CLINICAL UPDATE

Update in Pain Medicine

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INTRODUCTION

More than 75 million Americans have chronic or recurrent pain.[1] Pain accounts for 20% of all outpatient visits[2] and more than $100 billion dollars per year in direct (i.e., health care services) and indirect costs (i.e., lost productivity)[3]; analgesics account for 12% of all prescriptions.[4] Chronic pain is a leading cause of work loss, and disability and is a common reason for use of alternative medicine.[5] Our aims were to: review recent pain medicine studies and their key findings and understand how these new findings may impact generalist clinical practice.

We used a systematic search strategy for the period of January 1, 2006 through March 31, 2007 for human subject, English language, 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*, *chronic pain*, and *primary care*. Members of the Society of General Internal Medicine's Pain Medicine Interest Group also suggested other relevant articles. We narrowed the initial list of 314 references to 33. We independently rated the 33 remaining articles using a 5-point Likert scale (1 = poor to 5 = outstanding) on: impact on general internal medicine clinical practice, clinical policy and research, and the quality of the study methods. Based on ratings and consensus deliberations, we chose a subset of 12 articles. We categorized the articles into 5 topic areas: (1) chronic pain and comorbidities; (2) systems approaches to managing chronic pain; (3) opioids and chronic pain; (4) non-pharmacologic approaches to treating chronic pain; and (5) complementary and alternative pain treatments.

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CHRONIC PAIN AND COMORBIDITIES

Arnow BA, Hunkeler EM, Blasey CM, et al. Comorbid depression, chronic pain, and disability in primary care. *Psychosomatic Medicine.* 2006;68:262–268.

Major depression and chronic pain frequently coexist [6]. However, the strength of their association is unclear, especially in primary care settings. Arnow et al. conducted a large, cross-sectional survey to estimate the prevalence and strength of association between major depressive disorder (MDD) and chronic pain, and the "clinical burden" (i.e., decrements in health-related quality of life, increased somatic symptoms, and additional mental health illness) associated with these conditions individually and in combination. Participants were recruited from 31 internal medicine and family practice clinics within Kaiser Permanente Health Maintenance Organization (HMO) of Northern California. Eligible patients (n=10,710), randomly selected within 1 week of their clinic visit, were mailed a survey. Data from 5,808 respondents (54%) were analyzed. Assessments included psychiatric disorders[7] (depression, anxiety, and alcohol abuse or dependence), somatic symptom severity, health-related quality of life (HRQL), pain-related disability, and chronic pain. Chronic pain was dichotomized as "non-disabling" and "disabling."

Seven percent of respondents met criteria for MDD and 45% experienced chronic pain (28% had disabling pain). Among those with MDD, a significantly higher proportion reported chronic pain compared to those without MDD (66% vs. 43%). Coexisting MDD and chronic pain were associated with poorer HRQL, greater somatic symptom severity, and higher prevalence of panic disorder. The prevalence of alcohol abuse or dependence was two times higher in those with MDD compared to those without MDD. Anxiety disorders were six times more prevalent in those with MDD versus those without regardless of pain presence or disability level.

In summary, chronic pain is especially common among those with MDD. Additionally, the combination of MDD and chronic pain are associated with greater decrements in HRQL, more somatic preoccupation, and more frequent psychiatric comorbidity than MDD alone. The study was limited by a 54% response rate and restricted to patients with a recent clinic visit within an HMO. However, these findings strongly suggest that attention to the assessment and treatment of depression and chronic pain concurrently may be necessary to reduce the clinical burden associated with these conditions.

SYSTEMS APPROACHES TO MANAGING CHRONIC PAIN

Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. Pain Medicine 2007;8:573–84.

Despite limited training in pain medicine, primary care providers (PCPs) manage the bulk of patients with chronic pain. Opioid analgesics are gaining wider acceptance by PCPs, but are controversial for "at risk" patients with a history of substance use disorder or aberrant behavior.

Wiedemer et al. conducted a naturalistic prospective outcome study to measure the impact of a structured opioid renewal program for at risk patients with chronic pain requiring opioids. The study was conducted at the primary care clinic at the Philadelphia Veterans Affairs Medical Center. The intervention involved regular assessments and monitoring by a clinical pharmacist and a nurse practitioner that worked as a liaison between primary care and a multidisciplinary pain team. In addition, PCPs were trained in the use of opioid agreements and random drug testing. Outcomes included providers' use of and patients' adherence to opioid agreements and drug testing, provider satisfaction, and pharmacy costs.

