Pain Physician 2007; 10:329-356 • ISSN 1533-3159

Invited Review

Evidence-Based Interventional Pain Management: Principles, Problems, Potential and Applications

Laxmaiah Manchikanti[1], MD, Mark V. Boswell[2], MD, PhD, and James Giordano[3], PhD

From: [1]Pain Management Center of Paducah, Paducah, KY, [2]Texas Tech University Health Science Center, Lubbock, Texas, and [3]Georgetown University Medical Center, Washington, D.C.
Dr. Manchikanti[1] is Medical Director of the Pain Management Center of Paducah, KY, and Associate Clinical Professor of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY. Dr. Boswell[2] is Chairman of the Department of Anesthesiology and Director of the Messer Racz Pain Center, Texas Tech University Health Sciences Center, Lubbock, TX. Dr. Giordano[3] is Scholar in Residence, Center for Clinical Bioethics; Associate Professor, Division of Palliative Medicine, Georgetown University Medical Center, Washington, D.C.
Address Correspondence: Laxmaiah Manchikanti, MD
2831 Lone Oak Road
Paducah, Kentucky 42003
E-mail: Drm@apex.net
Disclaimer: Dr Giordano's work is supported, in part, by a Hunt-Travis Foundation Grant, and by Funding from the Samueli Institute.
Conflict Of Interest: None

Free Full Manuscript:
www.painphysicianjournal.com

Background: The past decade has been marked by unprecedented interest in evidence-based medicine (EBM) and a focus upon the use of innovative methods and protocols to provide valid and reliable information for and about healthcare. Thus (it is at least purported that), healthcare decisions are increasingly being based upon research-derived evidence, rather than on expert opinion or clinical experience alone. But this quest for evidence to support clinical practice also compels the question of whether the methods employed to acquire information, the ranking of information that is acquired, and the prudent use of this information are sound enough to actually sustain the validity of an evidence-based paradigm in practice. Moreover, it is becoming apparent that the scope, depth, and applicability of available evidence to effectively and ethically guide the myriad of situational decisions in clinical practice is not uniform across all medical fields or disciplines. In particular, comprehensive evidence synthesis or complete guidelines for clinical decision-making in interventional pain management remain relatively scarce.

EBM is defined as the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients. Thus, the practice of EBM requires the integration of individual clinical expertise with the best available external evidence from systematic research. To arrive at evidence-based medical decisions all valid and relevant evidence should be considered alongside randomized controlled trials, patient preferences, and resources.

Objective: To describe principles of EBM, and the methods and relative utility of evidence synthesis in interventional pain management.

Description: This review provides 1) an understanding of evidence-based medicine, 2) an overview of issues related to evaluating the quality of individual studies, analyses, narrative, and systematic reviews, 3) discussion of factors affecting the strength and value(s) of evidence, 4) analysis of specific reviews of interventional techniques, and finally, 5) the utility and purpose of guidelines in interventional pain management.

Conclusion: Interpreting and understanding evidence synthesis, systematic reviews and other analytic literature is a difficult task. It is crucial for pain physicians to understand the goals, principles, and process(es) of EBM so as to meaningfully improve its application(s). This knowledge affords better insight into not only the analytic reviews in interventional pain management provided herein, but ultimately allows future information to be selected, evaluated, and used with prudence in technically competent, ethically sound medical practice.

Key words: Interventional pain management, interventional techniques, evidence-based medicine, evidence synthesis, pragmatic or practical clinical trials, randomized trials, observational studies, non-randomized trials, systematic reviews, quality of evidence

Pain Physician 2007; 10:329-356

The trend to develop and implement research in support of evidence-based practice has been somewhat the convention of medicine for the past decade. This emphasis has been fostered, at least partly, by a perceived (if not defined and called for) need to improve patient care through applied clinical decision-making in diagnosis and treatment. Evidence-based practice or medicine (EBM) evolves through a methodical, rational accumulation, analysis, and understanding of the evidentiary knowledge that can be applied in the clinical setting(s) (1). However, one must remember that the actual value of any evidence is relative to the applications in which it will be used, and the circumstances in, and agents for whom such evidence may (or may not) have relevance.

The underlying concept of EBM is that a systematic review of the literature or synthesis of evidence will allow practitioners to apply the most effective treatments. Practicing medicine essentially means application of humanism, compassion, knowledge and skills, in addition to application of science and art in a logical manner (2-5).

Medicine is currently defined as: the art and science of diagnosis, treatment, and prevention of disease and the maintenance of good health (6). Osler wrote, "medicine is the art of probability." Thus, most clinical decisions are based upon the knowledge that health is a stochastic process, that outcomes are probabilistic, and that it is difficult to predict where a patient will fall in a bell-shaped curve (7). Consequently, medicine and healthcare are dependent on probabilities and decisions that are based on population-based information.

Evidence can be defined as any ground or reason for knowledge or certitude in knowledge; proof, whether immediate or derived by inference; a fact or body of facts on which a proof, belief, or judgment is based (8). But it is the nature of belief and the foundation upon which it rests that provides the utility of evidence (9,10). For medical purposes, evidence can be any data or information, whether solid or weak, obtained through experience, observational or experimental research (11). Thus, EBM is about solving clinical problems (12). In contrast to the traditional paradigm of medical practice, EBM acknowledges that intuition, unsystematic clinical experience, and pathophysiologic rationale are insufficient grounds for clinical decision-making, and stresses the examination of evidence from clinical research (13). EBM suggests that a formal set of rules must complement medical training and common sense for clinicians to interpret the results of clinical research effectively. Finally, EBM places a lower value on authority than does the traditional medical paradigm.

Yet, EBM is understood differently by academicians, practitioners, managed care executives, researchers, attorneys, policy makers and patients (14). EBM also has drawn widespread attention in many circles, including the Institute of Medicine (IOM), which called attention to a "chasm that exists between the care we get and the care we should be getting (15)." In "crossing the quality chasm," IOM called attention to the health system's ineffectiveness in applying new scientific discovery to the day-to-day practice of medicine. The Institute of Medicine also suggested that the time-lag between acquisition of knowledge and applications in practice might be as much as 20 years.

Healthcare decision makers consider justice as the fairest way of distributing services among a population of individuals, and temper the utilitarian frameworks of decision analysis and cost effectiveness with concern for equity, that is, the fairness of how opportunities to benefit from healthcare are distributed among members of a group or society.

For practical purposes, dichotomy exists among clinicians. It is claimed that most clinicians' practices do not reflect the principles of EBM but rather are based upon tradition, their most recent experience, what was learned (years ago) in medical school, or anecdotal information acquired from colleagues (7).

Shaneyfelt et al (16) described the frequent failure of clinicians to implement clinical interventions that have been shown to be efficacious (17,18). This trend has been more widely recognized, and in response, professional organizations have called for increased training in evidence-based practice for all healthcare professions and at all levels of education (19-25).

Practicing EBM is not simple. A single clinician cannot easily acquire and assimilate the amount of literature available, judge its quality, and translate these often divergent results into practice. The average physician devotes approximately 2 hours per week to reading professional clinical journals, and the volume of material available for review is often overwhelming (7). Consequently, EBM actually relies less on the integrative intellectual capability of the individual clinician, and more on systematically organized analysis and synthesis provided by the review and provision process itself. What remains critical is that every clinician must recognize and accept that evidence

is 1) multi-level, and 2) its meaning is relative to the circumstance(s) of application. Thus, while data may, and need be objective, these meanings have intrinsically subjective value dependent upon the audience. The meaning of any body of evidence may (and likely does) differ for physicians, administrators, payers, attorneys, and patients. Being able to interpret both the validity of evidence and its relative value is essential to resolving equipoise. Thus, the paradigm shift is from opinion-based medicine to EBM. This review provides an understanding of the nature, process and values of EBM, as directly relevant to interventional pain management.

Historical Aspects

While EBM is historically traceable to the 1700s, it was not explicitly defined and advocated until the late 1970s and early 1980s when a group of clinical epidemiologists at McMaster University — David Sackett, Brian Haynes, Peter Tugwell, and Victor Neufeld — planned and wrote a series of articles that provided clinically relevant advice on addressing and weighing the value of information appearing in the Canadian Medical Association Journal (26). Initially, the group proposed the term "critical appraisal" to describe the application of the basic rules of evidence as presented in that work.

The term "evidence-based medicine" first appeared in the autumn of 1990 as part of an informational document for physicians entering or considering applications to the residency program at McMaster University. The term subsequently appeared in print in the ACP journal club in 1991 (12). Subsequently, a group of evidence-based medical educators at McMaster University, together with a group of academic physicians primarily from the United States, formed the first International EBM Working Group, publishing a 25-part series, "*The Users Guide to the Medical Literature,*" in JAMA between 1993 and 2000, which ultimately resulted in a textbook (27-33).

During the 1990s, numerous organizations devoted to advancing EBM were developed in various countries around the world. The Cochrane Collaboration, which started in 1993 (25), publishes systematic reviews on a quarterly basis. By 2006, the Cochrane reviews contained approximately 2,700 complete reviews and 1,700 protocols for reviews in production (34).

The Agency for Healthcare Policy Research (AHCPR) was established in December 1989 under the Omnibus Budget Reconciliation Act of 1989; The agency was charged with enhancing the quality, appropriateness, and effectiveness of healthcare services and access to such services in the United States. The AHCPR identified those clinical areas with large resource costs and wide practice pattern variations. Consequently, the agency targeted the areas that were responsible for disproportionate government expenditures and to solve this issue developed 19 clinical practice guidelines at an agency budget of $750 million (35). The AHCPR also developed clinical practice guidelines for managing acute low back pain in adults (36) which led to considerable controversy among many medical specialties, and resulted in congressional testimony and final dissolution of the Agency and its intramural transformation into the Agency for Healthcare Research and Quality (AHRQ). The Agency for Healthcare Research and Quality was formed in December 1999 (35), under the rubric of "quality research for quality healthcare," as a mission statement. Thus, AHRQ attempts to bridge evidence gaps in research so as to increase ways that appropriate evidence can be utilized to enhance the quality of healthcare.

Such evidence-based data may be published in a variety of sources, including original journal articles, reviews and synopses of primary studies, practice guidelines, and medical textbooks. From this core concept of EBM, other, more tactical uses of data (and terms that reflect these applications) have been developed to fit the various needs and values of the healthcare profession (e.g., evidence-based healthcare, evidence-based practice of specific disciplines or fields viz. evidence based pain management, evidence-based palliative medicine, and evidence-driven medical law, etc.). Evidence-based publications in the field of interventional pain management are few (25,26,37-82).

Definitions

An operational definition of EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (26). Thus, EBM is essentially focused upon the use of the right (types and extent of) knowledge to guide the right and good intentions and actions of medical practice. This process is fundamental to prudential clinical decision-making (2,5,83). Hence, the practice of EBM requires the prudent, specific contextual application of knowledge gained by integration of individual clinical expertise and experience, in concert with the best available external evidence gained from systematic research (2,3,5,83,84). Practical and

ethical decisions that affect patient care should be made with due weight given to all valid, relevant information (10,85). This should include evidence derived not only from randomized, controlled trials, but from all types of evidence, in conjunction with both patient preference (to accept or refuse a particular treatment), and access to available, affordable resources. No single form of evidence should necessarily be the determining factor in decision-making. This explicitly indicates that there should be an active search for all information that is valid and relevant, and that ongoing assessment should be made to ascertain both the accuracy of information and the applicability of evidence to the decision in question.

In this light, evidence-based practice may (also) be seen as an integration of the best research evidence with patients' circumstances and values in making clinical decisions (29,86). As a distinctive approach to patient care, EBM involves 2 fundamental principles. First, scientific evidence alone is never sufficient to make a clinical decision. Decision makers must always consider the patients' values when evaluating the benefits, risks, and burdens associated with any/all treatment strategies (12). Second, while EBM posits a hierarchy of informational value(s) to guide clinical decision-making (12,13), this hierarchy is not absolute, and must reflect how different types and levels of evidence can be relative to, and inform the calculus of, circumstance(s), agents, and the consequences of decisions and actions (10,84-87).

This relevance to the nature and impact of circumstance(s) is upheld by the 4 basic contingencies that define evidence-based practice (88):

- First, it is crucial to recognize the patient's problem and construct a structured clinical question.
- Second, the medical literature must be thoroughly searched to retrieve the best available evidence to answer the clinical question.
- Third, the available evidence must be critically appraised.
- Fourth, this final body of evidence must be integrated with all aspects and contexts of the clinical circumstance (including imposing psycho-social factors) in order to facilitate the decisional process that determines the best clinical care of each patient.

It can be seen that a broad(er) definition of evidence-based clinical practice involves an approach to decision-making in which the clinician uses the best scientific evidence available, in consultation with the patient, to decide upon the option(s) that suit the patient (and his/her circumstances), and which ultimately will best resolve equipoise to effect good care and positive outcomes. This definition brings into consideration both patient compliance and physician adherence. In this way, the clinician's role is not simply making diagnostic and prognostic decisions, but also involves educating patients about treatment options and engaging them in care management decisions. This supports 1) a respect for the mutual autonomy of both physician and patient; 2) the patients' role in making informed decisions, and 3) a deliberative approach in which patients are reciprocally participatory in their own care (2,3,5,9,83,84).

While this definition appeals to both pragmatic and ethical considerations, another definition of EBM introduced by Bogduk et al (89-92) opines EBM to be "…the medical practice that uses techniques with proven reliability, validity, and efficacy, while shunning those that patently lack reliability, validity, or efficacy." These authors maintain that this approach does not include the formalities of listing, grading, and discussing individual publications, and does not dwell on methodology of systematic reviews. Further, in defining EBM, they were less conciliatory than some other definitions such as that provided by Sackett et al (26).

Thus, while EBM is clearly not "cookbook medicine," or "cost-saving medicine," it can be seen that EBM remains a somewhat less-than-concrete term that has been variably based not only on a particular view of what types of research are necessary, but also on considerable speculation and conjecture about the philosophic basis of knowledge, realities of values, and pragmatic influences that all of these variables exert upon clinical decision-making. This has led to questions of whether EBM is truly 1) based on evidence, and 2) what are the values that invite and sustain the use of that evidence.

Despite these practical and semantic differences, all definitions of EBM involve 3 critical, overarching processes (93,94):

- First, evidence-based practice involves the ongoing, systematic review of the "science" to support the clinical decisional process of diagnosis and treatment planning that is relevant to clinicians, and that is necessary for resolving clinical and personal equipoise, and informing patient consent (93).
- Second, evidence-based practice involves the integration of such scientific knowledge with the clinician's training and practical experience.

- Third, evidence-based practice should involve the active participation of patients in making decisions about their care (3,83,95-98).

