Editorial

Chronic Back Pain: Searching for Causes and Cures

Back pain is one of the 3 most common reasons for healthcare visits, with an episode in perhaps up to 75% of the population at some point[1]. Most acute back pain resolves within one to 3 months, but up to 15% of patients have persisting pain one year after an initial episode, while community-based surveys repeatedly report that at least 5% of the population complains of daily or almost daily back pain for 6 months or more (i.e., chronic back pain)[1]. For most patients there are few treatment alternatives; worse yet, complete relief is rare. Several factors help explain this state of affairs. One is that the etiopathogenesis and mechanisms leading to the majority of chronic back pain syndromes are unknown. The list of potential risk factors for back pain chronicity, encompassing a broad array of demographic, behavioral, and social risks, ranges from smoking and obesity, to occupations requiring manual labor or long-haul driving, to job dissatisfaction[2,3]. The medical differential diagnosis of persisting back pain is similarly lengthy, beginning with nonspinal pathology that may present with back pain, as well as a search for serious underlying spinal disorders (the so-called "red flags" of vertebral fracture, spinal tumor or infection, or cauda equina syndrome)[1]. For most chronic back pain patients, however, a definitive pathoanatomic diagnosis cannot be made[1], so one is left with collective diagnosis such as "nonspecific" back pain, musculoskeletal "strain," or "degenerative disk disease." Degenerative change of intervertebral disks begins early in life (mid-twenties), is nearly universal by age 50, yet is asymptomatic in the majority of individuals, or only weakly correlated with symptoms. It is noted that degeneration covers so many clinical, radiologic, and pathologic processes that the term is simply a symbol of ignorance[4]. Many chronic back cases commence with what appears to be trivial soft tissue or neural injury. The persistence of pain beyond the period of expected healing is hypothesized to result from neuronal hyperactivity, changes in membrane excitability, dysfunction of modulatory or inhibitory systems, central sensitization, or expression of new genes resulting in abnormal processing of normal afferent traffic[1], which possibly involve inflammatory cytokines [e.g., tumor necrosis factor-α (TNF-α), interleukins], mitogen-activated protein kinases (MAPK), and prostaglandins (PG). Unfortunately there is not yet a widely accepted animal model of chronic back pain to help guide research.

Given this atmosphere of uncertainty over etiopathogenesis and diagnosis, treatments proliferated and therapy became empiric. Over 20 years ago a seminal article proposed guidelines for distinguishing "useful from useless" therapy for low back pain[5]. Methodological criteria thought to be essential for establishing the validity and generalizability of outcome research for low back pain were: (1) a representative clinical sample described in demographic and clinical detail; (2) reporting of relevant outcomes, including physical symptoms, function, and psychological status; (3) random allocation; (4) blind outcome assessment; (5) documentation and assurance of equality of cointerventions; (6) measurement of compliance; (7) efforts to eliminate or to identify and quantify contamination of study groups by patients obtaining study treatments elsewhere; and (8) rigorous consideration of statistical and clinical significance of outcome. Refinements were added subsequently.

Because side effects were observed to be associated with placebo analgesia in chronic pain — and chronic back pain particularly was thought to be placebo-responsive — "active" placebos became the state of the art in back pain research to assure blinding[6], especially if the study drug produced obvious side effects like dry mouth, sedation, or nausea. Finally, to evaluate the integrity of the blind it was noted that study subjects (and the blinded study physician) should be asked to guess the study assignment at exit[7].

Although the quality of clinical trials for chronic back pain has improved remarkably in recent years, the field remains underserved. The medical mainstays of treatment, in usual order of use, have been nonsteroidal antiinflamma-

See Analgesic efficacy and safety of tramadol/acetaminophen combination tablets in treatment of chronic low back pain, *page 2454*

tory drugs (NSAID), antidepressants, and opioids. NSAID are effective for acute back pain, but few studies have addressed patients with chronic back pain, making it still uncertain whether these drugs are "useful or useless" therapy for this condition[8]. There is as yet no convincing evidence that these agents improve daily functioning[8]. Patients treated with antidepressants were more likely to experience a reduction in pain severity than those taking placebo, but again it is uncertain whether activities of daily living are improved[9]. Few studies addressed differences among drug classes, but those antidepressants inhibiting norepinephrine reuptake appear to be more effective than those inhibiting serotonin reuptake[9]. Benefit seems to be independent of depressed mood. Small and medium-size trials suggest opioids (e.g., oxycodone) and other compounds with mu agonist activity are effective[10,11], but the discontinuation rate due to adverse effects exceeds 20% in most trials, putting opioids on par with tricyclic antidepressants for tolerability. It is generally accepted that aspirin, acetaminophen, and NSAID enhance opioid analgesia, so combination treatment is a next logical step.

