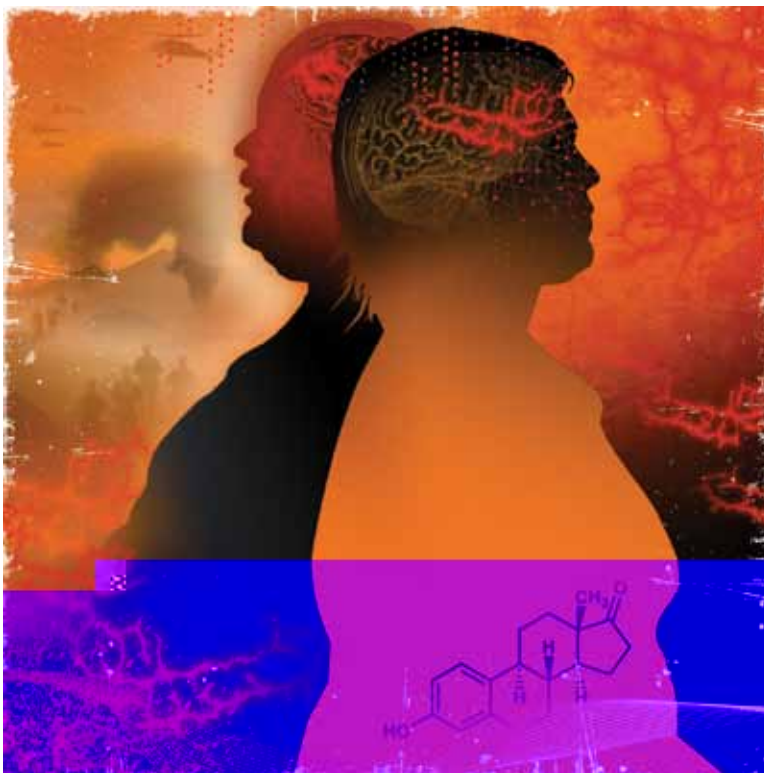


MEN, WOMEN, AND MIGRAINE: THE ROLE OF SEX, HORMONES, OBESITY, AND PTSD



COMMENTARY

Pain—It's not
that simple

The benefits of
interdisciplinary pain
management

CHRONIC PAIN PERSPECTIVESSM

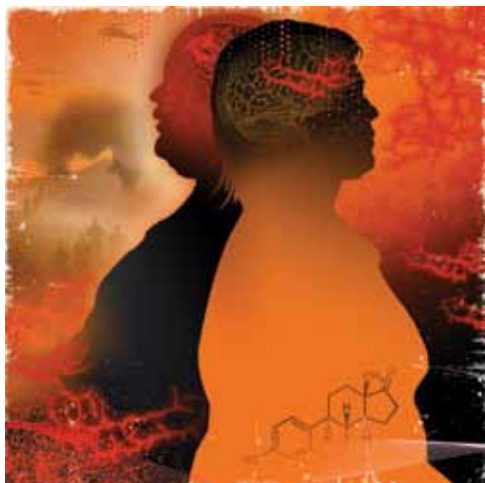
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Pain – It's not that simple

The complex problem of pain rarely has a simple solution. Here's why.

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HL. Mencken was a 20th century journalist and critic who provided us with a number of great quotes. One of my favorites is:

"There is always an easy solution to every human problem—neat, plausible, and wrong."¹

I like this quote because it applies to many aspects of pain. In this and upcoming issues of *Chronic Pain Perspectives*, we examine why chronic pain needs to be viewed as a complex situation that affects the mind, body, and soul of our patients, one in which the simple, neat solution is often not enough. Although we may wish to "tackle" pain as we would an objective value and reduce it with a unimodal approach, experience and several lines of research demonstrate that we are positioning ourselves, and our patients, for disappointment. The problem here is not in our patients, but in the

fact that their pain is not a discrete entity. Pain is a doorway into a sequela of suffering that needs to be appreciated and addressed if we have any hope of helping our patients return to functionality.

