Update in Pain Medicine

Daniel P. Alford, MD, MPH¹, Erin E. Krebs, MD, MPH², Ian A. Chen, MD, MPH³,
Christina Nicolaidis, MD, MPH⁴, Matthew J. Bair, MD, MS², and Jane Liebschutz, MD, MPH^{1,5}

¹ Boston University School of Medicine and Boston Medical Center, Boston, MA, USA; ² VA Center on Implementing Evidence-Based Practice and Indiana University School of Medicine, Indianapolis, IN, USA; ³ Eastern Virginia Medical School, Norfolk, VA, USA; ⁴ Oregon Health and Science University, Portland, OR, USA; ⁵ Boston University School of Public Health, Boston, MA, USA.

KEY WORDS: primary care; chronic pain; analgesics; opioids; complementary and alternative medicine.

J Gen Intern Med 25(11):1222–6

DOI: 10.1007/s11606-010-1452-4

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INTRODUCTION

More than 75 million Americans have chronic pain.¹ Pain accounts for 20% of all outpatient visits² and over \$100 billion dollars per year in direct and indirect costs;³ analgesics account for 12% of all prescriptions.⁴ Our aims were to review recent pain medicine studies and their key findings, and to discuss the implications of these findings for generalist clinical practice.

We systematically searched from January 1, 2008 through December 31, 2009 for peer-reviewed articles that could potentially change generalist care of patients with chronic pain. We searched MEDLINE and PubMed using the medical subject heading (MeSH) terms Pain, Arthritis, Fibromyalgia, Headache Disorders, Pain Measurement, Analgesics or *Narcotics*, and keywords for chronic, persistent, noncancer or primary care, excluding acute pain, postoperative pain, cancer pain, chest pain and pediatrics, and limiting to humans, English language and study type (trial, epidemiologic, review, meta-analysis or guideline). Members of the Society of General Internal Medicine's Pain Medicine Interest Group also suggested relevant articles. The search produced 1,051 references that were narrowed down to 47 based on relevance to generalist practice. Using a 5-point Likert scale, we independently rated these articles on impact on general internal medicine clinical practice, clinical policy and research and quality of study methods. We selected ten articles with the highest ratings.

ASSESSMENT

Krebs EE, Lorenz KA, Bair MJ et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med. 2009; 24 (6):733–738.

Single-item pain assessments do not adequately measure chronic pain, yet multi-dimensional pain scales such as the Brief Pain Inventory (BPI) are impractical for use in primary care. This study developed an ultra-brief pain measure derived from the BPI. Krebs et al. conducted a secondary data analysis of two primary care studies: a longitudinal study of 500 patients with chronic pain and a cross-sectional study of 646 veterans.

The authors assessed reliability (Cronbach's alpha), construct validity (Pearson's correlation coefficients) relative to other measures of pain and function, and responsiveness to change. The resulting scale consists of three items ("Pain average," "interference with Enjoyment of life" and "interference with General activity," or PEG). The PEG demonstrated good internal consistency (alpha 0.73–0.89), construct validity ($r=0.6$ – 0.95) and responsiveness to change.

Implications for Practice

The PEG is an appealing instrument to use in primary care because of its brevity and assessment of multiple domains of pain. This study suggests that the PEG has good psychometric properties, and its responsiveness to change is equivalent to the full BPI, from which it is derived. Replacing the commonly used single-item 0–10 Numeric Rating Scale with the three-item PEG may be a desirable strategy in primary care settings. The incremental "cost" of asking three items instead of one appears to be small relative to the potential gain in a more comprehensive understanding of patients' pain experiences.

COLLABORATIVE CARE

Becker A, Leonhardt C, Kochen MM, et al. Effects of two guideline implementation strategies on patient outcomes in primary care: a cluster randomized controlled trial. Spine. 2008;33(5): 473–480.

Although high-quality low back pain (LBP) guidelines are widely available, evidence-based LBP management strategies are inconsistently applied in primary care. The best methods of LBP guideline implementation are unclear. This trial randomized 118 German primary care practices to one of two LBP guideline implementation strategies or to a mailed guidelines control. The implementation strategies included physician education (three seminars and two academic detailing sessions) alone or physician education plus nurse training in motivational counseling (two full-day seminars and one to

Received June 3, 2010

Revised June 18, 2010

Accepted June 30, 2010

Published online July 15, 2010

three supervised practice sessions). Participating physicians enrolled 1,278 patients (fewer than the enrollment target of 1,874).