On the Necessity of Evidence-Based Medicine

The need for careful scientific evaluation of clinical practice became an increasingly prominent focus of both the medical and sociological communities during the second half of the twentieth century (98). Tunis et al (95) described that the demonstration of pervasive and persistent unexplained variations in clinical practice, coupled to high rates of inappropriate care and increased healthcare expenditures fueled a steadily increasing demand for evidence of clinical effectiveness (96,99-103). The past 2 decades have been marked by an unprecedented interest in EBM and practice guidelines that can provide valid and reliable information to inform and sustain technically appropriate and ethically sound medical treatment (37-82). Such evidence can be derived from a variety of approaches and sources.

Systematic reviews and meta-analyses represent rigorous methods of compiling scientific evidence to answer questions about diagnosis, treatment, and/or prevention (104). Similarly, another commonly used technique of evidence evaluation is health technology assessment (105). Practice guidelines may also provide valid and reliable information to support evidence-based intervention, provided that such guidelines are systematically developed from appropriate resources of existing information. Of course, evidence-based practice must be fluid, and as consistent with the self-critical and self-revisionist imperatives of scientific philosophy, should be adapted, modified, or rejected based on changing information and specific needs or constraints.

Principles of Evidence-Based Medicine

Hierarchy of Evidence

Evidence-based medicine is informed by hierarchical evidence, and this hierarchy characteristically informs clinical decision-making. Within this hierarchy, any empirical observation about the apparent relationship between events constitutes potential evidence (30), but the strength and lexical ordering of such evidence is dependent upon how it has been acquired and the depth of information provided. This hierarchy posits a descending order of evidentiary weight for 1) systematic reviews of randomized trials, 2) single randomized trials, 3) systematic review of observational studies addressing patient important outcomes, 4) single observational studies addressing patient-important outcomes, 5) physiologic studies, followed by 6) unsystematic clinical observations (30). However, it's important to reiterate that this hierarchy is not viewed as absolute. If treatment effects are sufficiently large and consistent, observational studies may provide more compelling evidence than randomized, controlled trials (30). In fact, observational studies have allowed extremely strong inferences about the efficacy of diagnosis, treatment, and the nature of the clinical relationship(s) between physicians, patients, the public, and colleagues. However, unsystematic clinical observations are often limited by small sample size, and more importantly, by deficiencies in the process(es) of inference (30).

Clinical Decision-Making

Scientific evidence alone is never sufficient to make a clinical decision (30). In current healthcare practice, judgments often reflect clinical or societal values concerning whether potential benefits are worth the burdens incurred (13). Guyatt and Drummond (30) pointed to values and preferences as the underlying processes brought to bear in weighing what patients and society will gain — or lose — when a clinical management decision is made. Health economies have played a major role in developing a science of measuring patient preferences (106-109).

Practical Clinical Trials

Tunis et al (95) reported that the prevalence and significance of knowledge gaps about clinical effectiveness can be readily appreciated by examining the results of most systematic literature reviews, technology assessments, and clinical practice guidelines. A consistent finding of most reviews appears to be that the quality of evidence available to answer critical questions relevant to the study is frequently suboptimal. For example, most systematic reviews performed in interventional pain management include studies that provide data that are not applicable to patient care in typical practice settings. Consequently, organizations that develop evidence-based clinical practice guidelines may not be able to develop clear, specific recommendations from such reports. The limited quantity and quality of available scientific information impedes 1) the development of guidelines, and 2) the efforts of public and private health insurers in developing evi-

dence-based coverage policies for many new and/or existing technologies (110,111), and these can lead to both 3) inappropriate spending being allocated for new technologies for which the long-term benefits and risks have not been determined, and 4) unintended effects of reducing the use of more effective, older technologies and techniques.

Clinical trials are either explanatory or pragmatic (112). Explanatory trials generally measure efficacy — the benefit a treatment produces under ideal conditions. Consequently, explanatory trials often use carefully-defined subjects in a well-controlled research setting. Patient selection in an explanatory approach is based on the principles of homogenous population, primarily aiming to further scientific knowledge.

In contrast, pragmatic trials, (i.e., practical clinical trials) measure effectiveness — the benefit the treatment produces in routine clinical practice. In this approach, the design reflects variations between patients that occur in "real life" clinical settings, and aims to inform choices between treatments. Consequently, to ensure generalizability, pragmatic trials should represent the patients to whom a given treatment is best applicable (112). The biases resulting from practical clinical trials are accepted as part of physicians' and patients' responses to treatment, and are considered in the overall evidence assessment. In practical trial approaches the treatment response is represented as the total difference between 2 treatments (i.e., the target treatment and other referent treatment(s), as well as accounting for any associated placebo-type effects), as this tends to reflect the most likely pattern of clinical responses observed in practice (113-125).

Placebo-controlled trials take a different approach in which an actual treatment is evaluated against a sham intervention that attempts to duplicate many of the supposedly (inactive) characteristics of the active treatment (e.g., setting, size, shape, and/or color of sham medication, similar but non-specific physical interventions etc.). While these are usually referred to as "placebo controls," this is increasingly being viewed as a misnomer in light of the fact that numerous factors inherent to the application and/or administration of (even a sham) treatment may elicit psychological and physiological responses that are in some way salutogenic; these are known as placebo effects and/or responses, and have become the focus of a considerable body of research, particularly in pain management (87,126,127). Ideal studies should not only be randomized and placebo controlled- incorporating usual patient setting and comparing effects of different treatment outcomes (113,114,117,119,125,128-139) but should also directly or indirectly assess viability and mechanisms of placebo effects (55-57,63-65,79,80,82,84,86,140-165).

Practical clinical trials best address questions about the benefits, burdens and risks of an intervention as they might occur in routine clinical practice (166). Thus, the most distinctive features of practical clinical trials are that they 1) select clinically relevant interventions to compare, 2) include a diverse population of study participants, 3) recruit participants from a variety of practice settings, 4) collect data on a broad range of health outcomes, and 5) simulate actual clinical practice(s). To do this effectively, a variety of approaches may be necessary. Moreover, the standard protocols of the clinical trial may not capture subtle, more qualitative variables of patient response(s), or less than obvious quantitative features. In light of this, a more extensive, heterodox palette of possible research approaches has been suggested, although the use of these techniques should be none the less rigorous (87). Findings from these approaches may better accommodate the value desiderata of various groups that hold stake in research outcomes, and thereby make a more meaningful contribution to the overall corpus of research (85,86).

The viability of such heterodox approaches may be of particular value given that practical clinical trials often are designed and used to compare alternative clinical strategies. Some of the practical clinical trials in pain management are well appreciated. For example, a practical clinical trial of acute low back pain randomized 323 patients to 1 of 3 widely used treatments which included physical therapy, chiropractic treatment, and self-care using an educational booklet. This study showed that physical therapy and chiropractic care increased patient satisfaction, and marginally reduced symptoms as compared with the self-care principles outlined in the booklet (167). A practical clinical trial of therapeutic massage compared with acupuncture also demonstrated that therapeutic massage was more effective and less costly than acupuncture in treating low back pain (168), although other studies have demonstrated the effectiveness of acupuncture against other, specific types of pain, and particular pain syndromes.

In interventional pain management, multiple practical clinical trials have been performed to evaluate the effectiveness of less expensive and/or safer modalities as compared to more invasive treatments

(113-125,136-138). However, these studies have generally failed to be recognized by the insurance and/or academic communities, who persist in favoring the results of randomized controlled trials, despite a growing body of evidence to suggest the equiviability of other, non-randomized, controlled approaches.

Randomized Trials – Not Always the Best Evidence

Originally an agricultural protocol, randomized controlled trials (RCTs) were first introduced into clinical medicine over half a century ago to evaluate streptomycin for the treatment of tuberculosis (169). Since the 1940s, RCTs have become the most widely accepted tool for assessing the effectiveness of therapeutic agents (170-172). While considered to be the acme of clinical research, the RCT is often difficult to conduct in interventional pain management settings and may "miss" particular geno- and/or phenotypic individual characteristics that may affect attribute-treatment interactions (unless particular individual characteristics are pre-selected prior to group randomization). But the basis and nature of any patient selection must be equally cautious, as any frank bias in patient selection for RCTs may affect the outcome of controlled trials (173). While the RCT (174,175) shows significant merit in evaluating experimental interventions, many stumbling blocks — including the issues of ethics, feasibility, cost, and reliability, and insurmountable challenges to randomized, double-blind trials in interventional pain management — continue to be factors that may limit its use and effectiveness (176-180).

What makes the RCT an ideal method for measuring treatment effects is the ability to assign subjects randomly. Participants in clinical trials are randomly assigned to a treatment or control group, thus reducing biases by making treatment and control groups equal with respect to all "features," except the treatment assignment (181). Consequently, differences in efficacy found by statistical comparisons can most likely be attributed to the difference between the treatment and control, provided randomization was appropriately performed (182). Still, the RCT does not necessarily provide an absolute definition of treatment effectiveness, as there are inherent limitations to both the applicability and generalizability of RCTs.

RCTs are often restricted to the study of (groups of) patients with specific disease, comorbidity, and/or use of medications. Thus, RCTs generally demonstrate efficacy rather than effectiveness. Further, while random assignment reduces the likelihood that bias can occur, it does not confer absolute protection against bias or selection error. In randomized trials, investigators characteristically rely on random allocation to distribute (any) differences equally across the control and experimental groups. As a result, randomized trials often balance external validity against internal validity (183).

While the RCT is designed to ensure that a difference in outcome between a treatment and control group is due to experimental effects, other factors such as chance, confounding, biases due to differences between the groups, and/or differences in handling the groups, could in fact be the source of observed effects. Confounding and bias are usually avoided by randomization, and the use of single- or double-blinding within the design. However, it should also be noted that individuals who volunteer to participate as research subjects may possess particular qualities and expectations (this latter point having particular weight when considering the ethical implications of non-treatment in the sham-controlled group). In many respects, volunteers will be quite different from patients (in "real world practice") who would serve as the subjects in an observational study (184).

There are numerous problems with several RCTs that have evaluated interventional pain management techniques. For example, in a large, well-conducted controlled trial by Carette et al (131) evaluating epidural corticosteroid injections for sciatica due to herniated nucleus pulposus, the authors failed to perform the procedures under fluoroscopic visualization. A study of the effectiveness of corticosteroid injections into facet joints for chronic low back pain (132) failed to provide the appropriate diagnosis prior to enrolling the patients in the therapeutic phase and consequently did not rule out false positives.

Three randomized trials evaluating the effectiveness of radiofrequency neurotomy (133-135) were excluded in an evidence synthesis in light of technical flaws. The first was a randomized, controlled trial of cervical radiofrequency for cervicogenic headache (133), in which patients received radiofrequency cervical facet joint denervation followed by lesion to the cervical dorsal root ganglion, while another group received local steroid/anesthetic injections to the greater occipital nerve, followed by transcutaneous electrical nerve stimulation, as necessary. Such methods are problematic, not only on the basis of possibly errant diagnosis, but also in the application of technique(s).

In the second, a randomized, double-blind, sham lesion-controlled trial study, radiofrequency denervation of lumbar facet joints was performed for the treatment of chronic low back pain (134). However, it is critical to note that only a single block producing 50% pain relief was utilized in the diagnostic inclusion criteria. The study was problematic on multiple grounds including the use of a single block, and there were several technical flaws noted in the performance of the procedure(s). The third study, a double-blind, placebo-controlled trial, while seemingly well performed, was excluded from the evidence synthesis due to similar methodological deficiencies (135).

In a special report evaluating the measurement of pain outcomes in randomized, controlled trials (185), 4 aspects of study results were addressed as being particularly relevant to providing clinically interpretable results, and/or concluding whether a treatment effect is both meaningful and real. First, the time course of pain relief accompanying a particular intervention should be consistent with understanding of pain pathology and treatment. Second, the report of percent of change is consistent with both the recommended analytical approach and issues relating to patient variability in baseline magnitude estimation (185). Third, reporting the proportion of patients responding to intervention(s) according to defined criteria can confirm results with greater clinical meaning (e.g.- the proportion of patients demonstrating a 50% or greater level of clinical improvement). Fourth, expanding response criteria conveys the extent of variability (heterogeneity) in treatment response. Describing heterogeneity may allow for understanding response(s) at the individual level (186), the importance of which is becoming increasingly recognized, as previously discussed.

In light of this, it is recommended that critical reporting elements for results and conclusions of evidence relevant to pain management must include:

- Time course of pain relief and function consistent with the disease
- Percentage change in pain intensity
- Responder proportions
- Proportions of patients experiencing varying degrees of responses.

The Value of Non-randomized Studies

There is equivocal discussion regarding the role of observational studies in the evaluation of medical treatment (23-26,187-192). An observational study is defined as an etiologic or effectiveness study using information from 1) an existing database, 2) a cross-sectional study, 3) a case series, 4) a case-controlled design, 5) a design with historical controls, or 6) cohort design (187). Observational designs lack the experimental element of random allocation to treatment or control groups, and rely on assessment of (observed) changes or differences in 1 characteristic (e.g., an exposure or intervention) and changes or differences in an outcome of interest. Norris and Atkins (189) used the term non-randomized study to refer to any protocol other than the RCT, including those studies in which the investigator assigns treatment groups on the basis of non-random strategy (non-randomized trial), observational studies in which the investigator does not assign treatments (such as case-control and cohort studies), and single-group studies (such as pre- versus post-treatment analysis in case series) that do not employ a comparison group.

Observational designs have long been used to evaluate educational programs (192), and in toxicologic studies that have examined exposures that might cause harmful effect(s) (193). In general, studies of risk factors cannot be randomized because they relate to inherent human characteristics or practices, and manipulation of these characteristics is not possible and/or exposing subjects to harmful risk factors is unethical (194). Observational data may also be needed to assess the effectiveness of an intervention in a natural setting rather than in the contrived environment of a controlled trial. Several publications have detailed the advantages and limitations of utilizing non-RCTs and observational data (84,86,188-190,195,196).

It is important to note that study designs other than RCTs can be critical to evaluate diagnostic (197) and prognostic strategies, as well as to assess the harms of particular interventions (198). Even so, debate continues on whether non-randomized studies can and should be used to formulate recommendations about treatment (199,200). The historical evidence of studies of vitamin supplementation and hormone replacement therapy, in which large clinical trials failed to confirm benefits reported by multiple observational studies (201,202), has prompted renewed attention on the pitfalls of drawing conclusions from non-randomized studies. Yet, in some areas of healthcare — among them surgery, interventional pain management, public health, and healthcare delivery — the bulk of evidence of clinical intervention and/or or policy effectiveness has been derived from non-randomized designs.