Pain does not travel alone

The research guides us to understand that when there is pain, there are current or emerging issues with mood, energy, cognition, and function. Although depression is found in approximately 10% to 15% of all patients seen in primary care, those who have chronic pain have been found to present with depression as much as 58% of the time,² making it the most common psychiatric comorbidity. Conversely, in a large study of primary care patients with major depressive disorder, chronic pain was present nearly 66% of the time.³

Beyond depression, the patient with chronic pain is more likely to have coexisting anxiety,³

The problem here is not in our patients, but in the fact that their pain is not a discrete entity.

panic,³ sleep dysfunction characterized by sleep maintenance insomnia and fatigue,⁴ restless leg syndrome,⁴ and loss of gray matter density that may be reversible.^{5,6}

This brings up the age-old intellectual question, “Which came first?” What we appreciate more and more—through understanding the common pathophysiological mechanisms seen in conditions such as migraine, depression, and cardiovascular disease,⁷—is that these disorders are co-developing and making their way into the chief complaint in various layers and word choices.

Pain does not stay in the same silo

As we focus more closely on pain as a foe that we can subdue, we find that it exerts an influence on many “friends,” and that pain and its elusive friends have the ability to jump from one arena into another, sometimes making the battle feel insurmountable. Recent research points

this out; in a 30-year study of headache, over the course of their illness patients were found to switch from their initial diagnosis of headache type to other headache diagnoses more than 80% of the time.⁸ [Figure]

What this creates is the awareness that we are not really fighting a single condition, but a complex picture of suffering, and that we must take into account many layers of the patient who presents to us. In this way we can push past the simple but disappointing solution to a more integrative, individualized, complex one that holds the potential for relief on multiple levels.

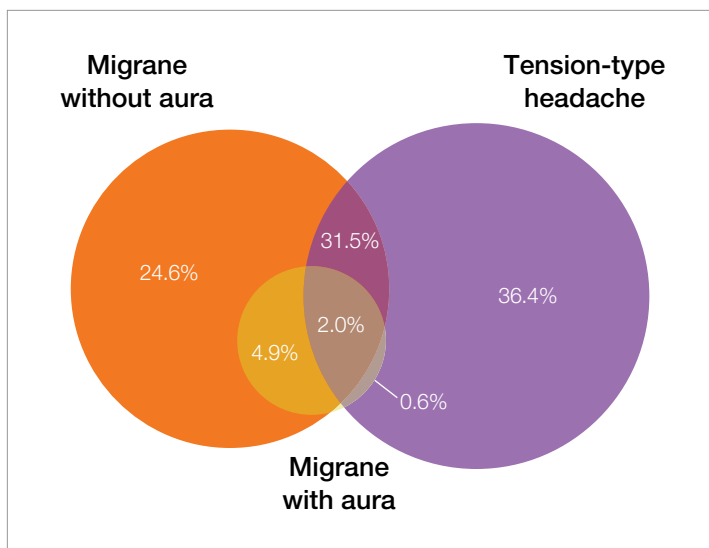
I’ll leave you with another Mencken quote that offers sage advice in this regard:

“The essence of science is that it is always willing to abandon a given idea, however fundamental it may seem to be, for a better one.”⁹

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FIGURE: Combinations of headache subtypes across 30 years among participants who met criteria for migraine or tension-type headache (n=346)



Source: Adapted from Merikangas KR, et al. Magnitude, impact, and stability of primary headache subtypes: 30 year prospective Swiss cohort study. *BMJ*. 2011;343:d5706

Men, women, and migraine: The role of sex, hormones, obesity, and PTSD

Links between migraine and certain comorbidities suggest new approaches to patient education, screening, and treatment.

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Migraine is a common neurologic disorder that occurs in approximately 3 times as many females as males in the United States. Among 30,000 respondents, the American Migraine Study II found that the prevalence of migraine was 18.2% among females and 6.5% among males, and was

much higher in females from age 12 across the lifespan.¹ In comparison, for tension-type headache the female to male ratio of occurrence is 5:4, occurring only slightly more in females.² The reasons for this disparity in migraine prevalence are not well understood. The disproportionate number of women of reproductive age

Disclosures

B. Lee Peterlin, DO, has received grant/research support from GlaxoSmithKline, has served as a consultant to Nautilus, and has served on the speaker's bureau of Zogenix. She holds a provisional patent for use of adiponectin-modulating drugs for migraine.

