohrrer C, et al. Acupuncture therapy in a group setting for chronic pain. *Pain Med*. 2017(0):1–11.
378. Geller JS, Kulla J, Shoemaker A. Group medical visits using an empowerment-based model as treatment for women with chronic pain in an underserved community. *Glob Adv Health Med*. 2015;4(6):27–60.
379. Cecchi F, Molino-Lova R, Chiti M, et al. Spinal manipulation compared with back school and with individually delivered physiotherapy for the treatment of chronic low back pain: a randomized trial with one-year follow-up. *Clin Rehabil*. 2010;24(1):26–36.
380. Cherkin DC, Anderson ML, Sherman KJ, et al. Two-year follow-up of a randomized clinical trial of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care for chronic low back pain. *J Am Med Assoc*. 2017;317(6):642–644.
381. National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health & Human Development. Epigenetics and Developmental Epigenetics: Condition Information. Available at: 〈https://www.nichd.nih.gov/health/topics/epigenetics/conditioninfo/Pages/default.aspx〉. Accessed July 15, 2017.
382. Janke EA, Collins A, Kozak AT. Overview of the relationship between pain and obesity: What do we know? Where do we go next? *J Rehabil Res Dev*. 2007;44(2):245–262.
383. Anandacoomarasamy A, Fransen M, March L. Obesity and the musculoskeletal system. *Curr Opin Rheumatol*. 2009;21(1):71–77.
384. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009;9:88.
385. Okifuji A, Hare BD. The association between chronic pain and obesity. *J Pain Res*. 2015;8:399–408.
386. Lei X, Seldin MM, Little HC, Choy N, Klonisch T, Wong GW. C1q/TNF-related protein 6 (CTRP6) links obesity to adipose tissue inflammation and insulin resistance. *J Biol Chem*. 2017;292(36):14836–14850.
387. Wearing SC, Hennig EM, Byrne NM, Steele JR, Hills AP. Musculoskeletal disorders associated with obesity: a biomechanical perspective. *Obes Rev*. 2006;7(3):239–250.
388. Hussain SM, Urquhart DM, Wang Y, et al. Fat mass and fat distribution are associated with low back pain intensity and disability: results from a cohort study. *Arthritis Res Ther*. 2017;19(1):26.

389. Ryan CG, Vijayaraman A, Denny V, et al. The association between baseline persistent pain and weight change in patients attending a specialist weight management service. *PLoS One*. 2017;12(6):e0179227.
390. Rappaport SM, Smith MT. Epidemiology. Environment and disease risks. *Science*. 2010;330(6003):460–461.
391. Weinhold B. Epigenetics: the science of change. *Environ Health Perspect*. 2006;114(3):A160–A167.
392. Thimmapuram J, Pargament R, Sibliss K, Grim R, Risques R, Toorens E. Effect of heartfulness meditation on burnout, emotional wellness, and telomere length in health care professionals. *J Community Hosp Intern Med Perspect*. 2017;7(1):21–27.
393. von Zglinicki T. Role of oxidative stress in telomere length regulation and replicative senescence. *Ann N Y Acad Sci*. 2000;908:99–110.
394. Jacobs TL, Epel ES, Lin J, et al. Intensive meditation training, immune cell telomerase activity, and psychological mediators. *Psychoneuroendocrinology*. 2011;36(5):664–681.
395. Nothlings U, Ford ES, Kroger J, Boeing H. Lifestyle factors and mortality among adults with diabetes: findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study. *J Diabetes*. 2010;2(2):112–117.
396. Minihane AM, Vinoy S, Russell WR, et al. Low-grade inflammation, diet composition and health: current research evidence and its translation. *Br J Nutr*. 2015;114(7):999–1012.
397. Kiecolt-Glaser JK. Stress, food, and inflammation: psychoneuroimmunology and nutrition at the cutting edge. *Psychosom Med*. 2010;72(4):365–369.
398. Pogacnik Murillo AL, Eckstein F, Wirth W, et al. Impact of diet and/or exercise intervention on infrapatellar fat pad morphology: secondary analysis from the intensive diet and exercise for arthritis (IDEA) trial. *Cells Tissues Organs*. 2017;203(4):258–266.