Like any investigational approach, observational studies can have flaws in design or analysis, including problems of heterogeneity and publication bias. However, all observational studies lack experimental power. Still, multiple reviews that have compared the evidence of treatment effects in randomized and non-randomized studies have suggested that (for selected medical topics), randomized and non-randomized studies may yield very similar results (200,203,204).

Clearly, observational, non-randomized studies have a role in those situations for which RCTs are not available, and (even when RCTs are available), when there is the need to quantify effectiveness of "real world" experience, environments, and circumstance(s) (84,86,87,181). A contemporary example of this was provided in the evaluation of drug-eluting stents: while RCTs have demonstrated short-term efficacy for relatively healthy patients, observational studies have begun to reveal long-term effectiveness and safety problems (such as the use of clopidogrel in differing groups of patients) (205).

A number of approaches to making statistical inferences from observational data have been described. Some focus on study design, while others assess the actual statistical techniques used (206). Despite these attempts, observational studies (even those with the most appropriate designs) do not automatically control for selection biases as do RCTs. To overcome this obstacle, it has been proposed that statistical methods involving matching, stratification, and/or covariance adjustment are essential (207). The goal of such statistical techniques is to create an analysis that resembles what would occur had the treatment been randomly assigned. Statistical methods in observational studies need to be evaluated for their capabilities to achieve balance on background characteristics that affect treated and control groups; the impact of outcome data should not play a role in the assessment of whether certain statistical methods are of merit (206).

Two statistical approaches that are often used to adjust for pretreatment balances include analysis of covariance, and propensity-score methods. These approaches are complementary (207). Other authors maintain that the instrumental variable method is better than the propensity score method because it eliminates bias due to unobserved variables, and the results better approximate those of RCTs (207). Due to inherent variations and differences in the final inferences based on the methods chosen, investigators should be cautious when conducting observational data analysis, and must consider the most important patient characteristics to be measured before treatment assignment.

The data collected from RCTs are strong only if it can be shown that in fact, a truly random sample of eligible patients participate and complete the protocol as designed. Consequently, when patients volunteer to be included in observational studies, rigorous and appropriate methods for dealing with selection bias and confounding issues must be part of the analytic plan (93).

Many non-randomized, observational trials in interventional pain management provide excellent information (113-125,136-138). The importance of non-randomized trials has also been demonstrated for surgical interventions (notably the Spine Patient Outcomes Research Trial [SPORT] studies) (208-211).

Evaluation Of The Evidence

Throughout the 1990s and into the 21st century, the Agency for Health Care Research and Quality (AHRQ) has been the foremost federal agency providing research support and policy guidance in health services research in the United States. Its ongoing work includes systems' rating of the quality of individual articles, as well as systems' grading the strength of a body of evidence (212).

The National Health and Medical Research Council of Australia considers scientific data to be at the core of evidence-based approaches to clinical or public health issues (213), emphasizing that evidence needs to be carefully gathered and collated from a systematic literature review of each particular issue in question.

The National Coordinating Center for Health Technology Assessment (NCCHTA) of the United Kingdom also publishes systematic reviews of clinical trials and other studies (214). The NCCHTA described how reviews, meta-analyses, literature reviews, and identification of primary studies were conducted when evaluating any investigation's quality, applications in other contexts, and when making recommendations for further research.

The Cochrane Collaboration (25) has also advanced many principles of evidence synthesis. The majority of Cochrane reviews are based on randomized trials. However, in recent years, both randomized and non-randomized controlled trials have been utilized in some studies. Non-randomized trials were used as part of the systematic review evaluating disc surgery (41,42), rehabilitation after lumbar disc surgery (44) ,and superficial heat or cold for low back pain (43).

Types of Reviews

A number of different types of reviews may be utilized to provide a broad overview of a focal topic and the relative strength of these may be evaluated. Characteristically, 3 types of approaches are utilized-the systematic review, narrative review, and health technology assessments (104, 105). A systematic review is a methodic investigation of the literature on a given topic in which the "subjects" are the scientific papers being evaluated (104). In contrast, a narrative review, while similar to a systematic review, does not employ the methodologic safeguards to control bias (Table 1). Thus, the major difference between these 2 approaches is that a systematic review attempts to minimize bias by the comprehensiveness and reproducibility of the search and selection of articles for review, and provides assessment of the methodologic quality of the studies (215-221).

A third type of review is the Health Technology Assessment (HTA), a multidisciplinary approach that studies the medical, social, ethical, and economic implications of the development, use, and diffusion of health technologies. HTAs have been described as, "the bridge between the world of research and the world of decision making" (105) and are being used with increasing frequency to influence both practice and policy. To effectively influence policy, HTAs must not only be scientifically accurate, but must also be optimally timed so as to affect the sensitivity of the political decision makers. Differences between systematic reviews and HTAs are illustrated in Table 2.

Yet, since the "foundation" of EBM practice is in the use of information gained from systematic reviews (or more correctly, in the synthesis of evidence from systematic reviews), it is vital to consider that the strength of this foundation reflects the quality of the systematic reviews, and it is therefore necessary to evaluate the evidence summaries and syntheses themselves before evidence-based decisional processes can be built upon them.

Assessment of Strength of the Evidence

Credible evidence is crucial to both clinicians and patients making informed choices about healthcare. Credible evidence reflects "empirical observations of real events [that is], systematic observations using rigorous experimental designs or non-systematic observations (e.g., experience) not revelations, dreams, or ancient texts" (222,223). Evidence may be sought from, and ultimately is applicable to different settings including clinical care, policy-making, dispute resolution, and law (224,225). However, any and all evidence must be both reliable and relevant. Further, while evidence must be scientific, its use and utility are often

Table 1. *Differences between narrative and systematic reviews*

Core Feature	Narrative Review	Systematic Review
Study Question	Often broad in scope.	Often a focused clinical question.
Data sources and search strategy	Specifications of database searched and search strategy are not typically provided.	Comprehensive search of many databases as well as the so-called gray literature. Explicit search strategy provided.
Selection of articles for study	Not usually specified. If specified, potentially biased.	Criterion-based selection, uniformly applied.
Article review or appraisal	Variable, depending on who is conducting the review.	Rigorous critical appraisal, typically using a data extraction form.
Study quality	Usually not assessed. If assessed, may not use formal quality assessment.	Some assessment of quality is almost always included as part of the data extraction process.
Synthesis	Often a qualitative summary.	Quantitative or qualitative summary.
Inferences	Occasionally evidence-based.	Usually evidence-based.

Adapted from Ref. 104

Table 2. *Differences between systematic reviews and health technology assessments (HTAs)*

	Systematic Reviews	HTAs
Methodological standards	Only include studies with the best methodological evidence	Include studies of topics of interest to policy-makers, even if evidence is suboptimal
Repeating previous studies	No need to repeat if previous studies were high quality, and no new high-quality evidence	The need to defend the report's conclusions often necessitates repetition
Breadth versus depth	Only include topics for which there is good evidence; topics driven by scientists' interests	Include topics most relevant to policy-makers; exclude those not of relevance even if there is good quality evidence
Inclusion of content experts and policy-makers	Content experts, but not policy-makers usually included	Can be concerns that content experts and policy-makers are biased
Performance of economic evaluations	Usually not done	Economic evaluations are an important component of HTAs, but lack of good evidence about effectiveness/ diagnostic accuracy limit their impact
Making policy recommendations	Almost never done	Sometimes done, but with caution
Active dissemination	Rarely done	Sometimes done

Adapted from Ref. 105

tempered by the realities of circumstance and effect. When addressing the quality of evidence that can and should be employed so as to facilitate decision-making, resolve equipoise, and increase the likelihood of desired health outcomes, the prudent use of current professional knowledge is indispensable to upholding the science and art of medical practice (86,226). Appropriate assessment of the evidence obtains the use of pertinent, valid, and relevant information through systematically acquiring, analyzing, and transferring research findings into clinical execution (as well as through management, and policy arenas) (228). Thorough assessment of evidence involves:

- Developing specific question(s) in ways that can be answered by a systematic review: specifying the populations, settings, problems, interventions, and outcomes of interest
- Stating criteria for eligibility (inclusion and exclusion) of literature to be considered before conducting literature searches, so as to avoid bias introduced by arbitrarily including or excluding certain studies
- Searching the literature to capture all the evidence about the question of interest
- Reviewing abstracts of publications to determine initial eligibility of studies
- Reviewing retained studies to determine final eligibility
- Abstracting data from these studies into evidence tables
- Determining the quality of studies and the overall strength of evidence
- Synthesizing and combining data from evidence tables, and deciding whether quantitative analyses (i.e. meta-analysis) are warranted; and
- Subjecting the findings to peer review, revising, and producing the final overview of evidence.

Grading Quality and Rating the Strength of Evidence

Grading the quality of individual studies and rating the strength of a body of evidence are both crucial elements in supporting the evidence-based foundations of practice knowledge. Quality refers to the extent to which all aspects of a study design and conduct can be shown to protect against systematic bias, non-systematic bias, and inferential error (215). An expanded definition holds that quality extends to a study's design, conduct, and analysis, and reflects minimal biases in selecting subjects, measuring outcomes and evaluating differences in the study groups (212). Specific sets of guidelines that have been formulated from synthesized sets of evidence reviews provide clear instructions on how systematic reviews (e.g., QUOROM), randomized controlled trials (e.g., CONSORT), observational studies (e.g., MOOSE), and

studies of diagnostic test accuracy (e.g., STARD) should be reported (187,188,190, 227-231). In addition, AHRQ (212), Cochrane reviews (232), and other reports evaluating evidence-based studies have been published (233-235). Specific criteria for evaluating systematic reviews, randomized, controlled trials, observational studies, and diagnostic test studies were developed by AHRQ (212). The AHRQ reviewed 20 systems of systematic reviews or meta-analyses. To arrive at a set of high-performing scales or checklists pertaining to systematic reviews, the AHRQ took into account 7 key domains as illustrated in Table 3 (212).

Strength of evidence also has a range of definitions, all taking into account the size, credibility, and robustness of the combined studies of a given topic. However, systems for grading the strength of a body of evidence are less uniform and consistent than those rating study quality (212). Selecting the evidence to be used in grading systems depends on 1) the reason for measuring evidence strength, 2) the type of studies that are being summarized, and the 3) structure of the review panel. Domains for rating the overall strength of a body of evidence are listed in Table 4. The National Health and Medical Research Council (NHMRC) (213) described 5 key points for considering levels of evidence as listed in Table 5. Not all systems are viable or facile; some are extremely cumbersome to use — requiring substantial resources — whereas others are incomplete and/or non-comprehensive. Multiple systems have been utilized in the preparation of specific clinical guidelines. Table 6 shows the designation of evidence levels (i.e., levels I through V) used in interventional pain management guideline preparation (37,38,212).

Randomized Clinical Trials

For the evaluation of randomized trials, 2 types of guidelines are available. These are the guidelines described by AHRQ (212) and those used in evaluation of interventions as described by the Cochrane Review Group (232).

The authors of AHRQ designated a set of high-performing scales or checklists pertaining to randomized clinical trials, by assessing coverage of the 7 domains described in Table 3. Criteria described by the Cochrane Review Group (for musculoskeletal disorders) include methodology of patient selection to evaluate treatment allocation and group similarity; intervention (blinding, control of co-interventions, the compliance rate); outcome measurements with blinding, measurement of at least 1 primary outcome, and description of withdrawal/dropout rate, which is unlikely to cause bias; statistics, and intention-to-treat analysis.

Table 3. *Domains in the Agency for Healthcare Research and Quality (AHRQ) criteria for evaluating 4 types of systems to grade the quality of individual studies*

Systematic reviews	**Randomized controlled trials**	**Observational studies**	**Diagnostic test studies**
Study question	Study question	Study question	*Study population*
Search strategy	*Study population*	Study population	*Adequate description of test*
Inclusion and exclusion criteria	*Randomization*	*Comparability of subjects*	*Appropriate reference standard*
Interventions	*Blinding*	*Exposure or intervention*	*Blinded comparison of test and standard*
Outcomes	*Interventions*	*Outcome measures*	*Avoidance of verification bias*
Data extraction	*Outcomes*	*Statistical analysis*	
Study quality and validity	*Statistical analysis*	Results	
Data synthesis and analysis	Results	Discussion	
Results	Discussion	*Funding or sponsorship*	
Discussion	*Funding or sponsorship*		
Funding or sponsorship			

Italics indicate elements of critical importance in evaluating grading systems according to empirical validation research or standard epidemiological methods.

Source: West et al (212)

Table 4. *Criteria for rating the overall strength of a body of evidence*

Domain	Definition
Quality	• The quality of all relevant studies for a given topic, where "quality" is defined as the extent to which a study's design, conduct and analysis has minimized selection, measurement, and confounding biases
Quantity	• The magnitude of treatment effect
	• The number of studies that have evaluated the given topic
	• The overall sample size across all included studies
Consistency	• For any given topic, the extent to which similar findings are reported from work using similar and different study designs.

Adapted from Ref. 212

Table 5. *The National Health and Medical Research Council (NHMRC) keypoints in consideration of level of evidence*

- Resolution of differences in the conclusions reached about effectiveness from studies at differing levels of evidence or within a given level of evidence.
- Resolution of the discrepancies is an important task in the compilation of an evidence summary.
- Inclusion of biostatistical and epidemiological advice on how to search for possible explanation for the disagreements before data are rejected as being an unsuitable basis on which to make recommendations.
- Recognition of the fact that it may not be feasible to undertake randomized controlled trials in all situations. Guidelines should be used on the best available evidence.
- Recognition of the fact that it may be necessary to use evidence from different study designs for different aspects of the treatment effect.

Adapted from Ref. 213

Table 6. *Levels of evidence*

Level I	Conclusive: Research-based evidence with multiple relevant and high-quality scientific studies or consistent reviews of meta-analyses
Level II	Strong: Research-based evidence from at least 1 properly designed randomized, controlled trial; or research-based evidence from multiple properly designed studies of smaller size; or multiple low quality trials.
Level III	Moderate: a) Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method); b) evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies, case-controlled studies, or interrupted time series with a control group); c) evidence obtained from comparative studies with historical control, 2 or more single-arm studies, or interrupted time series without a parallel control group.
Level IV	Limited: Evidence from well-designed non-experimental studies from more than 1 center or research group; or conflicting evidence with inconsistent findings in multiple trials
Level V	Indeterminate: Opinions of respected authorities, based on clinical evidence, descriptive studies, or reports of expert committees.

Adapted and modified from Refs. 37, 38, 212

Observational Studies

Both AHRQ and, more recently, the Cochrane Collaboration have recognized the importance of observational studies. The AHRQ considered several key domains and arrived at a set of 5 high-performing scales or checklists pertaining to observational studies (Table 3). Several other publications have described the process of analysis of observational studies and developed checklists for rating evidence available (187-190).