Of 335 patients referred to the program, 171 (51%) had documented aberrant behaviors (e.g., positive drug test), and 164 (49%) had a history of substance use disorder. In those with documented aberrant behaviors, 38% self-discharged from the program, 13% were referred for addiction treatment, and 4% were weaned off for consistently negative urine for prescribed opioids. Of the patients with a history of substance use disorder but no documented aberrant behaviors at the outset, all were adherent to the program. PCP's use of opioid treatments agreements increased fourfold and random drug testing increased substantially. PCPs expressed high levels of satisfaction with the program and significant pharmacy savings were shown.

The study was limited by lack of a comparison group. However, it demonstrated that a nurse practitioner/clinical pharmacist-run clinic, supported by a multi-specialty pain team, can facilitate the use of widely accepted tools such as opioid treatment agreements and urine drug screens by primary care providers in managing opioids in at risk chronic pain patients.

Ahles T, Wasson J, Seville J et al. A controlled trial of methods for managing pain in primary care patients with or without co-occurring psychosocial problems. *Ann Fam Med* 2006:4;341–350.

Behavioral treatments proven to aid pain outcomes include self-management, cognitive–behavioral therapy, and problem-solving therapy.[8,9]. PCPs are not trained to deliver these effective behavioral treatments especially in patients with psychosocial problems. Ahles et al. tested a "stepped" behavioral approach employing individualized self-management skills and problem-solving therapy for pain management in primary care.

The study was a randomized controlled trial in a rural practice-based research network for patients with at least moderate pain lasting for >1 month. Randomization was stratified by the presence or absence of psychosocial problems (self-reported impairment: emotional problems, social activities, social support, sexual problems, substance abuse or household violence). Patients without psychosocial problems (n=693) were randomized to self-management information delivered during a computer feedback session or usual care. The computer-generated feedback targeted both patients and their physicians and provided information from a self-care educational booklet. Patients with psychosocial problems (n=644) were randomized to three arms: computer feedback session alone, computer feedback plus nurse-educator-delivered intervention by phone over 6 months, or usual care. The nurse-educator intervention included: (1) assessment of pain, psychosocial problems, and management preferences, (2) self-management strategies, (3) problem-solving approach, and (4) feedback to the PCP.

The main outcomes included Medical Outcomes Study 36-Item Short-Form (SF-36)[10] domain scores, functional interference, and health care utilization. The participants had a mean age of mid-40s, and most were white, female, married, educated, and employed. The computer-generated feedback did not improve any outcomes in patients at 12-month follow-up. Compared to the usual care control group, the computer feedback plus nurse-educator intervention showed statistically significant improvements (p<.05) for all subscales of the SF-36 except for physical function and social function, with clinically relevant score increases of 6 to 12.5 at 6 months. At 12 months, subscales showed clinically relevant score increases of 5 to 13.9, although only changes in vitality and role emotional remained significant. At 6 and 12 months, functional interference scores were significantly improved. There, were no differences in utilization, although the study was underpowered to show small differences in the overall low utilization. A telephone-based nurse-educator intervention may be a useful treatment program for patients with chronic pain and psychosocial problems.

Mularski RA, White-Chu F, Overbay D, et al. Measuring pain as the 5th vital sign does not improve quality of pain management. *J Gen Intern Med.* 2006; 21:607–612.

The Veterans Health Administration launched the "Pain as the 5th Vital Sign" (P5VS) initiative in 1999 to improve pain management for veterans. The P5VS initiative required the assessment of pain intensity (0 to 10) at all clinical encounters. Mularski et al. sought to measure the initiative's impact on the quality of pain management in a general internal medicine clinic.

Medical records of 300 randomly selected patient visits were reviewed before and after implementation of the P5VS initiative. Seven process indicators were assessed to measure the quality of pain management. A subgroup analysis of patients reporting "substantial pain," defined as a pain score of 4 or greater, was also performed.

Even though pain intensity was documented more frequently (82% vs. 31%) after the initiative, the quality of pain care was unchanged after implementation. There were no significant differences among the process indicators of provider assessment, pain exam, orders to assess pain, new analgesic prescribed, change in existing analgesics, other pain treatment, or follow-up plans. Patients (n=79) who reported substantial pain often did not receive recommended care: 22% had no pain processes documented in the medical record, 27% had no further assessment, and 52% received no new pain therapy at that visit.

The study suggests that a simple pain intensity score assessment is insufficient to improve the evaluation and treatment of patients' pain.

Sullivan MD, Leigh J, Gaster B. Training internists in shared decision making about chronic opioid treatment for noncancer pain. *J Gen Intern Med.* 2006;21:360–62.