Anne H. Calhoun, MD, has no conflicts of interest to report.

Fred Balzac has no conflicts of interest to report.

As many as 70% of female migraineurs are aware of a menstrual association with their headaches.

with migraine suggests that hormonal factors may play a role, but the complex pathophysiology of migraine indicates additional factors are involved.³

Recent research on menstrual-related migraine and two significant comorbidities of migraine—obesity and posttraumatic stress disorder (PTSD)—shed new light on the differences in how men and women present with and experience this often disabling disorder.

Epidemiologic differences

The incidence of migraine, defined here as age of first onset, is different in boys and girls. For migraine without aura, age of first onset is approximately 10 to 11 years in boys versus 14 to 17 years in girls. For migraine with aura, age of first onset is approximately 5 years in boys and 12 to 13 years in girls.⁴

The picture of migraine differs by sex before and after puberty. Before age 12, boys have a higher incidence and prevalence of migraine. After age 12, prevalence increases for both sexes, peaking between age 35 to 45, with an increase in the female-to-male ratio from 2:1 at age 20 to 3.3:1 at age 40.^{5,6}

Disparities in migraine symptoms

Common symptoms associated with severe or unilateral migraine pain include photophobia, phonophobia, and nausea. In the American Migraine Study II, the most frequently reported symptoms were pulsatile pain (85% of migraineurs), light sensitivity (80%), sound sensitivity (76%), nausea (73%), unilateral pain (59%), blurred vision (44%), aura (36%), and vomiting (29%).¹ Females were more likely than males to report light sensitivity, sound sensitivity, and nausea. More females experienced 1 to 2 days of migraine-associated activity restriction than males (30.5% vs 22.9%).¹ Separate studies have shown neck pain to be second after menstruation in its predictive value for onset of migraine, and to be more prevalent than nausea at the time of treatment.^{7,8}

Migraine comorbidities

Migraine is known to be comorbid with a variety of disorders including psychiatric conditions such as depression and anxiety,^{9,10} and medical comorbidities such as stroke, epilepsy, and hypothyroidism.¹¹⁻¹³ In women, migraine is also comorbid with endometriosis.¹⁴

Hormonal factors: Menstrual-related migraine

With migraine disproportionately affecting women of reproductive age, as many as 70% of female migraineurs are aware of a menstrual association with their headaches.¹⁵ A menstrual migraine is defined as migraine without aura that occurs during the 5-day window that begins 2 days before the onset of bleeding and extends through the third day of active bleeding—and that occurs in at least two-thirds of menstrual cycles.¹⁶ Approximately 14% of women experience what is termed pure menstrual migraine, meaning the only time they experience migraine is during menstruation. For women who also have migraines triggered by other mechanisms, the menstrual migraine is typically their most severe migraine of the month.

For many women, menstrual migraines are more painful, longer lasting, and more resistant to acute therapy than migraines occurring at other times.^{17,18} It is specifically the reduction in estradiol in the late luteal phase that appears to be the greatest trigger for menstrual migraine.

About two-thirds of women with migraine improve in menopause, particularly those for whom migraine attacks were associated with menstruation.^{19,20} As disabling as menstrual-related migraine can be, clinically it is often found to coexist with chronic migraine and medication overuse headache.²¹

In a study that looked at the impact of eliminating menstrual migraine, investigators treated women with hormonal preventives based on the hypothesis that, because these agents confer no known benefit for migraines that are not hormonally triggered, use of these agents might allow them to separate out menstrual-related migraine and its effect on the overall clinical picture.²¹ Among 229 consecutive women seen in follow-up, 81% of those patients who were taking the hormonal preventive as prescribed had a complete resolution of menstrual-related migraine. Among those in whom menstrual migraine was eliminated, 58.9% reverted back to episodic migraine, compared with only 11% of patients whose menstrual-migraine was not eliminated.²¹ Resolution of menstrual-related migraine also was associated with resolution of medication overuse. Patients in whom menstrual-related migraine resolved were >2 times as likely to stop medication overuse as those in whom the migraines were not eliminated. The results offer preliminary evidence that hormonal regimens may be of benefit in preventing menstrual-related migraine.