The inclusion of observational studies improves systematic reviews by avoiding a number of problems associated with sole use of RCTs; the most obvious being that certain important health care problems have not been studied, or are very difficult, if not imossible to study with randomized trials. Randomized trials may also be inappropriate in that there may be insufficient information on the types of participants or outcomes which are of relevance to the review (e.g., rare side effects), or the data may only reflect short-term follow-up when important findings depend on longer-term evaluation. Inclusion of evidence from non-randomized studies may resolve some of these problems.

However, inclusion of non-randomized studies in systematic reviews may also pose problems, as unexpected biases may occur and threaten the validity of the study and the overall conclusions.

Studies of Diagnostic Tests

The AHRQ Assessment identified 6 checklists to evaluate the quality of diagnostic studies, identifying 5 key domains for judging the quality of diagnostic test reports (Table 3).

Due to difficulties in assessing the quality of diagnostic studies, a new tool, Quality Assessment of Diagnostic Accuracy Studies (QUADAS), was developed (233). This instrument fills a gap in systemic evaluation of diagnostic accuracy studies. The questions utilized by QUADAS for assessment of quality of individual articles or diagnostic tools include:

- Was the spectrum of patients representative of those who will receive the test in practice?
- Were selection criteria clearly described?
- Is the reference standard likely to correctly classify the target condition?
- Is the time period between reference standard and index test short enough to be reasonably assured that the target condition did not change between the 2 tests?
- Did the whole sample (or a random selection of the sample) receive verification using a reference standard of diagnosis?
- Did patients receive the same reference standard regardless of the index test result?
- Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
- Was the execution of the index test described in sufficient detail to permit replication of the test?
- Was the execution of the reference standard described in sufficient detail to permit its replication?
- Were the index test results interpreted without knowledge of the results of the reference standard?
- Were the reference standard results interpreted without knowledge of the results of the index test?
- Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
- Were un-interpretable/intermediate test results reported?
- Were withdrawals from the study explained?

Several studies have described checklists for evaluating studies of the diagnostic accuracy of medical tests. The key elements included 1) study design, 2) patient-care setting, 3) criteria for inclusion and exclusion of subjects, 4) planned sample size, 5) subgroup analysis, 6) methods to avoid spectrum bias (e.g., consecutive series, statistically selected random sample, stratified random sample), 7) methods to define the spectrum of disease, 8) methods and references for evaluated tests and criterion standard tests, 9) blinding of those performing evaluated tests and criterion standard tests to avoid reviewer bias, 10) methods to avoid verification bias, 11) methods for statistical analysis, 12) cutoffs used for quantitative tests and how they were determined, and 13) design features aimed at insuring compatibility with other studies (235-237). For studies of prognostic tests, it should be determined whether the criterion standard or the evaluated test influenced the treatment(s) (an effect known as treatment paradox).

Bossuyt et al (234) published standards for reporting of diagnostic accuracy. The STARD checklist for the reporting of diagnostic accuracy of studies includes methods (participants, test methods and statistical methods), results (participants, test results, and estimates) and discussion.

Numerous other checklists have been developed to evaluate the quality of studies (198,232-239), each focusing upon several of the aforementioned factors and criteria.

Analytical Preparation

Evidence linkages or synthesis are performed by systematic reviews and meta-analysis. In both types of assessment, methodological criteria and controls are crucial (Fig. 1). Research findings from the literature provide the cornerstone for guideline recommendations. However, published studies alone may not provide all necessary or complete information regarding details of clinical practice, particularly for interventional techniques. Consequently, additional sources of information and evidence, such as consensus, are sought. Consensus data are generally obtained from the guideline committees through members of the committee, or the consensus findings may be reviewed by other experts in the field or by open forum presentations.

Guideline recommendations generally are based directly on the evidence linkages developed during the review process. Characteristically, while all sources of evidence, including systematic reviews and consensus are utilized, these are separately considered and differentially weighted prior to formulation of the final (guideline or policy) recommendations (240).

The value of such information may need to be reconsidered, both in guideline and policy development. The factors and relationships that may influence this process have been discussed by Giordano (84,240).

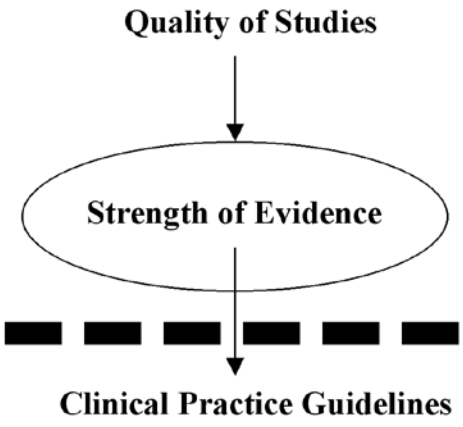

Fig. 1. *Continuum from study quality through strength of evidence to guideline development*

The dashed line is the theoretical dividing line between summarizing the scientific literature and developing a clinical practice guideline. Below the dashed line, guideline developers would decide whether the evidence represents all the relevant subsets of the populations (or settings, or types of clinicians) for whom the guideline is being developed.

Adapted from Ref. 212

Role of EBM in Interventional Pain Management

The ultimate goal of EBM is "the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients" (27). Given that the bedrock of EBM is integrating individual clinical expertise with the best available external evidence from systematic research, it becomes clear that without systematic reviews, EBM (as currently contemplated) is not possible. The most powerful of these reviews involve a synthesis of the evidence (221). Therefore, the evidence upon which EBM rests is determined by the quality of systematic reviews and their synthesis of the evidence. However, we agree with Jonas (10, 85) that the meaning of "evidence" in EBM is often (if not always) dependent upon "who is using the evidence."

To be sure, all information is leveled and has distinctly different value(s). The standard hierarchy of evidence based has characteristically been depicted as a lexical order from well-designed, randomized, controlled trials at 1 extreme, to opinions of experts or respected authorities at the other. Systematic reviews, for their part, may vary from qualitative reviews (where there is no attempt at a synthesis of the findings i.e., narrative reviews), to a highly systematic synthesis of the evidence (221). Systematic reviews differ from meta-analyses, in which the results of independent RCTs are pooled for a total effect size. Synthesis becomes necessary because discrepancies occur between individual RCTs and between RCTs and meta-analyses (221,241). As Coulter (221) has noted, the results of a single, double-blinded trial can be misleading, particularly if the number of subjects is insufficient to power the study and give it statistical legitimacy. Meta-analysis overcomes that problem by combining studies that are homogenous, so that the subject pool is larger. Thus, in actuality, what may be a "gold standard" is not the single random-based trial, but, is either the systematic review of RCTs or the results of a meta-analysis. Still, the inclusion of non-randomized trials in systematic literature reviews is becoming important and, as this paper has attempted to illustrate, at times crucial.

Coulter has proposed the following structured inquiry to assess the quality of systematic reviews (221):

1) Who did the review? Reviews are performed by a variety of researchers and institutions. These vary considerably in both expertise, and in the resourc-

es available to conduct the review. The effect of funding on results has been noted in the literature, and strongly consistent evidence shows that industry-sponsored research tends to draw pro-industrial conclusions (242). Other well-funded organizations include evidence-based practice centers established in the United States and Canada and funded through the Agency for Healthcare Research and Quality (AHRQ) (243). The most important issue is whether or not there were sufficient resources available to ensure that the review was comprehensive with adequate literature search analysis and expertise, and that the use of these resources did not incur bias.

2) What was the objective of the review? Most objectives involve effectiveness and/or complications of a medical technique. In general, randomized trials tend not to report complications and safety in detail, and these tend to be better reported in observational studies. As well, most interventional pain medicine techniques have not been studied using well-performed randomized, controlled trials. Much of the available literature reflects interventions performed as much as 10 to 15 years earlier, with inadequate or dated methodology.
3) How was the review done? Namely, how was the database searched; were appropriate search terms used; if inclusion and exclusion criteria were utilized, who did the reviews, how was the evidence evaluated, what synthesis was possible, and how was safety evaluated? Many systematic reviews in interventional pain management have had problems with the aforementioned issues.

Holmes et al (244) asserted that the evidence-based movement in health sciences constitutes a good example of economic and political hegemony at play in the contemporary scientific arena. While this statement may seem extreme, misleading meta-analyses and systematic reviews are not uncommon, particularly in the interventional pain management literature (23,24,36-40,50-54,245). However, there have been a significant number of appropriately performed systematic reviews which are often overlooked (77-82, 55-58,246). Overall, there is a surprising lack of data to show improved clinical outcomes based on EBM. In fact, it has been estimated that the improvement in therapeutic outcomes that are based on any evidence may be as low as 15% (247).

Irrespective of what level or type of evidence is used in the decision-making process, emphasis must be upon the accumulated knowledge and experience, and the use of professional prudence in adhering and utilizing accepted standards (3,5,83,247). While opinion and personal judgment certainly play a role in prudence, it is important to assert that mere opinion has been shown to be the least reliable approach, and ignoring or disregarding the differential value of distinct levels of evidence is both imprudent and inept.

Specific Reviews of Interventional Pain Management

Nelemans et al (71) reviewed multiple methods of treatment, reaching the singular conclusion that "convincing evidence is lacking regarding the effects of injection therapy on low back pain." In vaguely describing interventional techniques as "local injection therapy" they grouped specific therapeutics under an inaccurate classification, and failed to discuss the effectiveness or limitations of any 1 interventional protocol. Thus, while Manchikanti et al (248) have shown that the effectiveness of facet joint injections has been strongly documented by properly designed studies (61-66), Nelemans et al (71) described only 1 study of facet joint injections (which has been criticized extensively) and also erroneously combined epidural injections with other interventional techniques including trigger point, facet joint, and intradiscal injections.

The use of intradiscal injections, other than for provocative discography, is not a common practice (57,79). In addition, the combination of all types of epidural injections into a single category also poses major evaluative difficulty. Epidural injections are administered by multiple routes, including caudal, interlaminar, and transforaminal approaches (37-40,77,80, 81,249). Further analysis of the review by Nelemans et al (71) showed that 4 of the 5 studies involving caudal epidural steroid injections produced positive results, whereas 5 of 7 studies on interlaminar lumbar epidural steroid injections produced negative results (248).

Boswell et al (61,62) evaluated several types of therapeutic facet joint interventions, including intraarticular injections, medial branch blocks, and radiofrequency thermoneurolysis, and concluded that the evidence for therapeutic lumbar intraarticular facet joint injections supported use for short-term and long-term improvement, whereas, only limited support could be provided for cervical facet joint injections. Further, there was only moderate evidence to support the effectiveness of lumbar and cervical me-

dial branch blocks and for medial branch neurotomy.

In a review of randomized clinical trials of radiofrequency procedures for the treatment of spinal pain, Geurts et al (50), reached inaccurate conclusions that were supported in a subsequent editorial by Carr and Goudas (250). Geurts and coworkers (50) reviewed 6 studies, only 2 of which involved dorsal root ganglion radiofrequency procedures. Intra-articular radiofrequency, which is not an acceptable technique and has no physiologic or scientific basis because denervation should be performed on the medial branch nerves rather than the joint itself, was also inappropriately included in that review. Radiofrequency neurotomy of dorsal root ganglion is not a common procedure and has not been proven to be an effective modality for facet joint pain, however it is used for segmentally radiating pain.

Apart from the confusion regarding the identification of best evidence, 3 of the 3 studies demonstrated positive results for management of facet joint pain with radiofrequency neurolysis. This should have yielded moderate to strong evidence, rather than the conclusion of "insufficient evidence supporting the effectiveness of most radiofrequency treatments for spinal pain." (50, 256). Responding to this review, Bogduk (251) defended radiofrequency neurotomy, identified numerous deficiencies in the review, and elaborated on the practical difficulties of randomized trials. In addition, Bogduk described the tenor of the review as highly negativistic, and warned against the review and editorial being misused by organizations intent upon discrediting radiofrequency neurotomy.

Niemisto et al (51), within the framework of the Cochrane Collaboration Back Review Group, concluded that there was limited evidence that radiofrequency denervation had a positive short-term effect on chronic cervical zygapophysial joint pain and a conflicting short-term effect on chronic low back pain. They identified 7 randomized controlled trials as meeting the criteria and were included in the analysis, including 2 trials involving radiofrequency lesioning of the dorsal root ganglion for cervicobrachial pain and 1 trial involving intradiscal radiofrequency lesioning for discogenic pain. In spite of a multitude of problems, they included 2 studies which were not eligible for evidence synthesis because of faulty diagnostic methodology and technical issues. The conclusions of this review, though described as being within the framework of the Cochrane Collaboration Back Review Group guidelines, may have been unwarranted (61).

Manchikanti et al (66) utilized inclusion/exclusion criteria in their search strategies and assessed key domains in rating the quality of systematic reviews according to methods as described by AHRQ (212). Based on these criteria, after identifying 7 randomized trials of radiofrequency neurotomy for spinal pain, only 4 were related to medial branch neurotomy. The authors included only 2 randomized trials for evidence synthesis, and excluded 2 trials due to various deficiencies; as well, multiple observational studies, 4 prospective evaluations and 3 retrospective evaluations were considered in the evidence synthesis. Based on this, the authors concluded that the combined evidence for radiofrequency neurotomy of medial branches was strong for short-term relief and moderate for long-term relief of chronic spinal pain of facet joint origin (66).

In addition, numerous guidelines (37-39) and systematic reviews (61,62) concluded that the evidence for medial branch neurotomy was moderate. The analyses included observational studies, and separately evaluated the evidence for cervical, thoracic, and lumbar facet joint radiofrequency, and also noted strong evidence for those techniques recommended by Bogduk (252) and Lord et al (128). In a well known book by Natchemson and Jonsson (67), multiple reviews inaccurately reached negative conclusions about diagnostic and therapeutic interventional techniques, primarily due to a lack of proper evaluation of method(s) and outcomes of interventional techniques.

There have also been several systematic reviews of the effectiveness of epidural steroid injections. The first, by Kepes and Duncalf in 1985 (68) concluded that the rationale for steroid administration was not proven. However, utilizing the same studies a year later, Benzon (69) concluded that mechanical causes of low back pain, especially those accompanied by signs of nerve root irritation, may respond to epidural steroid injections (69). The differences between the conclusions of Kepes and Duncalf (68) and Benzon (69) may have been due to the fact that the former included studies on systemic steroids, whereas the latter was limited to epidural steroid injections alone.