Long-term opioid use for chronic pain is a controversial issue in primary care. Shared decision-making models have been shown to improve patient-centered care[11] and may improve care for pain. This study tested a shared decision-making model for opioid treatment of chronic pain in primary care and whether the model improved physician satisfaction and quality of care for patients with chronic pain.

Sullivan et al. conducted a randomized controlled trial of internal medicine residents (n=38) and attendings (n=7). Study participants were randomized to two 1-hour training sessions versus written educational materials of opioid management. Training sessions focused on applying the shared decision-making model with patients when discussing treatment goals, non-medication pain treatments, prescription of methadone as the long-acting opioid of choice, and the role of depression and its treatment in chronic pain. Three-month outcomes included provider satisfaction, degree of patient-centered treatment (doctor receptiveness, patient involvement, affective content of the relationship and information giving), and pain management practices (i.e., methadone prescribing, setting functional goals, opioid treatment agreements).

Compared to the control arm, participants in the shared decision-making model arm reported improvements in: overall satisfaction including relationship quality and appropriate use of time. The intervention group was significantly more likely to give patients information to assist with decision making, prescribe methadone, set functional goals, and complete opioid treatment agreements.

Training in a shared decision-making model improved attitudes and behaviors related to opioid treatment of chronic pain. Pain severity and function were not assessed, and self-reported behaviors were not confirmed. Study physicians' sense of collaboration and satisfaction in treating chronic pain patients was improved by a shared decision-making model.

OPIOIDS AND CHRONIC PAIN

Martell BA, O'Connor PG, Kerns RD et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy and association with addiction. *Ann Intern Med.* 2007;146: 116–127.

Back pain, the second leading symptom seen by US physicians, substantially impacts HRQL.[12] While opioids effectively treat acute pain, benefits of long-term use are unclear. Martell et al. systematically reviewed English-language studies from 1966 to March, 2005 to determine: (1) the prevalence of opioid treatment, (2) efficacy of opioids, and (3) the prevalence of substance use disorders among patients receiving opioids for chronic back pain.

In 11 studies, opioid prescribing varied by treatment setting: 11% to 66% in specialty settings and 3% to 31% in primary care. Opioid prescribing was more common in patients reporting higher disability, worse suffering, and poorer functioning but not necessarily higher pain levels. Of the 15 studies evaluating efficacy, 6 compared an opioid with a non-opioid or placebo, and 9 compared different opioids. All studies had heterogeneous study designs, none lasted more than 4 months, and 11 were industry sponsored. Of the studies comparing an opioid with a non-opioid or placebo, 4 found a non-significant pain reduction with opioids. The 5 most rigorously conducted studies comparing different opioids found a non-significant pain reduction from baseline. Across 5 studies measuring opioid misuse, the prevalence was 5% to 24%, and in 9 studies that assessed current and lifetime substance use disorder, the prevalence was 3% to 43% and 36% to 54%, respectively.

The efficacy of long-term opioids for chronic back pain remains unclear, while evidence does exist to support this treatment for short term use, that is, less then 4 months. Substance use disorders are common in patients taking opioids for back pain. However, the true prevalence of addiction (preexisting or iatrogenic) is still unknown. Despite common use of opioids for chronic back pain, this systematic review cannot provide evidence of long-term efficacy. In addition, evidence about developing addiction from prescribed opioids is too limited to draw any conclusions.

Olsen Y, Daumit G, Ford D. Opioid prescriptions by US primary care physicians from 1992–2001. *J Pain*, 2006; 7:225–235.

Little is known about PCPs opioid prescribing practices. This study assessed trends and factors associated with opioid prescribing of US PCPs nationwide over a 10-year period.

Olsen et al. analyzed cross-sectional demographic, clinical, and prescription data from the 1992–2001 National Ambulatory Medical Survey. Yearly response rates ranged from 63% to 73%; representing between 1,801 and 2,587 physicians and 20,760–36,875 patient visits. Only visits to PCPs were included. The primary outcome was prevalence of primary care visits (per 1,000) in which an opioid was prescribed. The analysis was adjusted for ethnicity, geography, and insurance status.