Migraine and obesity

Obesity, which results from excessive adipose tissue in relation to fat free mass, has been shown in clinical and population-based studies to be associated with migraine.²²⁻²⁵ Both migraine and the distribution of adipose tissue change substantially based on age and sex.²⁵ Following puberty, girls have an increase in the subcutaneous to visceral adipose tissue ratio as compared with boys, a pattern that continues through the reproductive years for women. Postmenopausal women see an increase in visceral adipose tissue volume and a decrease in the subcutaneous to visceral adipose tissue volume compared with premenopausal women. Similarly, migraine prevalence increases in women of reproductive age as compared with those of postreproductive age and it is greater in women of reproductive age as compared with men.²⁵

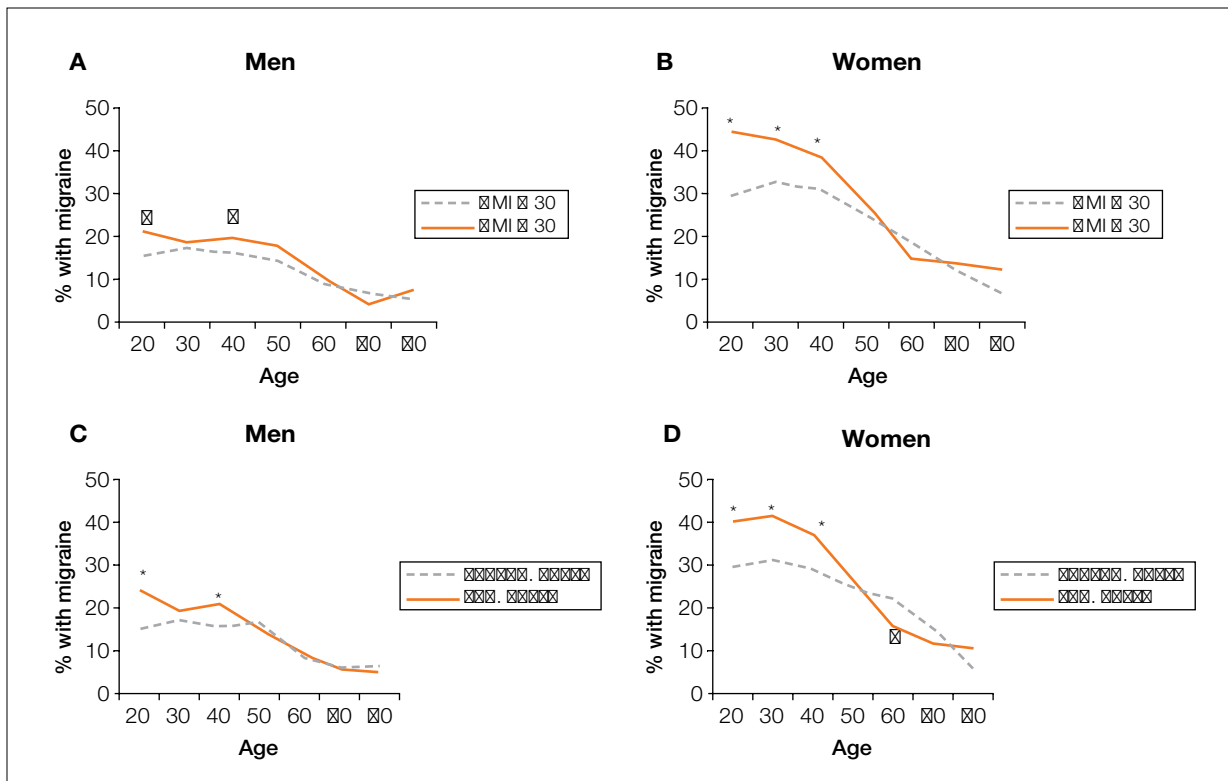
To evaluate the prevalence of migraine and severe headaches in men and women with and without total body obesity (TBO), as measured by body mass index (BMI) and abdominal obesity (Abd-O), Peterlin and colleagues analyzed

data from 21,783 participants in the National Health and Nutrition Examination Survey.²⁶ The investigators found that the relationship between migraine and obesity varies by age, sex, and the distribution of adipose tissue. For men and women of reproductive age, migraine prevalence increased in those with either TBO or Abd-O compared with those without. For postreproductive aged men and women (>55 years), migraine prevalence was not increased in those with either Abd-O or TBO. [Figure 1]