The Australian National Health and Medical Research Council Advisory Committee on epidural steroid injections extensively studied caudal, interlaminar, and transforaminal epidural injections, utilizing all the literature that was available at the time (249). They concluded that the balance of the published evidence supported the therapeutic use of caudal

epidurals. However, they also concluded that studies of lumbar interlaminar epidural steroids did not support utility against acute sciatica (70). In updated recommendations, Bogduk (70) argued against epidural steroids by the lumbar route, because many interventions were necessary for treatment, but supported the potential usefulness of transforaminal steroids for disc prolapse.

Koes et al (53) reviewed 12 trials of lumbar and caudal epidural steroid injections, and reported positive results from only 6 studies. This analysis noted that there were 5 studies of caudal epidural steroid injections and 7 studies of lumbar epidural steroid injections, all of which were randomized. Four of the 5 studies of caudal epidural steroid injections showed positive results, whereas 5 of 7 studies reported negative results for lumbar epidural steroid injections. Earlier, these authors concluded that the efficacy of epidural steroid injections had not yet been established and the benefits of epidural steroid injections, if any, seemed to be only of short duration (53). In the review of epidural steroid injections for low back pain and sciatica (71), (which included 3 more studies, for a total of 15 trials that met inclusion criteria), they again concluded that of the 15 trials, 8 reported positive results for epidural steroid injections and their basic conclusions remained the same. However, a potentially misleading flaw in both studies is that when caudal epidural steroid injections are separated from interlaminar epidural steroid injections, there is significant proof of effectiveness for epidural steroids.

Watts and Silagy (72) performed a meta-analysis of available data and defined efficacy in terms of pain relief (at least 75% improvement) for short-term (60 days) and long-term (1 year) benefit. They concluded that epidural steroid injections increased the odds ratio of pain relief to 2.61 in the short-term, and to 1.87 in the long-term, suggesting that epidural steroids were effective.

In a review of the literature, McQuay and Moore (73) concluded that epidural corticosteroid injections were effective for both back pain and sciatica, and emphasized that even though epidural steroid injections can optimize conservative therapy and provide substantial pain relief for up to 12 weeks in patients with acute or subacute sciatica, a few patients with chronic pain report complete relief. Consequently, most patients must return for repeat epidural injections. Bernstein (253) reviewed the effectiveness of injections in surgical therapy in chronic spinal pain and concluded that there was limited evidence to support the effectiveness of interlaminar or caudal epidural steroid injections for sciatica with low back pain. In a review of data provided by available systematic reviews and controlled studies of the treatment of regional musculoskeletal problems, Curatolo and Bogduk (74) concluded that epidural steroids may offer limited, short-term benefit for sciatica. Vroomen et al (75) reviewed conservative treatment of sciatica, assessing 19 randomized controlled trials that included epidural steroid injections, and concluded that epidural steroids may be beneficial for patients with nerve root compression. In a systematic review of 13 trials of epidural steroid therapy, Rozenberg et al (76) concluded that 5 trials demonstrated greater pain relief within the first month in the steroid group as compared to the control group, whereas, 8 trials found no measurable benefits.

Nelemans et al (71), in a review of injection therapy for subacute and chronic benign low back pain, included 21 randomized trials. Of these, 9 were of epidural steroids. They failed to separate caudal from interlaminar epidural injections, but concluded that convincing evidence was lacking regarding the effects of injection therapy on low back pain.

The evidence from well-designed systematic reviews is contradictory (77, 80, 81). Well-conducted evidence synthesis for caudal epidural steroid injections was strong for short-term relief and moderate for long-term relief in the management chronic low back and radicular pain. The evidence for interlaminar epidural steroid was strong for short-term and limited for long-term relief in managing lumbar radiculopathy, whereas, for cervical radiculopathy, the evidence was moderate. The evidence for transforaminal epidural steroid injections was strong for short-term and moderate for long-term improvement in managing lumbar nerve root pain, whereas, it was moderate for cervical nerve root pain and limited in managing pain secondary to lumbar post laminectomy syndrome and spinal stenosis. This suggests that further research is required based upon 1) better understanding of the pathologic mechanisms of different types of pain, 2) more specific application(s) of interventional technique(s), and 3) more stringent analyses of the methods of both the studies themselves and the reviews, before any meaningful conclusions may be drawn.

ASIPP Systematic Reviews and Guidelines

Toward these ends, the American Society of Interventional Pain Physicians (ASIPP) has attempted to provide systematic reviews and guidelines (37-40, 61-66, 77-82) based upon a critical appraisal of existing data using focused criteria. These provide somewhat more convincing evidence for diagnostic and therapeutic interventions as summarized below:

- For the diagnostic interventions, there was strong evidence to support the accuracy of facet joint nerve blocks in the diagnosis of lumbar and cervical facet joint pain, whereas, evidence was moderate for this technique in the diagnosis of thoracic facet joint pain.
- The evidence was strong for lumbar discography, whereas, the evidence was only limited for cervical and thoracic discography.
- Transforaminal epidural injections or selective nerve root blocks in the preoperative evaluation of patients with negative or inconclusive imaging studies was shown to be supported by moderate evidence; as was the evidence for sacroiliac joint injections in the diagnosis of sacroiliac joint pain with diagnostic blocks.
- The evidence for therapeutic lumbar intraarticular facet injections was moderate for short-term and long-term improvement, whereas, it was limited for cervical facet joint injections.
- There was moderate evidence in support of lumbar and cervical medial branch blocks, as well as medial branch neurotomy.
- The evidence strongly supported the effectiveness of percutaneous epidural adhesiolysis. For spinal endoscopic adhesiolysis, the evidence was strong for short-term relief, while there was only moderate evidence to support the ability of this approach to provide long-term relief.
- For sacroiliac intraarticular injections, the evidence was moderate for short-term relief, and limited for long-term relief. Similarly, the evidence supporting the effectiveness of radiofrequency neurotomy against sacroiliac joint pain was limited.
- There was strong evidence for the effectiveness of intradiscal electrothermal therapy for short-term relief of chronic discogenic low back pain, and moderate evidence to support long-term relief against this pathology. Evidence was limited for the effectiveness of annuloplasty.
- Analysis of the various techniques utilized for percutaneous disc decompression showed that evidence was moderate for short-term, and limited for long-term relief for automated percutaneous lumbar discectomy, percutaneous laser discectomy, nucleoplasty, and for the effective use of DeKompressor® technology.
- For vertebral augmentation procedures, the evidence was moderate for both vertebroplasty and kyphoplasty.
- The evidence for spinal cord stimulation in failed back surgery syndrome and complex regional pain syndrome was strong for short-term relief and moderate for long-term relief. The evidence for implantable intrathecal infusion systems was moderate to strong.

The European Guidelines

Medicine is becoming increasingly globalized, and we have come to recognize that what appear to be cultural differences in pain expression, and response to treatment may in fact reflect the interactions of geographically distributed genomic dispositions that are variably expressed through environmental constraints and factors (i.e., society and culture). Thus, any attempt to understand the human condition of pain and develop a comprehensive, integrative pain medicine, must both acknowledge the plurality of these genomic-phenotypic-environmental interactions, and accommodate a pluralistic approach to incorporating multi-societal and cultural data, so as to build what may be considered a truly "world literature" to support a global pain medicine. In this light, international guidelines become evermore relevant.

One of the primary objectives of the European evidence-based guidelines was to provide a set of recommendations that could support the utility of existing and future nationalLY and internationally developed and disseminated protocols. In preparing the European guidelines, Airaksinen et al (52) synthesized the extant evidence for interventional pain management techniques. Toward this goal, the authors analyzed (and recommended) various invasive procedures, including epidural steroids and spinal nerve root blocks with steroids, facet injections, intradiscal injections, sacroiliac joint injections, radiofrequency facet denervation, intradiscal electrothermal therapy, and spinal cord stimulation. None of the treatments were recommended in managing chronic, non-specific low back pain. However, The authors had favorable recommendations for targeted delivery of epidural steroid injections. Flaws in

this review included evaluation of chronic non-specific low back pain as a homogeneous clinical entity and use of a multitude of techniques for these problems.

Although the guidelines were published in 2006, the Working Group for Chronic Back Pain formulated the guidelines at its first meeting in May 2001. After 7 meetings, an outline draft of the guidelines was prepared in July 2004 and published in 2006. Thus, it took 5 years to publish the guidelines from start to finish. Generally, guidelines are only viable for 2 or 3 years. In addition, while the literature search was extensive, it only included RCTs up to November 2002.

Cochrane Reviews

Gatchel and McGeary highlighted some of the issues related to the Cochrane reviews in spine care (254-264). The most problematic feature noted was that the primary authors of most of the reviews of interventional pain management techniques were either non-physicians or physicians without expertise in interventional techniques, and thus the reviews may not necessarily reflect clinical applicability (although this point is most certainly defeasible). But as Mowatt et al (256) found, a considerable proportion of Cochrane reviews had strong evidence of either honorary or ghost authorship with somewhat vague disclosure policies, potentially masking possible conflicts of interest. Gatchel and McGeary (254) described these studies as "…simply nihilistic"; their critique focused upon arbitrary rating criteria in systematic reviews, meta-analyses, and RCTs. Yet, while these concerns are important, they reflect particular opinions in defense, or against various rehabilitation models and surgical techniques (260-262). Furlan et al (257) noted that the quality of individual reviews of the Cochrane Collaboration reviews varied considerably.

Cochrane reviews often include a number of low-quality trials that are combined with studies of better quality, consequently resulting in inconclusive judgment(s). Such methodologic issues can lead to invalid (and perhaps biased) conclusions that manifest potentially serious implications for the quality of patient care. But perhaps a larger issue is the need for more multi-national and multi-cultural studies to both be conducted, and melded into the database from which reviews and meta-analyses are derived. This may yield some provocative findings. It may well be that our knowledge of pain (together with our cumulative understanding of genomics and the brain) might reveal that while we are very similar as a species, what is common is the unique differences of individuals nested within (and perhaps caused by) specific socio-cultural and geographic environments. Interventional pain management must acknowledge and respond to these variables to be effective and sound as a therapeutic, humanitarian, enterprise.

The access, analyses and incorporation of international data are fundamental to establishing a global perspective, stimulating discourse, and ultimately developing applicable protocols, guidelines and policies through true dialectic.

Conclusion

Evidence provides insight to facts, and we need to recognize that insight(s) reflect meanings that are differentially relevant to distinct groups of moral agents (e.g.- patients, physicians, etc.). Evidence is a tool, and different types of evidence (like different types of tools) serve particular purposes for those who use them. But any tool must be well constructed and durable- yet must remain revisable to accommodate the purpose of the task at hand and the knowledge that defines both the tasks and the utility of the tool(s).

If the task at hand is the ongoing improvement of patient-centered pain medicine, and if we are to succeed at this task, then we must be empowered to 1) advance well-conducted research, 2) expand education, and 3) enthuse good practice by recognizing what is effective and what is not, and developing new techniques and approaches to therapeutics.

Evidence synthesis is complex and difficult, but so is the practice of interventional pain management. Difficult tasks require diligence, commitment, and knowledge (i.e., the "right" knowledge to inform and compel right and good decisions and actions). Such knowledge is powerful. It is hoped that by working together, as a community of clinicians, patients, researchers, administrators, and policy-makers, we can become empowered to maintain a global effort to enhance the standards and practices of pain care.

Acknowledgments

The authors are grateful to Sherry Loveless for graphic artistry and assistance with preparation of this manuscript and thank Tonie Hatton and Diane Neihoff, transcriptionists, for their assistance with preparation of this manuscript.

References

1. Jenicek M. How do we see medicine, health and disease? A basic set of rules and fundamental paradigms. In *Foundations of Evidence-Based Medicine*. The Parthenon Publishing Group, Inc., New York, 2005, pp, 3-13.
2. Giordano J. Pain, the patient and the physician: Philosophy and virtue ethics in pain medicine. In Schatman M (ed.) *Ethics of Chronic Pain Management*. Taylor-Francis, NY, 2006 pp 1-18.
3. Maricich Y, Giordano J. Pain, suffering and the ethics of pain medicine: Is a deontic foundation sufficient? *Am J Pain Manage* 2007;17:130-138.
4. Pellegrino ED. The internal morality of clinical medicine: a paradigm for the ethics of the helping and healing professions. *J Med Philos* 2001; 26:559-579.
5. Giordano J. Moral agency in pain medicine: Philosophy, practice and virtue. *Pain Physician* 2006; 9: 71-76.
6. Osler W, McCrae T. *The Principles and Practice of Medicine, Designed for the Use of Practitioners and Students of Medicine*. 10th ed., Appleton, New York, 1925.
7. Eisenberg JM, What does evidence mean? Can the law and medicine be reconciled? *J Health Polit Policy Law* 2001; 26:369-381.
8. *New Illustrated Webster's Dictionary of the English Language*. PAMCO Publishing Co., New York, 1992.
9. Giordano J. Pain as disease and illness: Part 2 – Structure and function of the ethics of pain medicine. *Prac Pain Management* 2006; 6:65-68.
10. Jonas WB. The evidence house: How to build an inclusive base for complementary medicine. *West J Med*. 2001; 175:79–80.
11. Jenicek M. The work of physicians with individuals and communities. Epidemiology and other partners in evidence-based medicine. In *Foundations of Evidence-Based Medicine*. The Parthenon Publishing Group, Inc., New York, 2005, pp, 3-13.
12. Haynes RB, Sackett RB, Gray JMA, Cook DC, Guyatt GH. Transferring evidence from research into practice, 1: the role of clinical care research evidence in clinical decisions. *ACP Journal Club* 1996; 125:A-14-15.
13. Napodano RJ. *Values in Medical Practice*. Human Sciences Press, New York, 1986.
14. Keckley PH. EBM in managed care: A survey of current and emerging strategies. *Mud Gen Med* 2004; 6:56.
15. The Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press; 2001.
16. Shaneyfelt T, Baum KD, Bell D, Feldstein D, Houston TK, Kaatz S, Whelan C, Green M. Instruments for evaluating education in evidence-based practice: a systematic review. *JAMA* 2006; 296:1116-1127.
17. McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, Kerr EA. The quality of health care delivered to adults in the United States. *N Engl J Med* 2003; 348:2635-2645.
18. Hayward RA, Asch SM, Hogan MM, Hofer TP, Kerr EA. Sins of omission: getting too little medical care may be the greatest threat to patient safety. *J Gen Intern Med*. 2005; 20:686-691.
19. Institute of Medicine. *Health Professions Education: A Bridge to Quality*. Washington, DC: National Academies Press; 2003.
20. Accreditation Council for Graduate Medical Education Outcome Project: general competencies. www.acgme.org/outcome/assess/compList.asp.
21. Association of American Medical Colleges. *Contemporary Issues in Medicine, II: Medical Informatics and Population Health*. Washington, DC: Association of American Medical Colleges; 1998.
22. Manchikanti L, Abdi S, Lucas LF. Evidence synthesis and development of guidelines in interventional pain management. *Pain Physician* 2005; 8:73-86.
23. Manchikanti L, Heavner J, Racz GB, Mekhail NA, Schultz DM, Hansen HC, Singh V. Methods for evidence synthesis in interventional pain management. *Pain Physician* 2003; 6:89-111.
24. www.ahrq. gov
25. The Cochrane Collaboration. *Evidence Health Care*. Available at: www.cochrane.org/docs/ebm.htm.
26. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312:71-2.
27. Sackett D, Richardson WS, Rosenberg W, Haynes B. *Evidence-based Medicine*. Churchill Livingstone, London, 1996.
28. McQuay H, Moore A. Introduction. In *Evidence-based Resource for Pain Relief*. Oxford University Press, New York, 1998, pp 1-3.
29. Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of EBM and patient choice. *ACP J Club*. 2002;136: A11-A14.
30. Guyatt G, Drummond R. Part 1. The basics: Using the medical literature. 1A. Introduction: The philosophy of evidence-based medicine. In. *Users' Guides to the Medical Literature. A Manual for Evidence-based Clinical Practice*. EBM Working Group. AMA Press, 2002, pp 3-12.
31. Guyatt G, Drummond R. Preface. In *Users' Guides to the Medical Literature. A Manual for Evidence-based Clinical Practice*. EBM Working Group. AMA Press, 2002, pp xiii-xvi.
32. Guyatt GH, Rennie D. Users' Guides to the Medical Literature [editorial]. *JAMA* 1993; 270:2096-2097.
33. Guyatt G, Drummond R. *Users' Guides to the Medical Literature. A Manual for Evidence-based Clinical Practice*. EBM Working Group. AMA Press, 2002.
34. Wiffen PJ. Evidence-based pain management and palliative care in issue 2 for 2006 of The Cochrane Library. *J Pain Palliat Care Pharmacother* 2006; 20:109-111.
35. Gonzalez EG, Materson (eds). *The nonsurgical management of acute low back pain*. Demos Vermane, New York 1997.
36. Bigos SJ, Boyer OR, Braen GR, Brown K, Deyo R, Haldeman S, Hart JL, Johnson EW, Keller R, Kido D, Liang MH, Nelson RM, Nordin M, Owen BD, Pope MH, Schwartz RK, Stewart DH, Susman J, Triano JJ, Tripp LC, Turk DC, Watts C, Weinstein JN. Acute low back problems in adults. Clinical Practice Guideline No.14, AHCPR Publication No. 95-0642. Rockville, Maryland. U.S.A., Agency for Health Care Policy and Research, Public Health Service, U.S., Department of Health and Human Services, December, pp. 1-60, 1994..
37. Boswell MV, Trescot AM, Datta S, Schultz DM, Hansen HC, Abdi S, Sehgal N, Shah RV, Singh V, Benyamin RM, Patel VB, Buenaventura RM, Colson JD, Cordner HJ, Epter RS, Jasper JF, Dunbar EE, Atluri SL, Bowman RC, Deer TR, Hansen HC, Staats PS, Smith HS, Burton AW, Kloth DS, Giordano J, Manchikanti L. Interventional techniques: Evidence-based practice guidelines in the management of chronic spinal pain. *Pain Physician* 2007; 10:7-112.
38. Boswell MV, Shah RV, Everett CR, Sehgal N, Mckenzie-Brown AM, Abdi S,