The prevalence of visits (per 1,000 visits) during which an opioid was prescribed increased from a low of 41 in 1992–1993 to a peak of 63 in 1998–1999 (p<.0001 for trend) and then dropped to 59 in 2000–2001. Several factors increased the adjusted odds ratio (aOR) of receiving opioids: Medicaid [aOR= 2.09, (1.82–2.4)], Medicare [aOR=2.0, (1.68–2.39)], a visit between 15–35 minutes [aOR=1.16, (1.05–1.27)], and receiving NSAIDs [aOR=2.27, (2.04–2.53)]. Factors which lowered the odds of receiving opioids included: Hispanic race [aOR= 0.67, (0.56–0.81)], other race, i.e., Asian/Native American [aOR=0.68, (0.52–0.90)], participation in a HMO [aOR=0.74, (0.66–0.84)], living in the Northeast [aOR=0.6, (0.510.69)], or the Midwest [aOR=0.75, (0.66–0.85)].

Study limitations included the cross-sectional design and lack of information about disease severity within groups being compared. However, this study demonstrates that substantial variations in opioid prescribing practices exist among PCPs, suggesting differences in the quality of pain management across the United States.

Ives TJ, Chelminski PR, Hammett-Stabler CA et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Services Research.* 2006; 6:46.

Despite growing public health concerns of opioid misuse and addiction, there is scant information regarding the prevalence and risk of opioid analgesic misuse in clinical populations.[13] This prospective cohort study estimated the prevalence and predictors of opioid misuse in an academic internal medicine practice.

Ives et al. followed 196 primary care patients in a chronic pain management program for 1 year. Patients were referred to the

program with difficult to manage pain or suspicions of opioid misuse. A multidisciplinary team (clinical pharmacist, internist, psychiatrist, nurse, and program assistant) developed a multimodality (pharmacologic and non-pharmacologic) pain management plan for each patient in conjunction with the PCP. The primary outcome was opioid misuse defined as: a negative urine toxicology screen (UTS) for the prescribed medications; or positive UTS for non-prescribed opioids, cocaine, or amphetamines; or evidence of multiple prescriptions from different providers, prescription diversion, or forgery.

Most patients were white, with a mean age of 52 years, and nearly half were women. Patients were predominantly low income; more than half were disabled and 29% had a history of substance abuse disorder. One-year data were available for 96% of the patients. Opioid misuse occurred in 32% of patients. The significant factors associated with opioid misuse on multivariate analyses were age (aOR=0.95, 95% CI 0.90–0.99), prior driving under the influence or drug convictions (aOR=2.58, 1.01–6.59), history of cocaine abuse (aOR=4.30, 1.76–10.4), and history of alcohol abuse (aOR=2.60, 1.12–6.26).

The selective nature of the study population limits the generalizability of the prevalence estimate. However, this study characterizes factors associated with opioid misuse and provides a practical working definition of misuse that emphasizes the role of UTS in monitoring patients on long-term opioid therapy. Access to prior drug- and alcohol-related conviction data may be useful when available.

NON-PHARMACOLOGIC APPROACHES TO TREATING CHRONIC PAIN

Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the spine patient outcomes research trial (SPORT): a randomized trial. *JAMA* 2006:296(20):2441–2450.

Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): observational cohort study. *JAMA* 2006:296(20):2451–2459.

Lumbar diskectomy is the most common surgery performed for back and radicular leg symptoms in U.S. patients.[14] However, controversy exists regarding its efficacy compared to non-operative care.

The Spine Patient Outcomes Research Trial (SPORT) studies assessed the efficacy of surgery compared to non-operative care for lumbar intervertebral disk herniation. The study involved a concurrent randomized controlled trial (RCT) and an observational cohort study and included 13 interdisciplinary spine clinics in 11 U.S. states. Participants were surgical candidates with imaging-confirmed lumbar disk herniation and signs and symptoms of radiculopathy lasting at least 6 weeks. Patients undergoing operative diskectomy vs. non-operative therapy were compared. Non-operative therapy included physical therapy, education/counseling with home exercise instruction, and NSAIDs, if tolerated. Physicians caring for patients in the non-operative arm were also provided with a list of other therapies and encouraged to individualize treatment. Main outcomes included bodily pain and physical function as measured by the SF-36[10] back-pain-specific physical function as measured by the Oswetry Disability Index[15], sciatica severity, satisfaction, self-reported improvement, and employment status at 3, 6, 12, and 24 months. Participants who refused randomization at baseline were entered into the cohort study.

In the RCT, 232 participants were randomized to surgery, but half (50%) did not undergo surgery. Of the 240 participants randomized to non-operative care, 30% had surgery. Both groups showed significant improvements. The intention to treat analysis favored surgery, but all differences were small and not statistically significant.

In the cohort study, 521 participants chose surgery and 96% underwent the procedure. Of those who chose non-operative care (n=222), 22% eventually underwent surgery. Both groups improved over time, but the surgery arm showed greater improvements on all measures. Improvements were clinically significant, with a 15-point difference between groups on both SF-36[10] scales for bodily pain and physical function at 3 months. Differences narrowed slightly, but persisted for the entire 2-year study period.