Vo et al observed similar findings for women of reproductive age in analyses of data from the Omega study. In a cohort of 3,733 women during early pregnancy, researchers found that obesity was associated with increased odds for migraine and that the risk of migraine increased with increasing obesity.²⁷ Specifically, while the overall odds of migraine in women with obesity of any level was 48% greater than in women without obesity (OR 1.48; 95%CI: 1.12-1.96), those women with severe or class II obesity (BMI 35 to 39.9) had a >200% increased risk (OR 2.07; 95%CI: 1.27-3.39), and those with morbid or class III obesity (BMI \geq 40) had a

Investigators found that the relationship between migraine and obesity varies by age, sex, and the distribution of adipose tissue.

■ **FIGURE 1:** Migraine prevalence in men and women in relation to TBO and Abd-O



Total body obesity (TBO) was estimated based on BMI. Abdominal obesity (Abd-O) was estimated based on waist circumference. *P \leq .001; † P \leq .01; ‡ P \leq .05

Source: Adapted with permission from Peterlin BL, et al. Migraine and obesity: Epidemiology, mechanisms, and implications. *Headache*. 2010;50:631-636.

The benefits of interdisciplinary pain management

Studies show equal or better clinical outcomes compared with standard treatments, low risk, and reduced costs of care.

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The Institute of Medicine (IOM) published a consensus report in June 2011 on the “national challenge” of chronic pain.¹ Below the heading “Underlying Principles,” the report states,

“Given chronic pain’s diverse effects, interdisciplinary assessment and treatment may produce the best results for people with the most severe and persistent pain problems.”¹

Yet much of the medical community tends to treat pain as a physical problem with pharmaco-

logic solutions, effectively dismissing the value of interdisciplinary pain management and the biopsychosocial model underlying this approach, even though its interrelated factors are clearly linked to improved physical symptoms and decreased use of costly medical resources.^{2,3} However, over the past 2 decades an undeniable body of evidence favoring an interdisciplinary approach has been growing.

Rationale and research

Success with a multimodal approach to pain management has been demonstrated for a

Disclosures

Carl Noe, MD, has served as a consultant to Palladian Partners, Inc., a health communications and services company. Charles F. Williams has no conflicts of interest to disclose.

number of pain conditions, perhaps most clearly in studies of chronic low back pain (LBP). In one study, 108 patients (63% with LBP) underwent multiple sessions of individual cognitive behavioral therapy (CBT), physical therapy, aquatic physical therapy, occupational therapy, group education, and group relaxation.⁴ At program enrollment, program completion, and long-term follow-up, researchers gathered data on changes in pain severity, emotional stress, interference of pain on functioning, perceived control of pain, helpfulness of treatment, and hours resting. At 6 months and 1 year following completion of the study, all 6 measures showed statistically significant improvement over baseline, with 95% confidence intervals in 5 of the 6 showing no overlap between pre-program and follow-up measures. [TABLE 1]

In a systematic review of 10 randomized controlled trials encompassing 1964 patients with disabling LBP, researchers found strong evidence that intensive multidisciplinary biopsychosocial rehabilitation improves function when compared with inpatient or outpatient treatments. The review also found moderate evidence of pain reduction with multidisciplinary care compared with non-multidisciplinary care.⁵

Studies of musculoskeletal pain also have reported good results with interdisciplinary care. In a study of interdisciplinary pain management for chronic musculoskeletal pain, military personnel were to receive either interdisciplinary care with physical therapy, occupational therapy, and psychosocial intervention, or standard anesthesia treatment alone.⁶ At 6 months and 1 year, data collected on pain, disability, functional status, and fitness for return

to duty showed that interdisciplinary care was far superior to standard care.