Bowman RC, Deer TR, Datta S, Colson JD, Spillane WF, Smith HS, Lucas-Levin LF, Burton AW, Chopra P, Staats PS, Wasserman RA, Manchikanti L. Interventional techniques in the management of chronic spinal pain: Evidence-based practice guidelines. *Pain Physician* 2005; 8:1-47.

39. Manchikanti L, Staats PS, Singh V, Schultz DM, Vilims BD, Jasper JF, Kloth DS, Trescot AM, Hansen HC, Falasca TD, Racz GB, Deer T, Burton AW, Helm S, Lou L, Bakhit CE, Dunbar EE, Atluri SL, Calodney AK, Hassenbusch S, Feler CA. Evidence-based practice guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician* 2003; 6:3-80.
40. Manchikanti L, Singh V, Kloth DS, Slipman CW, Jasper JF, Trescot AM, Varley KG, Atluri SL, Giron C, Curran MJ, Rivera JJ, Baha A, Bakhit CE, Reuter M. Interventional techniques in the management of chronic pain: Part 2.0. *Pain Physician* 2001; 4:24-96.
41. Gibson JN, Waddell G. Surgery for degenerative lumbar spondylosis: Updated Cochrane Review. *Spine* 2005; 30:2312-2320.
42. Gibson JN, Grant IC, Waddell G. The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. *Spine* 1999; 24:1820-1832.
43. French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. Superficial heat or cold for low back pain. *Cochrane Database Syst Rev* 2006; (1):CD004750.
44. Ostelo RW, de Vet HC, Waddell G, Kerckhoffs MR, Leffers P, van Tulder MW. Rehabilitation after lumbar disc surgery. *Cochrane Database Syst Rev* 2002; (2): CD003007.
45. Turner JA, Sears JM, Loeser JD. Programmable intrathecal opioid delivery systems for chronic non-cancer pain: A systematic review of effectiveness and complications. *Clin J Pain* 2007; 23:180-195.
46. Percutaneous Discectomy. Washington State Department of Labor and Industries, Office of Medical Director; February 24, 2004.
47. Murtagh J, Foerster V. Radiofrequency neurotomy for lumbar pain [Issues in emerging health technologies issue 83]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.
48. Intradiscal Electrothermal Therapy (IDET). Technology Assessment Update. Washington State Department of Labor and Industries, Office of the Medical Director; September 30, 2003.
49. Belozer M, Wang G. Epidural adhesiolysis for the treatment of back pain. *Health Technol Assess* 2004; 5:1-19.
50. Geurts JW, van Wijk RM, Stolker RJ, Groen GJ. Efficacy of radiofrequency procedures for the treatment of spinal pain: A systematic review of randomized clinical trials. *Reg Anesth Pain Med* 2001; 26:394-400.
51. Niemisto L, Kalso E, Malmivaara A, Seitsalo S, Hurri H. Cochrane Collaboration Back Review Group. Radiofrequency denervation for neck and back pain: A systematic review within the framework of the Cochrane Collaboration back review group. *Spine* 2003, 28:1877-1888.
52. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, Mannion AF, Reis S, Staal JB, Ursin H, Zanoli G. Chapter 4: European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006; 15:S192-S300.
53. Koes BW, Scholten RJ, Mens JM, Bouter LM. Efficacy of epidural steroid injections for low-back pain and sciatica: a systematic review of randomized clinical trials. *Pain* 1995; 63:279-288.
54. van Tulder MWV, Koes BW, Bouter LM. Conservative treatment of acute and chronic nonspecific low back pain. A systematic review of randomized controlled trials of the most common interventions. *Spine* 1997; 22:2128-2156.
55. McKenzie-Brown AM, Shah RV, Sehgal N, Everett CR. A systematic review of sacroiliac joint interventions. *Pain Physician* 2005; 8:115-125.
56. Hansen HC, McKenzie-Brown AM, Cohen SP, Swicegood JR, Colson JD, Manchikanti L. Sacroiliac joint interventions: A systematic review. *Pain Physician* 2007; 10:165-184.
57. Buenaventura RM, Shah RV, Patel V, Benyamin R, Singh V. Systematic review of discography as a diagnostic test for spinal pain: An update. *Pain Physician* 2007; 10:147-164.
58. Trescot AM, Chopra P, Abdi S, Datta S, Schultz DM. Systematic review of effectiveness and complications of adhesiolysis in the management of chronic spinal pain: An update. *Pain Physician* 2007; 10:147-164.
59. Andersson GB, Mekhail NA, Block JE. Treatment of intractable discogenic low back pain. a systematic review of spinal fusion and intradiscal electrothermal therapy (IDET). *Pain Physician* 2006; 9:237-248.
60. Appleby D, Andersson G, Totta M. Meta-analysis of the efficacy and safety of intradiscal electrothermal therapy (IDET). *Pain Med* 2006; 4:308-316.
61. Boswell MV, Colson JD, Spillane WF. Therapeutic facet joint interventions in chronic spinal pain: A systematic review of effectiveness and complications. *Pain Physician* 2005; 8:101-114.
62. Boswell MV, Colson JD, Sehgal N, Dunbar EE, Epter R. A systematic review of therapeutic facet joint interventions in chronic spinal pain. *Pain Physician* 2007; 10:229-254.
63. Sehgal N, Shah RV, McKenzie-Brown A, Everett CR. Diagnostic utility of facet (zygapophysial) joint injections in chronic spinal pain: A systematic review of evidence. *Pain Physician* 2005; 8:211-224.
64. Seghal N, Dunbar EE, Shah RV, Colson JD. Systematic review of diagnostic utility of facet (zygapophysial) joint injections in chronic spinal pain: An update. *Pain Physician* 2007; 10:213-228.
65. Everett CR, Shah RV, Sehgal N, McKenzie-Brown AM. A systematic review of diagnostic utility of selective nerve root blocks. *Pain Physician* 2005; 8:225-233.
66. Manchikanti L, Singh V, Vilims BD, Hansen HC, Schultz DM, Kloth DS. Medial branch neurotomy in management of chronic spinal pain: Systematic review of the evidence. *Pain Physician* 2002; 5:405-418.
67. Nachemson AL, Jonsson E (eds). *Neck and Back Pain. The Scientific Evidence of Causes, Diagnosis, and Treatment*. Lippincott Williams &Wilkins, Philadelphia, 2000.
68. Kepes ER, Duncalf D. Treatment of backache with spinal injections of local anesthetics, spinal and systemic steroids. *Pain* 1985; 22:33-47.
69. Benzon HT. Epidural steroid injections for low back pain and lumbosacral radiculography. *Pain* 1986; 24:277.
70. Bogduk N. Epidural steroids for low back pain and sciatica. *Pain Digest* 1999; 9:226-227.
71. Nelemans PJ, DeBie RA, DeVet HCW, Sturmans F. Injection therapy for subacute and chronic benign low back pain. *Spine* 2001; 26:501-515.
72. Watts RW, Silagy CA. A meta-analysis on the efficacy of epidural corticosteroids in the treatment of sciatica. *Anaesth Intens Care* 1995; 23:564-569.
73. McQuay HJ, Moore RA. Epidural corticosteroids for sciatica. In *An Evidence-Based Resource for Pain Relief*. Oxford

University Press, Oxford, 1998; pp 216-218.

74. Curatolo M, Bogduk N. Pharmacologic pain treatment of musculoskeletal disorders: Current perspectives and future prospects. *Clin J Pain* 2001; 17:25-32.
75. Vroomen PC, De Krom MC, Slofstra PD, Knottnerus JA. Conservative treatment of sciatica: A systematic review. *J Spin Disord* 2000; 13:463-469.
76. Rozenberg S, Dubourg G, Khalifa P, Paolozzi L, Maheu E, Ravaud P. Efficacy of epidural steroids in low back pain and sciatica: A critical appraisal by a French task force of randomized trials. *Revue du Rhumatisme* 1999; 66:79-85.
77. Boswell MV, Hansen HC, Trescot AM, Hirsch JA. Epidural steroids in the management of chronic spinal pain and radiculopathy. *Pain Physician* 2003; 6:319-334.
78. Chopra P, Smith HS, Deer TR, Bowman RC. Role of adhesiolysis in the management of chronic spinal pain: A systematic review of effectiveness and complications. *Pain Physician* 2005; 8:87-100.
79. Shah RV, Everett CR, McKenzie-Brown AM, Sehgal N. Discography as a diagnostic test for spinal pain: A systematic and narrative review. *Pain Physician* 2005; 8:187-209.
80. Abdi S, Datta S, Lucas LF. Role of epidural steroids in the management of chronic spinal pain: a systematic review of effectiveness and complications. *Pain Physician* 2005; 8:127-143
81. Abdi S, Datta S, Trescot AM, Schultz DM, Adlaka R, Atluri SL, Smith HS, Manchikanti L. Epidural steroids in the management of chronic spinal pain: A systematic review. *Pain Physician* 2007; 10:185-212.
82. Datta S, Everett CR, Trescot AM, Schultz DM, Adlaka R, Abdi S, Atluri SL, Smith HS, Shah RV. An updated systematic review of diagnostic utility of selective nerve root blocks. *Pain Physician* 2007; 10: 113-128.
83. Giordano J. On knowing: Domains of knowledge and intellectual virtue in practical pain management. *Prac Pain Management* 2006; 6:65-67.
84. Giordano J. Pain research: Can paradigmatic revision bridge the needs of medicine, scientific philosophy and ethics? *Pain Physician* 2004; 7:459-463.
85. Jonas WB. Building an evidence house: challenges and solutions to research in complementary and alternative medicine. *Forsch Komplementärmed Klass Naturheilkd* 2005; 12:159-167.
86. Giordano J. Good as gold? The randomized controlled trial: pragmatic and ethical issues in pain research. *Am J Pain Manage* 2006 16; 68-71.
87. Giordano J, Engebretson J, Garcia MK. Challenges to CAM research: Focal issues influencing integration into a cancer care model. *J. Integrative Cancer Ther* 2005; 4:210-218.
88. Hatala R, Guyatt G. Evaluating the teaching of evidence-based medicine. *JAMA* 2002; 288:1110-1112.
89. Bogduk N, Govind J. *Medical Management of Acute Lumbar Radicular Pain: An Evidence-Based Approach*. Cambridge Press, Newcastle 1999.
90. Bogduk N, McGuirk B. *Medical Management of Acute and Chronic Low Back Pain. An Evidence-Based Approach: Pain Research and Clinical Management*. Amsterdam: Elsevier Science BV, 2002.
91. Bogduk N, McGuirk B. *Management of Acute and Chronic Neck Pain. An Evidence-Based Approach*. Elsevier, 2006.
92. Bogduk N. *Medical Management of Acute Cervical Radicular Pain: An Evidence-based Approach*, 1st edition. University of Newcastle, Newcastle Bone and Joint Institute, Australia, 1999.
93. Field MJ, Lohrs KN. *Guidelines for Clinical Practice: From Development to Use. Institute of Medicine*. Washington, DC: National Academy Press; 1992.
94. Muir Gray JA. E*vidence-Based Medicine: How to Make Health Policy and Management Decisions*. London: Churchill Press; 1997.
95. Tunis SR, Stryer DB, Clancy CM. Practical Clinical Trials. Increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003; 290:1624-1632.
96. Wennberg J, Gittelsohn A. Small area variation in health care delivery. *Sci Am* 1973; 182:1102-1108.
97. Giordano J. The moral community of the clinical pain medicine encounter. *Prac Pain Management* 2006; 6: 60-63.
98. Starr P. *The Social Transformation of American Medicine*. Basic Books, New York 1982.
99. Schuster MA, McGlynn EA, Brook RH. How good is the quality of health care in the United States? *Milbank Q* 1998; 76:517-563
100. Eddy DM, Billings J. The quality of medical evidence: Implications for quality of care. *Health Aff (Milwood)* 1988; 7:19-32.
101. McNeil BJ. Shattuck lecture – hidden barriers to improvement in the quality of care. *N Engl J Med* 2001; 345:1612-1620.
102. Eisner W. Spinal fusion: CMS says "show us the evidence in November," *Orthopedics This Week,* 2006; www.ryortho.com/newsletters/volume2/issue24/07-25-06.
103. McCrory DC, Turner DA, Patwardhan MB, Richardson WL.. Spinal fusion for degenerative disc disease affecting the lumbar spine [draft evidence report/technology review prepared for the Medicare Coverage Advisory Committee meeting], 2006; as yet unpublished; www.cms.hhs.gov/determinationprocess/downloads/id41ta.pdf.
104. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: Synthesis of best evidence for clinical decisions. *Ann Intern Med* 1997; 126:376-380.
105. Rotstein D, Laupacis A. Differences between systematic reviews and health technology assessments: A trade-off between the ideals of scientific rigor and the realities of policy making. *Int J Technol Assess Health Care* 2004; 20:177-183.
106. Drummond MF, Richardson WS, O'Brien B, Levine M, Heyland D. Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? EBM Working Group. *JAMA* 1997; 277:1552-1557.
107. Feeny DH, Furlong W, Boyle M, Torrance GW. Multi-attribute health status classification systems. Health Utilities Index. *Pharmacoeconomics* 1995; 7:490-502.
108. Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, Napper M, Robb CM. Eliciting public preferences for healthcare: a systematic review of techniques. *Health Technol Assess* 2001; 5:1-186.
109. Guyatt G, Drummond R. Part 2.Beyond the basics: Using and teaching the principles of evidence-based medicine. 2B1. Therapy and validity. In. *Users' Guides to the Medical Literature. A Manual for Evidence-based Clinical Practice*. EBM Working Group. AMA Press, 2002, pp 247-308.
110. Tunis R, Kang JL. Improvements in Medicare coverage of new technology. *Health Aff* (Milwood) 2001; 20:83-85.
111. Garber AM. Evidence-based coverage policy. *Health Aff (Milwood)* 2001; 20:62-82.
112. Roland M, Torgerson DJ. What are pragmatic trials? *BMJ* 1998; 316:285.
113. Manchikanti L, Rivera JJ, Pampati V, Damron KS, MCManus CD, Brandon DE,