Due to the large degree of cross-over in the RCT and potential selection bias in the observational study, conclusions regarding the superiority or equivalence of treatments are not warranted. Because all patients had imaging-confirmed, symptomatic, and persistent disk herniations, not simply low back pain, the results should not be generalized to the broader population of patients with chronic low back pain.

It is unlikely that we will have a clearer answer in the near future, as it will be hard to improve on the methods of this rigorously conducted, well-funded large trial. However, providers may be reassured that most back pain improves—even for patients that meet strict criteria for disc surgery—and that following patient preference may be a reasonable and evidence-based approach.

COMPLEMENTARY AND ALTERNATIVE PAIN TREATMENTS

Brinkhaus B, Witt CM, Jena S, et al. Acupuncture in patients with chronic low back pain: a randomized controlled trial. *Arch Intern Med.* 2006;166:450–457.

Despite the lack of evidence for complementary and alternative medicine (CAM) treatments for pain conditions, one third of U.S. adults with low back pain seek pain relief using CAM, including acupuncture.[5] The Acupuncture Randomized Trial in Low Back Pain, a multi-center trial, tested the efficacy of acupuncture in reducing chronic low back pain.

Eligible patients were aged 40 to 75 years, with greater than 6 months of low back pain of unclear etiology, moderate pain intensity, and receiving only NSAID analgesia. Participants were randomized to acupuncture (n=146), sham acupuncture (n=73), or wait-list control (n=79). The primary outcome was change in pain intensity on visual analog scale at 8 weeks. By week 8, acupuncture significantly decreased pain compared to wait-list control, but not to the sham acupuncture. Results remained similar at 26 and 52 weeks for all outcome measures. Fifteen patients (11%) receiving acupuncture and 12 patients (17%) receiving sham acupuncture (p=.20) reported adverse effects, including hematoma and bleeding.

The authors concluded that acupuncture (including sham acupuncture) was more effective than no acupuncture (wait list) in patients with chronic low back pain. This is one of the

largest and most rigorous trials to investigate the efficacy of acupuncture for low back pain. Study strengths included: assessment of intervention credibility, interventions delivered by qualified and experienced medical acupuncturists, and high follow-up rates.

The lack of difference between acupuncture and sham acupuncture suggests that sham acupuncture may also have specific analgesic effects that need further exploration. Expectation bias (active treatment vs. wait list) and placebo (active vs. sham were similar) effects could confound outcomes. Future head-to-head trials comparing acupuncture and other interventions for treating chronic low back pain are needed.

Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis *NEJM*. 2006; 354(8):795–808.

The dietary supplements glucosamine and chondroitin sulfate have been promoted as safe and effective treatment options for osteoarthritis symptoms. A meta-analysis of studies evaluating these supplements suggested potential benefit, but questioned the quality of included studies.[16] The Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) was a 24-week randomized double-blind, placebo- and celecoxib-controlled multi-center trial to evaluate the efficacy and safety of glucosamine, chondroitin sulfate, and glucosamine plus chondroitin sulfate in the treatment of painful knee osteoarthritis.

The GAIT study included adult patients who had clinical and radiographic evidence of knee osteoarthritis, had an elevated Western Ontario and McMaster Osteoarthritis Index (WOMAC)[17] pain scores, and were physically functional. The 1,583 eligible patients were randomized to receive daily doses of 1,500 mg glucosamine, 1,200 mg chondroitin sulfate, both glucosamine and chondroitin sulfate, 200 mg of celecoxib, or placebo for 24 weeks. The primary outcome was a reduction in the WOMAC pain scale of 20%.

Overall, glucosamine and chondroitin sulfate were not significantly better than placebo in reducing knee pain by 20%. Compared to placebo (60.1%), the response to glucosamine was 64% (p=.30), to chondroitin sulfate was 65.4% (p=.17), to combined treatment was 66.5% (p=.09), and to celecoxib was 70.1% (p=.008). Subgroup analysis of patients with moderate-to-severe pain demonstrated that combination therapy significantly decreased pain compared to placebo (p=.002). Adverse events were infrequent and mild and evenly distributed among the groups.

The large placebo response and relatively mild degree of pain from osteoarthritis among the participants may have limited the ability to detect a difference in treatment efficacy. While glucosamine and chondroitin sulfate alone or in combination did not show efficacy in the overall study group, combination therapy may have efficacy in patients with more severe symptoms from knee osteoarthritis.

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