Most participants were male (58%) and employed (55%). Compared with those in the control group, patients in the nurse training group improved significantly more on the primary outcome of functional capacity at 6 months ($p=0.032$). There was no difference between the physician education only and control groups ($p=0.120$). Intervention patients reported fewer days in pain than control patients (16.4 and 17.9 fewer days).

Implications for Practice

Intervention effects were small, but the results have significant implications for generalist practice. First, the study enrolled a broad group of patients with LBP, of whom <50% had pain at follow-up. Many patients had resolution of their pain, which may partially explain the modest intervention effects on pain-related function. Second, the intervention was relatively non-intensive and was delivered distal to the clinical encounter. Although this likely reduced the intervention effect, implementation of a similar intervention in actual practice would be more feasible. Considering these factors, the finding of a small improvement in patient function is impressive.

The trial's finding that training both clinic nurses and physicians improved patient function, whereas training physicians alone did not, supports the concept of team-based primary care for back pain. Although some guideline-recommended practices can be implemented by physicians alone (e.g., limiting imaging tests), others may be challenging for physicians to implement without support (e.g., counseling for increased physical activity).⁵ Nurses may be better equipped to provide patient education and counseling interventions.

Dobscha SK, Corson K, Perrin NA et al. Collaborative care for chronic pain in primary care: a cluster randomized trial. *JAMA*. 2009; 301(12):1242–1252.

Collaborative interventions based on the chronic care model have been studied in numerous conditions,⁶ but have not been rigorously evaluated for chronic pain management. Dobscha et al. evaluated a multifaceted collaborative care intervention for chronic musculoskeletal pain in five Veterans Affairs (VA) primary care clinics. They randomized 42 primary care clinicians to the collaborative care intervention or usual care control. The intervention included pain management training for clinicians, pain education classes for patients, and care management by a full-time psychologist who assessed patients, developed tailored care recommendations collaboratively with a pain consultant and followed up with patients by phone. Patients ($n=401$) with chronic musculoskeletal pain of at least moderate pain severity and disability were enrolled.

Most participants were male (92%) and had long-standing pain (mean=10 years); 32% were employed. The mean number of contacts with the collaborative care team was ten, including an average of five phone contacts. On the primary outcome (pain-related disability) at 12 months, intervention patients improved significantly more than controls ($p=0.004$). A higher proportion of intervention patients experienced clinically important improvements of $\geq 30\%$ than controls (22% vs. 14%, $p=0.04$, NNT=12.7). Secondary outcomes of pain intensity and

depression severity were also improved in the intervention group. The intervention cost \$1,200 per patient.

Implications for Practice

This trial showed that a collaborative primary care-based intervention can lead to modest, yet important improvements in pain outcomes among highly disabled, long-term pain sufferers. The collaborative care team directly intervened with patients by clinically assessing and reassessing them, delivering education to them, and providing their clinicians with individualized treatment recommendations. Even then, the intervention was relatively inexpensive, as it involved only one additional full-time clinician (the psychologist care manager) and 10% of an internist consultant's time. Considering the amount of health care consumed by patients with severe chronic pain,⁷ an investment in collaborative care could be a bargain.

Clinician satisfaction, an important outcome, was not reported in this study. In a previous paper, Dobscha et al. reported three-fourths of VA primary care clinicians rated chronic pain management as a major source of frustration.⁸ Improving satisfaction of primary care providers is another compelling reason to implement collaborative care interventions that support both patients and providers in addressing chronic pain.

CHRONIC PAIN AND DEPRESSION

Kroenke K, Bair MJ, Damush TM, et al. Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. *JAMA*. 2009;301(20): 2099–2110.

Pain and depression frequently coexist (30%–50% co-occurrence), leading to poor health-related quality of life (HRQoL).^{9,10} This study evaluated a stepped-care intervention including optimized antidepressant therapy combined with a pain self-management program to improve pain and depression outcomes. The study randomized 250 patients with chronic low back, hip, or knee pain of moderate severity and depression of moderate severity to intervention versus usual care. At 12 months, intervention patients were more likely than controls to experience a 50% reduction from baseline in depression severity (37.4% versus 16.5%, RR 2.3, $p<0.001$). Intervention patients also showed statistically significant improvements in pain severity and interference and in secondary outcomes (anxiety and HRQoL).