A systematic review of randomized controlled trials found strong evidence that multidisciplinary care is more effective for non-malignant chronic pain diagnoses (chronic LBP, back pain, fibromyalgia, and mixed chronic pain) than standard medical treatment, and moderate evidence for its effectiveness compared with other nonmultidisciplinary treatments.⁷ According to the study authors, the data support, at minimum, offering a range of treatments—including individual exercising, training in relaxation techniques, group therapy with a clinical psychologist, patient education, physiotherapy, and medical training therapy—and providing neurophysiology information. They also point out that no particular combination or duration of therapy has proved superior to others in clinical outcomes.

Risks of interdisciplinary care versus standard care

Therapies employed in interdisciplinary pain management are relatively low-risk compared with other interventions, such as opioid use or surgery. A 2010 Cochrane review of opioid use for chronic non-cancer pain found that concerns about long-term use of opioids can present a potential barrier to treatment. Opioids often lead to adverse effects (gastrointestinal effects such as constipation and nausea; headache; fatigue; urinary complications) severe enough to warrant discontinuation.⁸ This review found the rate of opioid addiction in these study populations was extremely low,

Over the past 2 decades, an undeniable body of evidence favoring an interdisciplinary approach has been growing.

TABLE 1

Variance of outcomes of a comprehensive pain management program with 1-year follow-up (n=46)

Mean ± standard error (95% confidence interval)			
Variables	Pretreatment	Posttreatment	1-year follow-up
Pain severity	8.8 ± .29 (8.21-9.40)	6.59 ± .31 (5.96-7.21)*	6.94 ± .45 (6.03-7.84)*
Interference	10.43 ± .30 (9.83-11.04)	8.04 ± .42 (7.19-8.90)*	7.35 ± .56 (6.22-8.48)*
Distress	7.07 ± .49 (6.08-8.05)	3.91 ± .38 (3.15-4.67)*	5.57 ± .45 (4.65-6.48)
Control	5.91 ± .29 (5.10-6.72)	8.8 ± .24 (8.16-9.45)*	8.67 ± .29 (8.02-9.33)*
Helpfulness	2.37 ± .22 (1.93-2.81)	7.35 ± .29 (6.76-7.93)*	7.13 ± .4 (6.34-7.93)*
Hours resting**	5.45 ± .51 (4.42-6.48)	2.63 ± .24 (2.14-3.12)*	3.29 ± .44 (2.40-4.18)*

* No overlap in confidence interval between pretreatment and either posttreatment or 1-year scores

**n=40

Source: Adapted with permission from Oslund S, et al. Long-term effectiveness of a comprehensive pain management program: strengthening the case for interdisciplinary care. *Proc (Bayl Univ Med Cent)*. 2009;22(3):211-214.

Studies comparing interdisciplinary care with spine fusion surgery for chronic back pain found interdisciplinary care to be a reasonable alternative.

however, and concluded that potential iatrogenic opioid addiction should not be a barrier for well-selected and well-supervised patients. As this study indicates, patients who gain pain relief from prescribed opioids might become drug dependent, but will not become addicted.

Also, although opioids are widely used, their ability to control pain varies. A study from the Mayo Comprehensive Rehabilitation Center of 233 consecutively enrolled patients with chronic nonmalignant pain found 48% were using opioids daily at baseline, at a cost of \$23.13 per day or \$8326.90 per year (average wholesale price) per patient.⁹ Patients who completed a 3-week multidisciplinary intervention significantly reduced their medication use at 6-month follow-up, for an estimated annual savings of \$2404.80 per patient.