399. Green JA, Hirst-Jones KL, Davidson RK, et al. The potential for dietary factors to prevent or treat osteoarthritis. *Proc Nutr Soc*. 2014;73(2):278–288.
400. Cooper MA, Ryals JM, Wu PY, Wright KD, Walter KR, Wright DE. Modulation of diet-induced mechanical allodynia by metabolic parameters and inflammation. *J Peripher Nerv Syst*. 2017;22(1):39–46.
401. Schwalfenberg GK. The alkaline diet: is there evidence that an alkaline pH diet benefits health? *J Environ Public Health*. 2012;2012:(Art. ID.:):727630.
402. Sui BD, Xu TQ, Liu JW, et al. Understanding the role of mitochondria in the pathogenesis of chronic pain. *Postgrad Med J*. 2013;89(1058):709–714.
403. Morris G, Berk M, Galecki P, Walder K, Maes M. The neuro-immune pathophysiology of central and peripheral fatigue in systemic immune-inflammatory and neuro-immune diseases. *Mol Neurobiol*. 2016;53(2):1195–1219.
404. Neustadt J, Pieczenik SR. Medication-induced mitochondrial damage and disease. *Mol Nutr Food Res*. 2008;52(7):780–788.
405. Marriage B, Clandinin MT, Glerum DM. Nutritional cofactor treatment in mitochondrial disorders. *J Am Diet Assoc*. 2003;103(8):1029–1038.
406. Apostolova N, Victor VM. Molecular strategies for targeting antioxidants to mitochondria: therapeutic implications. *Antioxid Redox Signal*. 2015;22(8):686–729.
407. Agarwal KA, Tripathi CD, Agarwal BB, Saluja S. Efficacy of turmeric (curcumin) in pain and postoperative fatigue after laparoscopic cholecystectomy: a double-blind, randomized placebo-controlled study. *Surg Endosc*. 2011;25(12):3805–3810.
408. Daily JW, Yang M, Park S. Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: a systematic review and meta-analysis of randomized clinical trials. *J Med Food*. 2016;19(8):717–729.
409. Perkins K, Sahy W, Beckett RD. Efficacy of curcuma for treatment of osteoarthritis. *J Evid Based Complementary Altern Med*. 2017;22(1):156–165.
410. Onakpoya IJ, Spencer EA, Perera R, Heneghan CJ. Effectiveness of curcuminoids in the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomized clinical trials. *Int J Rheum Dis*. 2017;20(4):420–433.
411. Gaffey A, Campbell J, Porritt K, Slater H. The effects of curcumin on musculoskeletal pain: a systematic review protocol. *JBI Database System Rev Implement Rep*. 2015;13(2):59–73.
412. Korzenik J, Koch AK, Langhorst J. Complementary and integrative gastroenterology. *Med Clin North Am*. 2017;101(5):943–954.
413. Langhorst J, Wulfert H, Lauche R, et al. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. *J Crohns Colitis*. 2015;9(1):86–106.
414. Marx W, McCarthy AL, Ried K, et al. The effect of a standardized ginger extract on chemotherapy-induced nausea-related quality of life in patients undergoing moderately or highly emetogenic chemotherapy: a double blind, randomized, placebo controlled trial. *Nutrients*. 2017;9(8) pii: E867.
415. Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutr J*. 2014;13(20).
416. Lakhan SE, Ford CT, Tepper D. Zingiberaceae extracts for pain: a systematic review and meta-analysis. *Nutr J*. 2015;14:50.
417. Terry R, Posadzki P, Watson LK, Ernst E. The use of ginger (Zingiber officinale) for the treatment of pain: a systematic review of clinical trials. *Pain Med*. 2011;12(12):1808–1818.
418. Lantz RC, Chen GJ, Sarihan M, Solyom AM, Jolad SD, Timmermann BN. The effect of extracts from ginger rhizome on inflammatory mediator production. *Phytomedicine*. 2007;14(2-3):123–128.
419. Bartels EM, Folmer VN, Bliddal H, et al. Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage*. 2015;23(1):13–21.
420. Daily JW, Zhang X, Kim DS, Park S. Efficacy of ginger for alleviating the symptoms of primary dysmenorrhea: a systematic review and meta-analysis of randomized clinical trials. *Pain Med*. 2015;16(12):2243–2255.