Implications for Practice

This trial demonstrated that optimized antidepressant therapy combined with a pain self-management program was beneficial for treating patients with co-occurring depression and pain. Improvements in depression and pain were seen early and sustained over 12 months. The improvements in pain severity and interference are noteworthy since analgesics were not a specific intervention component. The optimized antidepressant therapy included an algorithmic approach using several classes of antidepressants. This pragmatic, patient-tailored approach is more similar to clinical practice than an

inflexible testing of a single drug or class. Practitioners should screen for co-morbid depression and pain in their patients, and consider optimized antidepressant therapy and self-management strategies as essential tools in the treatment of these patients.

OPIOIDS AND CHRONIC PAIN

Weisner CM, Campbell CI, Ray GT, et al. Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain* 2009;145(3): 287–293.

The efficacy and risks of long-term opioids in patients with substance abuse histories are poorly understood and prescribing practices not well described. Experts recognize that patients with substance use disorders commonly have pain that needs to be treated, but advise caution when prescribing opioids in this context. This study examined trends and characteristics of long-term opioid use in patients with non-cancer pain and substance use disorders (SUD). Administrative data from two large community health plans (Kaiser Permanente of Northern California and Group Health Cooperative of Seattle Washington) were evaluated. Long-term opioid use was defined as treatment >90 days. From 1997–2005, opioid prescribing increased dramatically for patients with SUD diagnosed prior to opioid prescription and was highest for those with an opioid use disorder. Patients with a SUD history were prescribed significantly more opioids (dose, potency and supply) and more concurrent sedative-hypnotics compared to patients without SUD histories. Additional findings were that more than a third of patients with a SUD history and almost three-fourths with a prior opioid use disorder received these diagnoses from addiction or psychiatric providers, rather than from the prescriber of the long-term opioid.

Implications for Practice

The increasing opioid prescribing for patients with SUD reported in this study are of unclear clinical appropriateness. Experimental studies¹¹ have shown higher pain sensitivity among these patients, and observational studies¹² have shown they have a greater risk of prescription opioid misuse. This study did not examine whether opioid prescribers were aware of their patients' substance use histories. At a minimum, generalists should screen all patients with chronic pain for a history of substance abuse before prescribing long-term opioids. Single-item screening^{13,14} tests for at-risk substance use are now available. Patient monitoring with "universal precautions"¹⁵, including opioid treatment agreements and urine drug testing, are recommended for all patients prescribed long-term opioids for chronic pain. The level of monitoring may be reasonably intensified (e.g., pill counts and random urine drug testing) for patients with a history of substance use disorders. In addition, based on the high rate of concurrent sedative use, generalists should carefully educate these patients about the risk of over-sedation.

Chou R, Fanciullo GJ, Fine PG et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113–130.

A multidisciplinary expert panel, commissioned by the American Pain Society and the American Academy of Pain

Medicine, conducted a systematic review of the evidence and developed evidence-based guidelines for use of chronic opioid therapy in chronic non-cancer pain. They reviewed the literature through November 2007, including 8,034 relevant abstracts. The expert panel met three times between September 2006 and January 2008, using methods adapted from the GRADE working group and multi-stage Delphi process. The panel found that evidence was limited, with many "research gaps," but concluded that chronic opioids "can be an effective therapy for carefully selected and monitored patients with chronic non-cancer pain." Recommendations were provided on topics including: patient selection, medication management plans, monitoring strategies, prevention and management of adverse effects, and use of psychotherapeutic co-interventions.

Implications for Practice

These recommendations provide a reasonable and comprehensive guide for general internists when prescribing long-term opioids for chronic pain. As the authors acknowledge, many of their recommendations are limited by reliance on low-quality evidence. The Chou et al. companion paper on research gaps in opioid use provides important background to the guidelines.¹⁶ Recommendations related to assessing substance abuse risk, using informed consents and monitoring strategies, including urine drug testing for "high risk" patients, and counseling patients about driving risk are likely to become accepted "standard of care" until research emerges to better guide clinical practice.

CANNABIS AND CHRONIC PAIN

Martin-Sanchez E, Furukawa TA, Taylor J, Martin JLR. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med* 2009;10(8):1353–1368.