Two studies comparing interdisciplinary care with spine fusion surgery for chronic back pain found interdisciplinary care to be a reasonable alternative for many patients. In a study of patients with chronic LBP who had previous surgery for disc herniation, spinal fusion showed no benefit over cognitive intervention and exercise after 1 year.¹⁰ [TABLE 2] A multicenter trial comparing surgical stabilization of the lumbar spine with an intensive rehabilitation program based on CBT found no clear evidence that spinal fusion provided greater benefit.¹¹

What interdisciplinary pain management looks like

Key disciplines of an interdisciplinary pain management program are medicine, psychology, and rehabilitation. However, programs vary in available services and professional disciplines, setting, and duration. A fully integrated pain treatment center offers a range of therapies that may include transcutaneous electrical nerve stimulation, CBT, biofeedback, physical therapy, psycho-educational group treatment, and medications such as nonnarcotic analgesics and nerve blocks. Additional disciplines may include outcome database managers, vocational specialists, nutrition, case management, nursing, chaplaincy, and other disciplines an individual patient may need.

Patients should be evaluated by a pain medicine specialist and a behavioral medicine specialist. Treatment recommendations should include a structured curriculum including education, CBT, and physical therapy to address fear avoidance behavior, medication use, disability, affective distress, health care overutilization, quality of life, activities of daily living, and other patient-centric goals of rehabilitation. The interdisciplinary treatment team should be housed in the same facility and meet at least once per week to discuss new and existing patients and monitor progress toward outcome goals.

At our clinic, the Eugene McDermott Center for Pain Management at the University of Texas Southwestern Medical Center in Dallas, each patient undergoes consecutive evaluations by a pain physician, psychologist, physical therapist, and perhaps a psychiatrist. A case manager helps patients navigate through the evaluation and treatment process. At weekly case conferences, the team meets to discuss new patients, review the progress of current patients, and reinforce or modify treatment plans.

Individualizing goals

“Among steps to improving care, health-care providers should increasingly aim at tailoring pain care to each person’s experience and self-management of pain should be promoted.”

Pain influences and inhibits numerous areas of a patient’s life. For many chronic pain patients, duration of pain brings with it the belief that “hurt equals harm.” As a result, they decrease physical activities, become socially isolated, and

TABLE 2
Primary and secondary outcomes comparing spinal fusion with CBT and exercise

Outcome	Lumbar fusion (n=28)	CBT/exercises (n=29)
Oswestry*		
Baseline	47	45.1
1-year	38.1	32.3
Back pain**		
Baseline	64.6	64.7
1-year	50.7	49.5
Leg pain**		
Baseline	52.7	55.3
1-year	45	47.7
Working	10%	40%

*Oswestry Disability Questionnaire in which the sum of response scores ranges from 0 to 100, where 100 represents the worst possible pain and disability.

**Based on a vertical visual analog scale ranging from 0 to 100, where 100 reflected the worst pain imaginable.

Source: Adapted from Brox JI, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: A prospective randomized controlled study. *Pain*. 2006;122(1):145-155. This table has been reproduced with permission of the International Association for the Study of Pain® (IASP®). The table may not be reproduced for any other purpose without permission.

often feel unable to effectively manage, control, and conquer their pain. The longer chronic pain endures, the more deleterious the psychosocial consequences, even if pain and dysfunction do not worsen.

Chronic pain causes patients to feel a domino effect of psychological and cognitive disturbances including anxiety, depression, anger, and sleep disturbance. Disability caused by pain may bring on economic and domestic difficulties. Relationships can suffer, in part because it is hard for others to understand the impact of pain, especially when there is no obvious pathology.

Part of the evaluation process is to assess these possibilities and to address them in a concerted way. We encourage patients to focus on making progress toward their treatment goals rather than hoping to find a definitive cure for a pain generator that may or may not be identifiable. Therefore, in addition to the standard outcomes we aim for with each patient (eg, improvement in physical and psychological function measures), we establish individual treatment goals based on the initial interviews and the patient's desire to return to work, get into vocational retraining or education, or achieve other productivity or recreational outcomes.

Patients typically receive 8 to 10 sessions of CBT, with each session covering a topic such as sleep hygiene, assertiveness training, anger management, or controlling automatic thoughts that lead to catastrophization or fear of the pain getting worse.