Wilson SR. 1 day lumbar epidural adhesiolysis and hypertonic saline neurolysis in treatment of chronic low back pain: A randomized, double-blind trial. *Pain Physician* 2004; 7:177-186.

114. Manchikanti L, Rivera JJ, Pampati V, Damron KS, Beyer CD, Brandon DE, Wilson SR. Spinal endoscopic adhesiolysis in the management of chronic low back pain: A preliminary report of a randomized, double-blind trial. *Pain Physician* 2003; 6:259-268.
115. Manchikanti L, Manchikanti KN, Damron KS, Pampati V. Effectiveness of cervical medial branch blocks in chronic neck pain: A prospective outcome study. *Pain Physician* 2004; 7:195-202.
116. Manchikanti L, Pampati V, Bakhit CE, Rivera JJ, Beyer CD, Damron KS, Barnhill RC. Effectiveness of lumbar facet joint nerve blocks in chronic low back pain: A randomized clinical trial. *Pain Physician* 2001; 4:101-117.
117. Manchikanti L, Damron KS, Cash KA, Manchukonda R, Pampati V. Therapeutic medial branch blocks in managing chronic neck pain: A preliminary report of a randomized, double-blind, controlled trial: Clinical Trial NCT00333272. *Pain Physician* 2006; 9:333-346.
118. Manchikanti L, Manchikanti KN, Manchukonda R, Pampati V, Cash KA. Evaluation of therapeutic thoracic medial branch block effectiveness in chronic thoracic pain: A prospective outcome study with minimum 1-year follow up. *Pain Physician* 2006; 9:97-105.
119. Manchikanti L, Damron KS, Cash KA, Manchukonda R, Pampati V. Evaluation of lumbar facet joint nerve blocks in the management of chronic low back pain: a preliminary report of a randomized, double-blind controlled trial. Clinical Trial NCT00355914. 2007; in press.
120. Manchikanti L, Singh V, Rivera J, Pampati V, Beyer C, Damron K, Barnhill R. Effectiveness of caudal epidural injections in discogram positive and negative chronic low back pain. *Pain Physician* 2002; 5:18-29.
121. Manchikanti L, Pampati V, Rivera JJ, Beyer CD, Damron KS, Barnhill RC. Caudal epidural injections with Sarapin or steroids in chronic low back pain. *Pain Physician* 2001; 4:322-335.
122. Bogduk N, Karasek M. Two-year follow-up of a controlled trial of intradiscal electrothermal annuloplasty for chronic low back pain resulting from internal disc disruption. *Spine J* 2002; 2:343-350.
123. Dreyfuss P, Halbrook B, Pauza K, Joshi A, McLarty J, Bogduk N. Efficacy and validity of radiofrequency neurotomy for chronic lumbar zygapophysial joint pain. *Spine* 2000; 25:1270-1277.
124. Barnsley L. Percutaneous radiofrequency neurotomy for chronic neck pain: outcomes in a series of consecutive patients. *Pain Med* 2005; 6:282-286.
125. Fuchs S, Erbe T, Fischer HL, Tibesku CO. Intraarticular hyaluronic acid versus glucocorticoid injections for nonradicular pain in the lumbar spine. *J Vasc Interv Radiol* 2005; 16:1493-1498.
126. Manchikanti L, Pampati V, Damron KS. The role of placebo and nocebo effects of perioperative administration of sedatives and opioids in interventional pain management. *Pain Physician* 2005; 8:349-355.
127. Giordano J, Boswell MV. Pain, placebo and nocebo: epistemic, ethical and practical issues. *Pain Physician* 2005; 8:331-333.
128. Lord SM, Barnsley L, Wallis BJ, McDonald GJ, Bogduk N. Percutaneous radiofrequency neurotomy for chronic cervical zygapophyseal-joint pain. *N Engl J Med* 1996; 335:1721-1726.
129. Van Kleef M, Barendse GA, Kessels A, Voets HM, Weber WE, de Lange S. Randomized trial of radiofrequency lumbar facet denervation for chronic low back pain. *Spine* 1999; 24:1937-1942.
130. Pauza KJ, Howell S, Dreyfuss P, Peloza JH, Dawson K, Bogduk N. A randomized, placebo-controlled trial of intradiscal electrothermal therapy for the treatment of discogenic low back pain. *Spine J* 2004; 4:27-35.
131. Carette S, Leclaire R, Marcoux S, Morin F, Blaise GA, St-Pierre A, Truchon R, Parent F, Levesque J, Bergeron V, Montminy P, Blanchette C. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med* 1997; 336:1634-1640.
132. Carette S, Marcoux S, Truchon R, Grondin C, Gagnon J, Allard Y, Latulippe M. A controlled trial of corticosteroid injections into facet joints for chronic low back pain. *N Engl J Med* 1991; 325:1002-1007.
133. Haspeslagh SR, Van Suijlekom HA, Lame IE, Kessels AG, van Kleef M, Weber WE. Randomised controlled trial of cervical radiofrequency lesions as a treatment for cervicogenic headache [ISRCTN07444684]. *BMC Anesthesiol* 2006; 6:1.
134. Van Wijk RM, Geurts JW, Wynne HJ, Hammink E, Buskens E, Lousberg R, Knape JT, Groen GJ. Radiofrequency denervation of lumbar facet joints in the treatment of chronic low back pain: a randomized, double-blind, sham lesion-controlled trial. *Clin J Pain* 2005; 21:335-344.
135. Leclaire R, Fortin L, Lambert R, Bergeron YM, Rossignol M. Radiofrequency facet joint denervation in the treatment of low back pain: a placebo-controlled clinical trial to assess efficacy. *Spine* 2001; 26:1411-1416.
136. Manchikanti L, Pampati V, Damron KS, MCManus CD, Jackson SD, Barnhill RC, Martin JC. A randomized, prospective, double-blind, placebo-controlled evaluation of the effect of sedation on diagnostic validity of cervical facet joint pain. *Pain Physician* 2004; 7:301-309.
137. Manchikanti L, Damron KS, Rivera J, McManus CD, Jackson SD, Barnhill RC, Martin JC. Evaluation of effect of sedation as a confounding factor in the diagnostic validity of lumbar facet joint pain: A prospective, randomized, double-blind, placebo-controlled evaluation. *Pain Physician* 2004; 7:411-417.
138. Manchikanti L, Pampati V, Damron KS, McManus CD, Jackson SD, Barnhill RC, Martin JC. The effect of sedation on diagnostic validity of facet joint nerve blocks: An evaluation to assess similarities in population with involvement in cervical and lumbar regions. *Pain Physician* 2006; 9:47-52.
139. King W, Lau P, Lees R, Bogduk N. he validity of manual examination in assessing patients with neck pain. *Spine J* 2007; 7:22-26.
140. Carragee EJ, Haldeman S, Hurwtiz E. The pyrite standard: the Midas touch in the diagnosis of axial pain syndromes. *Spine J* 2007; 7:27-31.
141. Cohen SP, Raja SN. Pathogenesis, diagnosis, and treatment of lumbar zygapophysial (facet) joint pain. *Anesthesiology* 2007; 106:591-614.
142. Saal JS. General principles of diagnostic testing as related to painful lumbar spine disorders. *Spine* 2002; 27:2538-2545.
143. Cohen SP, Larkin TM, Barna SA, Palmer WE, Hecht AC, Stojanovic MP. Lumbar discography: A comprehensive review of outcome studies, diagnostic accuracy, and principles. *Reg Anesth Pain Med* 2005; 2:163-183.
144. Bogduk N, Lord S. Cervical zygapophysial joint pain. *Neurosurg Q* 1998; 8:107-117.
145. Schwarzer AC, Derby R, Aprill CN, Fortin J, Kine G, Bogduk N. The value of the

provocation response in lumbar zygapophysial joint injections. *Clin J Pain* 1994; 10:309-313.

146. Barnsley L, Lord S, Bogduk N. Comparative local anesthetic blocks in the diagnosis of cervical zygapophysial joints pain. *Pain* 1993; 55:99-106.
147. Lord SM, Barnsley L, Bogduk N. The utility of comparative local anesthetic blocks versus placebo-controlled blocks for the diagnosis of cervical zygapophysial joint pain. *Clin J Pain* 1995; 11:208-213.
148. Hogan QH, Abram SE. Neural blockade for diagnosis and prognosis. *Anesthesiology* 1997; 86:216-241.
149. Hildebrandt J. Relevance of nerve blocks in treating and diagnosing low back pain – is the quality decisive? *Schmerz* 2001; 15:474-483.
150. North RB, Kidd DH, Zahurak M, Piantadosi S. Specificity of diagnostic nerve blocks: a prospective, randomized study of sciatica due to lumbosacral spine disease. *Pain* 1996; 65:77-85.
151. Cohen SP, Larkin TM, Chang AS, Stojanovic MP. The causes of false-positive medial branch (facet joint) blocks in soldiers and retirees. *Mil Med* 2004; 169:781-786.
152. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The false-positive rate of uncontrolled diagnostic blocks of the lumbar zygapophysial joints. *Pain* 1994; 58:195-200.
153. Barnsley L, Lord S, Wallis B, Bogduk N. False-positive rates of cervical zygapophysial joint blocks. *Clin J Pain* 1993; 9:124-130.
154. Manchikanti L, Singh V, Pampati V. Are diagnostic lumbar medial branch blocks valid? Results of 2-year follow up. *Pain Physician* 2003; 6:147-153.
155. Manchikanti L, Manchikanti KN, Damron KS, Pampati V. Effectiveness of cervical medial branch blocks in chronic neck pain: A prospective outcome study. *Pain Physician* 2004; 7:195-201.
156. Manchikanti L, Hirsch JA, Pampati V. Chronic low back pain of facet (zygapophysial) joint origin: Is there a difference based on involvement of single or multiple spinal regions? *Pain Physician* 2003; 6:399-405.
157. Manchikanti L, Singh V, Pampati V, Damron KS, Beyer CD, Barnhill RC. Is there correlation of facet joint pain in lumbar and cervical spine? An evaluation of prevalence in combined chronic low back and neck pain. *Pain Physician* 2002; 5:365-371.
158. Manchikanti L, Pampati V, Fellows B, Rivera J, Damron K, Beyer C, Cash K. Influence of psychological factors on the ability of diagnose chronic low back pain of facet joint origin. *Pain Physician* 2001; 4:349-357.
159. Manchikanti L, Boswell MV, Singh V, Pampati V, Damron KS, Beyer CD. Prevalence of facet joint pain in chronic spinal pain of cervical, thoracic, and lumbar regions. *BMC Musculoskelet Disord* 2004; 5:15.
160. Manchukonda R, Manchikanti KN, Cash KA, Pampati V, Manchikanti L. Facet joint pain in chronic spinal pain: an evaluation of prevalence and false positive rate of diagnostic blocks. *J Spinal Disord Tech* 2007; in press.
161. Manchikanti L, Pampati V, Fellows B, Bakhit CE. The diagnostic validity and therapeutic value of medial branch blocks with or without adjuvants agents. *Curr Rev Pain* 2000; 4:337-344.
162. Barnsley L, Lord SM, Wallis BJ, Bogduk N. The prevalence of chronic cervical zygapophyseal joint pain after whiplash. *Spine* 1995; 20:20-26.
163. Lord SM, Barnsley L, Wallis BJ, Bogduk N. Chronic cervical zygapophysial joint pain with whiplash: A placebo-controlled prevalence study. *Spine* 1996; 21:1737-1745.
164. Manchikanti L, Singh V, Rivera J, Pampati V. Prevalence of cervical facet joint pain in chronic neck pain. *Pain Physician* 2002; 5:243-249.
165. Manchikanti L, Singh, V, Pampati V, Beyer C, Damron K. Evaluation of the prevalence of facet joint pain in chronic thoracic pain. *Pain Physician* 2002; 5:354-359.
166. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chronic Dis* 1967; 20:637-648.
167. Cherkin DC, Deyo RA, Battie M, Street J, Barlow W. A comparison of physical therapy, chiropractic manipulations, and provision of an educational booklet for the treatment of patients with low back pain. *N Engl J Med* 1998; 339:1021-1029.
168. Cherkin DC, Eisenberg D, Sherman KJ, Barlow W, Kaptchuk TJ, Street J, Deyo RA. Randomized trial comparing traditional Chinese medical acupuncture, therapeutic massage, and self-care education or chronic low back pain. *Arch Intern Med* 2001; 161:1081-1088.
169. A Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948; 2:769-782.
170. Byar DP, Simon RM, Friedewald WT, Schlesselman JJ, DeMets DL, Ellenberg JH, Gail MH, Ware JH. Randomized clinical trials: Perspectives on some recent ideas. *N Engl J Med* 1976; 1976; 295:74-80.
171. Feinstein AR. Current problems and future challenges in randomized clinical trials. *Circulation* 1984; 70:767-774.
172. Abel U, Koch A. The role of randomization in clinical studies: Myths and beliefs. *J Clin Epidemiol* 1999; 52:487-497.
173. Sacks H, Chalmers TC, Smith H Jr. Randomized versus historical controls for clinical trials. *Am J Med* 1982; 72:233-240.
174. Kjaergard LK, Als-Nielsen B. Association between competing interests and authors' conclusions: Epidemiological study of randomised clinical trials published in the BMJ. *BMJ* 2002; 325:1-4.
175. Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, Kuderer NM, Lyman GH. The uncertainty principle and industry sponsored research. *Lancet* 2000; 356:635-638.
176. Hopwood MB, Manning DC. Lumbar epidural steroid injections: Is a clinical trial necessary or appropriate? *Reg Anesth Pain Med* 1999; 24:5-7.
177. Fairbank J. Randomized controlled trials in the surgical management of spinal problems. *Spine* 1999; 24:2556-2561.
178. Carey TS. Randomized controlled trials in surgery. An essential component of scientific progress. *Spine* 1999; 23:2553-2555.
179. Lenrow DA, Chou LH. Randomized controlled trials in interventional spine: Perils and Pitfalls. *Pain Physician* 2003; 6:83-88.
180. Manchikanti L, Pampati V. Research designs in interventional pain management: Is randomization superior, desirable or essential? *Pain Physician* 2002; 5:275-284.
181. D'Agostino RB Jr., D'Agostino RB Sr. Estimating treatment effects using observational data. *JAMA* 2007; 297:314-316.
182. D'Agostino RB Sr, Kwan H. Measuring effectiveness: what to expect without a randomized control group. *Med Care.* 1995; 33(4 suppl):AS95-AS105.
183. Kane RL. Approaching the outcomes question. In Kane RL (ed). *Understanding Health Care Outcomes Research*. Aspen Publication, Gaithersburg, 1997, pp 1-15.
184. Daly LE, Bourke GJ. Epidemiological and clinical research methods. In Daly LE, Bourke GJ (eds). *Interpretation and Uses of Medical Statistics*. Blackwell Science, 2000, Oxford, pp 143-201.
185. Special report: Measuring and report-