In this issue of *The Journal* Peloso and colleagues provide evidence supporting efficacy of a combination of tramadol (a norepinephrine and serotonin reuptake inhibitor with a major metabolite having mu agonist activity) and acetaminophen for chronic low back pain, using standardized measures to report significant improvements in pain, disability, and life quality. This is a model study for chronic back pain research in several aspects. There is an extended washout period for patients to discontinue current analgesics and establish baseline pain. The study presents an efficacy analysis along with assessment for "survival time" of efficacy to estimate durability of effect. This latter analysis is conspicuous by its absence in most randomized trials in chronic back pain. Finally, there is a careful assessment of side effects.

To their credit the authors also acknowledge limitations in their work, which are the limitations of the field, and then proceed to point back pain research toward necessary methodological improvements, along with a conservative assessment of their results. The authors' exclusion criteria describe in detail what patients did not have. But what is the diagnosis? The authors call our attention to the so-called Quebec Task Force descriptive classification of back pain[12]. Recognizing the imprecision of pathoanatomic diagnosis, this system simply records back pain descriptively as pain without radiation, pain with proximal (above the knee) radiation, pain with distal (below the knee) radiation, pain and radiation above or below the knee with neurologic signs, and finally presumptive compression of spinal nerve root. While many may find it unsatisfactory to resort to description rather than diagnosis, at this stage of our knowledge such classifications at least permit researchers and clinicians to understand the applicability of results to their populations.

The next issue is whether or how much patients improved, and at what "costs." In contrast to the availability of objective endpoints for therapeutic studies in rheumatoid arthritis clinical trials, outcomes in chronic back pain traditionally have been limited to self-reported measures of pain intensity and functional status, and associated outcomes such as reduction of depressive symptoms or number or amount of supplementary analgesics used. Recently, 2 study groups, the International Forum for Primary Care Research on Low Back Pain[13] and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials[14], developed guidelines for standardized sets of outcome measures. The goal has not been to recommend specific instruments as gold standards, but to identify core domains (pain, function, life quality) and standardized measures to improve comparability of results across pain studies, thereby facilitating metaanalysis or cost-effectiveness analysis, as well as the conduct of multicenter trials. Peloso and colleagues adopt these guidelines, including use of measures to evaluate function and life quality with both disease-specific and generic instruments, on the grounds that disease-specific instruments (such as the Roland and Morris Disability Scale) are arguably more sensitive to clinically important improvement, while generic measures (like the Medical Outcome Study Short Form-36) make it possible to compare outcomes across different diseases. Regarding the "cost" of improvement, the percentage of patients who withdrew due to limiting adverse events in the opioid group was 28% compared to 8% from the placebo group. This highlights the need for more tolerable therapies, but also brings up the issue of longer-term efficacy and safety. The prescription of opioids for chronic back pain and other musculoskeletal disorders is increasing markedly, such that practice is outstripping data[15,16], perhaps in the hope that a "cure" is at hand[17]. The larger and longer-term trials needed to establish the safety and effectiveness of opioids for back pain are lacking, but crucial[17].

The path for additional research seems rather straightforward. One approach recommended by many authorities is determining if agents effective for one type of chronic pain (e.g., diabetic neuropathy, rheumatoid arthritis) can be generalized to other syndromes like chronic back pain. In terms of this strategy, nonselective and selective cyclooxygenase-2-specific inhibitors warrant further consideration for chronic back pain trials. Anticonvulsants (e.g., gabapentin), known to be efficacious for some neuropathic pain syndromes, have a tolerable side effect profile, and deserve evaluation for back pain. Recent therapeutic approaches for blocking the effects of inflammatory cytokines in rheumatoid arthritis (etanercept and anakinra) may be applicable to chronic back pain, especially if safety concerns can be overcome. Another is to explore drug combinations based on selecting agents with differing therapeutic mechanisms. Rational combination therapy capitalizing on agents with

differing mechanisms of action is limited of course by uncertainty over back pain pathogenesis and mechanisms of analgesia. But if the safety and effectiveness of primary analgesics is confirmed, they may become a cornerstone of combination therapy. Finally, it is likely that not all patients with chronic back pain will respond to pharmacotherapy alone. There is evidence that exercise and behavioral therapies reduce chronic back pain and improve function[18]. For these individuals, research is needed to determine if combination treatment should be defined as the best available medical therapies together with behaviorally-oriented rehabilitation programs.

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