At our center we spend an hour educating patients about pain medications, explaining how they work and why some pose risks. Patients undergo 6 to 8 sessions of physical therapy and graded exercise, starting slow and gradually building to a level that does not aggravate their pain. Teaching them correct posture and how to lift objects also is important.

Planning for long-term success

Pain management takes place on numerous levels that incorporate self care, primary care, specialty care, and the multimodal care of interdisciplinary pain centers. To avoid relapse after patients have been treated at an interdisciplinary pain center, it is important that they have a clear idea of how to proceed with their individualized programs in a self-directed manner. Those who do well in the program and return to work or the home environment may be vulnerable to stressors that can lead to relapse.

Patients who fear they cannot control the pain or that they may do something to worsen it are at risk of becoming depressed, dependent, or guarded in their activities.¹² Our program is developing a system to monitor patients more closely after they finish their program to identify those who may be spiraling downward. Patients are invited to return at any time for "booster" sessions.

Primary care involvement can strengthen patient resolve

"Also, primary care physicians—who handle most front-line pain care—should collaborate with pain specialists in cases where pain persists."¹¹

The degree to which primary care physicians (PCPs) want to be involved with chronic pain management varies, of course. Interdisciplinary programs should explore the comfort level of individual providers and work with them accordingly—at the very least communicating with and including the PCP in the patient's process so that he or she understands what the patient has encountered and achieved.¹³ This collaborative approach enables PCPs to motivate patients to continue the progress they've made, reinforce the biopsychosocial model for treating pain, and communicate with the interdisciplinary team about patients who may be relapsing.

Barriers to interdisciplinary care

"System and organizational barriers, many of them driven by current reimbursement policies, obstruct patient-centered care."¹¹

The IOM has estimated the direct and indirect costs of pain in America to be over a half a trillion dollars per year. The potential for interdisciplinary pain care to contribute to national deficit reduction is real and is not limited to chronic pain. In fact, the application of interdisciplinary evaluations and treatment to acute and subacute pain may be more important to reduce costs related to preventing high-risk patients from becoming chronic.

A cost-utility analysis of 994 patients in pain clinics with acute back pain at high risk of becoming chronic who were provided early intervention with an interdisciplinary approach resulted in fewer health care visits and fewer missed days of work compared with patients who received usual care.¹⁴

We encourage patients to focus on making progress toward their treatment goals rather than hoping to find a definitive cure for a pain generator that may or may not be identifiable.

To help curtail overutilization of health care resources in this country, we have to acknowledge psychosocial issues and embrace interdisciplinary pain programs when treating patients with pain.

Additional cost savings could be realized by routinely applying the biopsychosocial model to acute and subacute pain. Through well-developed evaluation systems, we could identify patients at high risk of progressing to chronicity. Screening for risk stratification is key to reducing the large number of chronic pain patients who are over-medicated, disabled, and depressed. Just as it makes sense to reduce individuals' cardiac risk factors and not wait until they are in heart failure to act, employing a comprehensive interdisciplinary program for acute pain would be less expensive than waiting to treat pain that has become chronic.

However, only some insurers cover use of interdisciplinary pain programs, often to a limited extent, and may employ carve outs for specific therapies. Medicare does not reimburse well for interdisciplinary treatment. Consequently, many programs are paid through worker's compensation. It is therefore challenging for interdisciplinary programs to remain viable.

Further benefits to the wider community

Our current health care system in the United States is not financially sustainable. To help curtail overutilization of health care resources in this country, we have to acknowledge psychosocial issues and embrace interdisciplinary pain programs when treating patients with pain. But it will take time and a huge cultural change for this to happen.

The future may require a combination of interdisciplinary treatment with a strong component of analgesic treatments rather than an "all or none" approach in which patients receive either "behavioral" treatment or "medical" treatment only. By definition, interdisciplinary pain treatment requires medicine as a discipline to reduce pain using *everything* medicine has to offer to accomplish this end.

Helpful information for you and your patients

The American Academy of Pain Management (AAPM) offers professional credentialing in pain management and accredits pain management clinics in the United States. You may be able to locate a specialist or clinic in your area

at the academy's Web site: https://members.aapainmanage.org/aapmssa/censsacustlkup.query_page.

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