Cannabis has been used for the treatment of various conditions, including chronic pain; however, little is known about its effectiveness or harms. The authors conducted a systematic review and meta-analysis of double-blind randomized controlled trials comparing cannabis preparations to placebo in patients with chronic pain. Cannabis preparations varied in dose, duration and route of administration (oral or nasal). The authors excluded one study of smoked cannabis on "ethical grounds." Of 229 studies, 18 met the inclusion criteria, but only 7 trials could be quantitatively analyzed because of data reporting limitations.

Cannabis reduced pain intensity compared to placebo, with an overall effect size of -0.61 (-0.84 to -0.37). The identified harms included euphoria (OR 4.11; NNH 8), dysphoria (OR 2.56; NNH 29), disturbances in perception (OR 4.5; NNH 7) and motor function (speech, ataxia, twitching, numbness; OR 3.9; NNH 5), altered cognitive function (OR 4.4; NNH 8) and gastrointestinal side effects (risks noted, but no summary due to heterogeneity.)

Implications for Practice

This study summarizes the evidence for benefits and harms of cannabis-derived compounds in the treatment of chronic pain. Notable limitations of the existing literature include small

sample sizes ($n=13-177$), short follow-up periods (mean=25 days), incomplete outcome reporting and exclusion of studies of smoked cannabis. Benefits and risks do not seem very dissimilar from other pharmacologic treatments (e.g., opioids) for chronic pain. This study offers preliminary evidence to inform the complex clinical decisions of risk-benefit for individual patients. Clearly, more rigorous studies are needed to better understand the risks and benefits of cannabis preparations for treating chronic pain.

COMPLEMENTARY AND ALTERNATIVE TREATMENTS

Cherkin DC, Sherman KJ, Avins AL, et al. A randomized trial comparing acupuncture, simulated acupuncture, and usual care for chronic low back pain. *Arch Intern Med.* 2009;169(9):858-866.

Back pain is the leading reason for visits to acupuncturists.¹⁷ Several recent European trials have suggested that real acupuncture and "sham" acupuncture are equally effective.¹⁸⁻²⁰ This four-arm randomized controlled trial compared individually tailored acupuncture, standard acupuncture, simulated acupuncture (non-insertive) and usual care for 638 adults with mechanical low back pain. Detailed blinding procedures prevented acupuncture patients from knowing their treatment assignment. At 8 weeks, all three acupuncture arms had significantly lower pain disability scores than the usual care arm. Clinically meaningful improvements occurred in 60% of acupuncture patients compared with 30% in usual care ($P<0.001$). Improvements persisted at 1 year. There were no differences between individually tailored, standard and simulated acupuncture.

Implication for Practice

Acupuncture appears to be effective for improving back pain-related disability. Interestingly, insertion of needles and individual tailoring by acupuncturists did not make a difference in outcomes. For practitioners, the mechanism for effectiveness may not be as relevant as having an effective non-pharmacological therapy with minimal risks in the armamentarium of treatment options for the low back pain. Clinical trials evaluating the efficacy of acupuncture for various conditions have been conducted; however, most were poorly designed, and few included treatment protocols that can be applied in actual clinical practice. This study was rigorously conducted and raises questions about the putative mechanism of action for acupuncture's effectiveness. Similarly, although exercise for back pain has been shown to improve work disability,²¹ it doesn't appear that the type of exercise itself makes the difference.²² Thus, physicians should encourage patients who express interest in acupuncture to pursue it as a reasonable option.

TREATMENT FOR SPECIFIC TYPES OF CHRONIC PAIN

Chou R, Carson S, Chan BK. Gabapentin versus tricyclic antidepressants for diabetic neuropathy and post-herpetic neuralgia: discrepancies between direct and indirect meta-analyses of randomized controlled trials. *J Gen Intern Med.* 2009;24(2):178-188.

Tricyclic antidepressants (TCA) and gabapentin have been recommended as first-line treatments for neuropathic pain.²³ Previous systemic reviews have suggested that TCAs were superior to gabapentin, but head-to-head trials were not included in those analyses. Additionally, the quality and interpretability of neuropathic pain trials have been questioned because many of the placebo-controlled trials were published in different time periods (TCAs before 1991 and gabapentin after 1998).