ing pain outcomes in randomized controlled trials. *Technol Eval Cent Asses Program Exec Summ* 2006; 21:1-2.

186. Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *Milbank Q* 2004; 82:661-687.
187. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *J Am Med Assoc* 2000; 283:2008–2012
188. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; 52:377-384.
189. Norris SL, Atkins D. Challenges in using nonrandomized studies in systematic reviews of treatment interventions. *Ann Intern Med* 2005; 21:1112-1119.
190. Tooth L, Ware R, Bain C, Purdie DM, Dobson A. Quality of reporting of observational longitudinal research. *Am J Epidemiol* 2005; 161:280-288.
191. Peipert JF, Phipps MG. Observational studies. *Clin Obstet Gynecol* 1998; 41:235-244.
192. Sipe TA, Curlette WL. A meta-synthesis of factors related to educational achievement. *Int J Educ Res* 1997; 25:583-598.
193. Ioannidis JP, Lau J. Pooling research results. *Jt Comm J Qual Improv* 1999; 25:462-469.
194. Lipsett M, Campleman S. Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. *Am J Public Health* 1999; 89:1009-1017.
195. Mann CC. Can meta-analysis make policy? *Science* 1999; 266:960-962.
196. Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol* 1999; 28:1-9.
197. Tatsioni A, Zarin DA, Aronson N, Samson DJ, Flamm CR, Schmid C, Lau J. Challenges in systematic reviews of diagnostic technologies. *Ann Intern Med* 2005; 142:1048-1055.
198. Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. *Ann Intern Med* 2005; 142:1090-1099.
199. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7: iii-x, 1-173.
200. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; 342:1887-1892.
201. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321-333.
202. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996; 334:1145-1149.
203. Ioannidis JPA, Haidich AB, Pappa M, Pantazis N, Kokori SI, Tektonidou MG, Contopoulos-Ioannidis DG, Lau J. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA* 2001; 286:821-830.
204. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000; 342:1878-1886.
205. Eisenstein EI, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007; 297:159-168.
206. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized studies. *Stat Med*. 2007; 26:20-36.
207. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007; 297:278-285.
208. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, Abdu WA, Hilibrand AS, Boden SD, Deyo RA. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): A randomized trial. *JAMA* 2006; 296:2441-2450.
209. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, Abdu WA, Hilibrand AS, Boden SD, Deyo RA. Surgical and nonsurgical management of sciatica secondary to a lumbar disc herniation: 10 year results from the Maine lumbar spine study. *Spine* 2005; 30:927-935.
210. Atlas SJ, Deyo RA, Keller RB, Chapin AM, Patrick DL, Long JM, Singer DE. The Maine Lumbar Spine Study, Part II. 1-year outcomes of surgical and nonsurgical management of sciatica. *Spine* 1996; 21:1777-1786.
211. Atlas SJ, Keller RB, Wu YA, Deyo RA, Singer DE. Long-term outcomes of surgical and nonsurgical management of lumbar spinal stenosis: 8 to 10 year results from the Maine lumbar spine study. *Spine* 2005; 30:936-943.
212. West S, King V, Carey TS, Lohr KN, McKoy N, Sutton SF, Lux L. Systems to rate the strength of scientific evidence. Evidence Report/Technology Assessment No. 47 University of North Carolina: Agency for Healthcare Research and Quality. AHRQ Publication No. 02-E016; April 2002.
213. How to use the evidence: Assessment and application of scientific evidence. National Health and Medical Research Council, Canberra, Commonwealth of Australia, 2000, pp 1-84.
214. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Systematic reviews of trials and other studies. *Health Technol Assess* 1998; 2: pp 1-276.
215. Lohr KN, Carey TS. Assessing "best evidence": Issues in grading the quality of studies for systematic reviews. *Jt Comm J Qual Improv* 1999; 25:470-479.
216. Mulrow CD. The medical review article: State of the science. *Ann Intern Med* 1987; 106:485-488.
217. Clark HD, Wells GA, Huet C, McAlister FA, Salmi LR, Fergusson D, Laupacis A. Assessing the quality of randomized trials: Reliability of the Jadad scale. *Control Clin Trials* 1999; 20:448-452.
218. Chalmers TC, Smith H Jr., Blackburn B, Silverman B, Schroeder B, Reitman D, Ambroz A. A method for assessing the quality of a randomized control trial. *Control Clin Trials* 1981; 2:31-49.
219. Hemminki E. Quality of reports of clini-

cal trials submitted by the drug industry to the Finnish and Swedish control authorities. *Eur J Clin Pharmacol* 1981; 19:157-165.

220. Khan KS, Daya S, Jadad A. The importance of quality of primary studies in producing unbiased systematic reviews. *Arch Intern Med* 1996; 156:661-666.
221. Coulter ID. Evidence summaries and synthesis: necessary but insufficient approach for determining clinical practice of integrated medicine? *Integr Cancer Ther* 2006; 5:282-286.
222. Lohr KN. Rating the strength of scientific evidence: relevance for quality improvement programs. *Int J Qual Health Care* 2004; 16:9-18.
223. Eddy DM. The use of evidence and cost effectiveness by the courts: how can it help improve health care? *J Health Polit Policy Law* 2001; 26:387-408.
224. Mulrow CD, Lohr KN. Proof and policy from medical research evidence. *J Health Polit Policy Law* 2001; 26:249–266.
225. Kassirer JP, Cecil JS. Inconsistency in evidentiary standards for medical testimony: disorder in the courts. *J Am Med Assoc* 2002; 288:1382–1387.
226. Lohr KN (ed). *Medicare: A Strategy for Quality Assurance*. Institute of Medicine. Washington, DC: National Academy Press, 1990.
227. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; 354:1896–1900.
228. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *J Am Med Assoc* 2001; 285:1987–1991.
229. www.consort-statement.org/QUOROM.pdf
230. The STARD Group. *The STARD Initiative – Towards Complete and Accurate Reporting of Studies on Diagnostic Accuracy*. November, 2001.
231. Mokkink LB, Terwee CB, Knol DL, Stratford PW, Alonso J, Patrick DL, Bouter LM, de Vet HC. Protocol of the COSMIN study: Consensus-based Standards for the selection of health Measurement Instruments. *C Med Res Methodol* 2006; 6:2.
232. van Tulder M, Assendelft W, Koes B, Bouter LM. Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. *Spine*. 1997; 22:2323-2330.
233. Whiting P, Rutjes A, Reitsma J, Bossuyt P, Kleijnen J. The Development of QUADAS: A tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; 3:25.
234. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC; Standards for Reporting of Diagnostic Accuracy. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD initiative. *Clin Chem* 2003; 49:1-6. www.clinchem.org/cgi/content/full/49/1/1
235. Bruns DE, Huth EJ, Magid E, Young DS. Toward a checklist for reporting of studies of diagnostic accuracy of medical tests. *Clin Chem* 2000; 46:893-895.
236. Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988; 240:1285-1293.
237. Bornhoft G, Maxion-Bergemann S, Wolf U, Kienle GS, Michalsen A, Vollmar HC, Gilbertson S, Matthiessen PF. Checklist for the qualitative evaluation of clinical studies with particular focus on external validity and model validity. *BMC Med Res Methodol* 2006; 6:56.
238. Phillips C, LaPole LM. Quantifying errors without random sampling. *BMC Med Res Methodol* 2003; 3:9.
239. Royle P, Waugh N. A simplified search strategy for identifying randomised controlled trials for systematic reviews of health care interventions: a comparison with more exhaustive strategies. *BMC Med Res Methodol* 2005; 5:23
240. Giordano J. Technology, techniques and tekne: On the ethical use of guidelines in the practice of interventional pain medicine. *Pain Physician* 2007; 10:1-5.
241. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997; 337:536-542.
242. Krimsky S. The funding effect in science and its implications for the judiciary. *J Law Policy* 2005; 13:43, 59.
243. Participating AHRQ Evidence-based Practice Centers. February 2006.Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.ahrq.gov/clinic/epc/epcenters.htm.
244. Holmes D, Murray SJ, Perron A, Rail G. Deconstructing the evidence for evidence-based discourse in health sciences: truth, power and fascism. *Int J Evidence-Based Healthcare* 2006;4: 180-186.
245. Manchikanti L. Evidence-based interventional pain medicine: Is there any evidence? *Pain Physician* 2002; 5:1-7.
246. McQuay H, Moore A (eds). *An Evidence-Based Resource for Pain Relief*. Oxford University Press, New York, 1998.
247. Smith R. Where is the wisdom? The poverty of medical evidence. *BMJ* 1991; 303:798-799.
248. Manchikanti L, Jasper J, Singh V. Cochrane review is mixing apples and oranges. *Spine* 2001; 26:2641-2643.
249. Bogduk N, Christophidis N, Cherry D. Epidural use of steroids in the management of back pain. Report of working party on epidural use of steroids in the management of back pain. National Health and Medical Research Council. Canberra, Commonwealth of Australia, 1994, pp 1-76.
250. Carr DB, Goudas LC. Evidence-based pain medicine: The good, the bad, and the ugly. *Reg Anesth Pain Med* 2001; 26:389-393.
251. Bogduk N. In defense of radiofrequency neurotomy. *Reg Anesth Pain Med* 2002; 27:439-447.
252. Bogduk N. Percutaneous radiofrequency cervical medial branch neurotomy. In *Practice Guidelines for Spinal Diagnostic and Treatment Procedures, 1st edition*. International Spine Intervention Society, 2004, pp 249-284.
253. Bernstein RM. Injections and surgical therapy in chronic pain. *Clin J Pain* 2001; 17:S94-S104.
254. Gatchel RJ, McGeary D. Cochrane collaboration-based reviews of healthcare interventions: Are they unequivocal and valid scientifically, or simply nihilistic? *Spine J* 2002; 2:315-319.
255. Hoving JL, Gross AR, Gasner D. A critical appraisal of review articles on the effectiveness of conservative treatment for neck pain. *Spine* 2001; 26:196-205.
256. Mowatt G, Shirran L, Grimshaw JM, Rennie D, Flanagin A, Yank V, MacLennan G, Gotzsche PC, Bero LA.. Prevalence of honorary and ghost authorship in Cochrane Reviews. *JAMA* 2002; 287:2769-2771.
257. Furlan AD, Clarke J, Esmail R, Sinclair S, Irvin E, Bombardier C. A critical review of reviews on the treatment of chronic low back pain. *Spine* 2001; 26:E155-E162.
258. Balk EM, Bonis PA, Moskowitz H, Schmid CH, Ioannidis JP, Wang C, Lau J. Correlation of quality measures with estimates of treatment effect in meta-

analyses of randomized controlled trials. *JAMA* 2002; 287:2973-2982.

259. Hopayian K. The need for caution in interpreting high quality systematic reviews. *Br Med J* 2001; 323:681-684.
260. Gatchel RJ, Okifuji A. Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. *J Pain* 2006; 7:779-793.
261. Proctor TJ, Mayer TG, Theodore B, Gatchel RJ. Failure to complete a functional restoration program for chronic musculoskeletal disorders: a prospective 1-year outcome study. *Arch Phys Med Rehabil* 2005; 86:1509-15. Erratum in: *Arch Phys Med Rehabil* 2005; 86:2228.
262. Errico TJ, Gatchel RJ, Schofferman J, Benzel EC, Faciszewski T, Eskay-Auerbach M, Wang JC. A fair and balanced view of spine fusion surgery. *Spine J* 2004; 4:S129-S138.
263. Jadad A, McQuay HS. Meta-analyses to evaluate analgesic interventions: A systematic qualitative review of their methodology. *J Clin Epidemiol* 1996; 49:235-243.
264. Gatchel RJ, Matt-Maddrey A. Experimental design issues in clinical research of musculoskeletal pain disabilities. *Crit Rev Phys Rehab Med* 2000; 12:9-101.