421. Sandberg O, Aspenberg P. Different effects of indomethacin on healing of shaft and metaphyseal fractures. *Acta Orthop*. 2015;86(2):243–247.
422. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. *Am J Ther*. 2000;7(2):115–121.
423. Marx W, McKavanagh D, McCarthy AL, Bird R, Ried K, Chan A. The effect of ginger (Zingiber officinale) on platelet aggregation: a systematic literature review. *PLoS One*. 2015;10(10):e0141119.
424. Huang KC, Huang TW, Yang TY, Lee MS. Chronic NSAIDs use increases the risk of a second hip fracture in patients after hip fracture surgery: evidence from a STROBE-compliant population-based study. *Medicine (Baltimore)*. 2015;94(38):e1566.
425. Bird JK, Murphy RA, Ciappio ED, McBurney MI. Risk of deficiency in multiple concurrent micronutrients in children and adults in the United States. *Nutrients*. 2017;9(7) pii: E655.

426. Rehm CD, Drewnowski A. Trends in consumption of solid fats, added sugars, sodium, sugar-sweetened beverages, and fruit from fast food restaurants and by fast food restaurant type among us children, 2003-2010. *Nutrients*. 2016;8(12) pii: E804.
427. Al-Eisa ES, Alghadir AH, Gabr SA. Correlation between vitamin D levels and muscle fatigue risk factors based on physical activity in healthy older adults. *Clin Interv Aging*. 2016;11:513–522.
428. de Oliveira DL, Hirotsu C, Tufik S, Andersen ML. The interfaces between vitamin D, sleep and pain. *J Endocrinol*. 2017;234(1):R23–R36.
429. Martin KR, Reid DM. Is there role for vitamin D in the treatment of chronic pain? *Ther Adv Musculoskelet Dis*. 2017;9(6):131–135.
430. Scott JF, Das LM, Ahsanuddin S, et al. Oral vitamin D rapidly attenuates inflammation from sunburn: an interventional study. *J Invest Dermatol*. 2017;137(10):2078–2086.
431. Demirkaya S, Vural O, Dora B, Topcuoglu MA. Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. *Headache*. 2001;41(2):171–177.
432. Chiu HY, Yeh TH, Huang YC, Chen PY. Effects of intravenous and oral magnesium on reducing migraine: a meta-analysis of randomized controlled trials. *Pain Physician*. 2016;19(1):E97–E112.
433. Brill S, Sedgwick PM, Hamann W, Di Vadi PP. Efficacy of intravenous magnesium in neuropathic pain. *Br J Anaesth*. 2002;89(5):711–714.
434. Rondon LJ, Privat AM, Daulhac L, et al. Magnesium attenuates chronic hypersensitivity and spinal cord NMDA receptor phosphorylation in a rat model of diabetic neuropathic pain. *J Physiol*. 2010;588(Pt 21):4205–4215.
435. Bujalska-Zadrozny M, Tatarkiewicz J, Kulik K, Filip M, Naruszewicz M. Magnesium enhances opioid-induced analgesia—what we have learnt in the past decades? *Eur J Pharm Sci*. 2017;99:113–127.
436. Abdulrazaq M, Innes JK, Calder PC. Effect of omega-3 polyunsaturated fatty acids on arthritic pain: a systematic review. *Nutrition*. 2017;39-40:57–66.
437. Lee YH, Bae SC, Song GG. Omega-3 polyunsaturated fatty acids and the treatment of rheumatoid arthritis: a meta-analysis. *Arch Med Res*. 2012;43(5):356–362.
438. Green R, Allen LH, Bjorke-Monsen AL, et al. Vitamin B12 deficiency. *Nat Rev Dis Primers*. 2017;3:17040.
439. Yang YX, Metz DC. Safety of Proton Pump Inhibitor exposure. *Gastroenterology*. 2010;139(4):1115–1127.
440. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. *BMJ Open*. 2017;7(6):e015735.
441. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2015;2015(1):Art. No.: CD004376.
442. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev*. 2014;2014(4) Art. No.: CD007912.
443. Hearing CM, Chang WC, Szuhany KL, Deckersbach T, Nierenberg AA, Sylvia LG. Physical exercise for treatment of mood disorders: a critical review. *Curr Behav Neurosci Rep*. 2016;3(4):350–359.