The authors performed two meta-analyses that evaluated the effects of gabapentin versus TCAs in direct (head-to-head) and indirect comparisons (each drug versus placebo). Included trials were rated for quality (randomization, allocation concealment, blinding and intention-to-treat analysis). Gabapentin was superior to placebo for pain relief in six trials (RR 2.18, 1.78-2.67, $p<0.00001$), and TCAs were also superior to placebo for pain relief in nine trials (RR 5.27, 3.05-9.11, $p<0.0001$). Indirect comparisons of these 15 trials suggest gabapentin to be inferior to TCAs (RR 0.41, 0.23-0.74), but the direct, head-to-head comparisons ($n=3$ trials) showed no difference (RR=0.99, 0.76-1.29).

Implications for Practice

This study suggests that gabapentin and TCAs do not differ in efficacy when compared head-to-head, but that TCAs are slightly superior to gabapentin in indirect comparisons. For several reasons, trial results should be interpreted with caution. First, the placebo response rates were considerably different between gabapentin (24%) and TCAs (6%). Second, sample sizes were markedly different between trials (gabapentin median 112 and TCAs median 26). Third, none of the TCA trials met methodological quality standards. Lastly, none of the trials for either drug lasted longer than 12 weeks. Clinicians should be aware of the possible differences in outcomes due to quality and methodological variations in trials. The treatment of neuropathic pain with either gabapentin or TCAs is reasonable and should depend on factors such as patient preference, cost or side effects.

Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA.* 2009;301(2):198-209.

Although prior meta-analyses have shown tricyclic antidepressants (TCA) to be effective in reducing pain in fibromyalgia syndrome (FMS),^{24,25} newer classes of anti-depressants have not been evaluated. This meta-analysis reviewed 18 randomized controlled trials (2,296 total patients) comparing antidepressant with pharmacological placebo for treatment of FMS. Outcomes included standardized measures of pain, fatigue, sleep quality, depressed mood and HRQoL. The authors compared antidepressant classes as well as individual antidepressants.

Overall, antidepressants significantly improved pain [effect size (ES)=-0.43, $p<0.001$], depressed mood (ES=-0.26, $p<0.001$), sleep (ES=-0.32, $p<0.001$) and HRQoL (ES=-0.31, $p<0.001$), but had no effect on fatigue. TCAs showed large effects for pain, fatigue and sleep, a small effect for HRQoL and no effect for depressed mood. Selective serotonin reuptake inhibitors (SSRI) showed a small effect for pain, depressed mood and HRQoL, but no effect on fatigue or sleep. Serotonin-norepinephrine reuptake inhibitors (SNRI) showed small effects for pain, sleep,

depressed mood and HRQoL, and no effect on fatigue. MAO inhibitors showed a moderate effect for pain, but none for fatigue, sleep or depressed mood. Amitriptyline and duloxetine had the strongest evidence for symptom improvement of the individual medications.

Implications for Practice

When considering pharmacotherapy for FMS, antidepressants should be among the first choices. Among the antidepressant choices, TCAs, particularly amitriptyline, has consistently been shown to have a strong effect on many FMS symptoms, an effect that has been stronger than with SSRIs and SNRIs, albeit with a higher rate of side effects. Providers should educate patients to expect only small to moderate improvement in symptoms that characterize FMS—pain, sleep disturbance and depressed mood—as well as in HRQoL. Fatigue is unlikely to improve with antidepressants. Side effect profiles should be weighed against expected improvement in symptoms. In addition, treatment should include evidence-based non-pharmacological treatments, such as such as tailored exercise, heated pool therapy, cognitive behavioral therapy and relaxation techniques.²⁶

Acknowledgements: All authors are members of the Society of General Internal Medicine's Pain Medicine Interest Group. This paper derives from the presentation "Update in Pain Medicine" at the 33rd annual meeting of SGIM on April 2010 in Minneapolis, Minnesota. The authors thank Joel Hoyte at Boston Medical Center for his administrative support in coordinating the submission of this manuscript. Drs. Bair and Krebs are supported by VA HSR&D Research Career Development Awards.

Potential Financial Conflicts of Interest: Dr. Bair has consulted for Abbott and Cephalon. The other authors reported no potential conflicts of interest.

Corresponding Author: Daniel P. Alford, MD, MPH; Clinical Addiction Research and Education Unit, Section of General Internal Medicine, Boston Medical Center, 801 Massachusetts Avenue, 2nd Floor, Boston, MA 02118, USA (e-mail: dan.alford@bmc.org).

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