444. Choy EH. The role of sleep in pain and fibromyalgia. *Nat Rev Rheumatol*. 2015;11(9):513–520.
445. Schuh-Hofer S, Wodarski R, Pfau DB, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. *Pain*. 2013;154(9):1613–1621.
446. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *J Am Med Assoc*. 2004;291(10):1238–1245.
447. Herman PM. Evaluating the economics of complementary and integrative medicine. *Glob Adv Health Med*. 2013;2(2):56–63.
448. Ratcliffe J, Thomas KJ, MacPherson H, Brazier J. A randomised controlled trial of acupuncture care for persistent low back pain: cost effectiveness analysis. *Br Med J*. 2006;333(7569):626.
449. Herman PM, Szczurko O, Cooley K, Mills EJ. Cost-effectiveness of naturopathic care for chronic low back pain. *Altern Ther Health Med*. 2008;14(2):32–39.
450. Taylor P, Pezzullo L, Grant SJ, Bensoussan A. Cost-effectiveness of acupuncture for chronic nonspecific low back pain. *Pain Pract*. 2014;14(7):599–606.
451. Whitehurst DG, Bryan S, Hay EM, Thomas E, Young J, Foster NE. Cost-effectiveness of acupuncture care as an adjunct to exercise-based physical therapy for osteoarthritis of the knee. *Phys Ther*. 2011;91(5):630–641.
452. Wonderling D, Vickers AJ, Grieve R, McCarney R. Cost effectiveness analysis of a randomised trial of acupuncture for chronic headache in primary care. *Br Med J*. 2004;328(7442):747.
453. Wu MY, Huang MC, Chiang JH, Sun MF, Lee YC, Yen HR. Acupuncture decreased the risk of coronary heart disease in patients with fibromyalgia in Taiwan: a nationwide matched cohort study. *Arthritis Res Ther*. 2017;19(1):37.
454. Lin CW, Haas M, Maher CG, Machado LA, van Tulder MW. Cost-effectiveness of guideline-endorsed treatments for low back pain: a systematic review. *Eur Spine J*. 2011;20(7):1024–1038.
455. Luciano JV, D'Amico F, Feliu-Soler A, et al. Cost-utility of group acceptance and commitment therapy for fibromyalgia versus recommended drugs: an economic analysis alongside a 6-month randomized controlled trial conducted in Spain (EFFIGACT Study). *J Pain*. 2017;18(7):868–880.
456. Mahrer NE, Gold JI, Luu M, Herman P. A cost-analysis of an interdisciplinary pediatric chronic pain clinic. *J Pain*. 2018;19(2):158–165.
457. Kligler B, Homel P, Harrison LB, Levenson HD, Kenney JB, Merrell W. Cost savings in inpatient oncology through an integrative medicine approach. *Am J Manag Care*. 2011;17(12):779–784.
458. 〈Acufinder.com〉. How Much Does an Acupuncture Treatment Cost? 2017. Available at: 〈https://www.acufinder.com/Acupuncture+Information/Detail/How+much+does+an+acupuncture+treatment+cost+〉. Accessed August 15, 2017.
459. Carnes D, Homer KE, Miles CL, et al. Effective delivery styles and content for self-management interventions for chronic musculoskeletal pain: a systematic literature review. *Clin J Pain*. 2012;28(4):344–354.
460. Costhelper health. How Much Does a Chiropracter Cost? 〈http://health.costhelper.com/chiropractor.html〉. 2017 Accessed August 15, 2017.
461. 〈howmuchisit.org〉. How Much do Pilates Classes Cost? 〈https://www.howmuchisit.org/pilates-classes-cost/〉. 2017 Accessed August 15, 2017.
462. Holistic Medicine Health Library. Feldenkrais. 〈https://consumer.healthday.com/encyclopedia/holistic-medicine-25/mis-alternative-medicine-news-19/feldenkrais-647530.html〉. 2017 Accessed August 15, 2017.
463. Schoomaker E, Buckenmaier IIIC. *Call to Action: "If Not Now, When? If Not You, Who?" Pain Med*. 2014;15(S1):S4–S6.
464. Murthy VH. Ending the opioid epidemic—a call to action. *N Engl J Med*. 2016;375(25):2413–2415.