Systematic Review

An Update of the Systematic Assessment of Mechanical Lumbar Disc Decompression with Nucleoplasty

Laxmaiah Manchikanti, MD[1], Frank J.E. Falco, MD[2], Ramsin M. Benyamin, MD[3], David L. Caraway, MD[4], Timothy R. Deer, MD[5], Vijay Singh, MD[6], Haroon Hameed, MD[7], and Joshua A. Hirsch, MD[8]

From: [1]Pain Management Center of Paducah, Paducah, KY, and University of Louisville, Louisville, KY; [2-7]Mid Atlantic Spine & Pain Physicians of Newark, Newark, DE,and [2]Temple University Hospital, Philadelphia, PA; [3]Millennium Pain Center, Bloomington, IL,and University of Illinois, Urbana-Champaign, IL; [4]St. Mary's Pain Relief Center, Huntington, WV; [5]The Center for Pain Relief, Charleston, WV, and West Virginia University School of Medicine, Charleston, WV; [6]Spine Pain Diagnostics Associates, Niagara, WI; and [8]Massachusetts General Hospital, and Harvard Medical School, Boston, MA.

Additional author affiliation and Conflicts of interest on P SE45

Address Correspondence: Laxmaiah Manchikanti, MD 2831 Lone Oak Road Paducah, KY 42003 E-mail: drlm@thepainmd.com

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: None.

Manuscript received: 12-07-12
Accepted for publication: 12-11-12

Free full manuscript: www.painphysicianjournal.com

Background: Lumbar disc prolapse, protrusion, and extrusion account for less than 5% of all low back problems, but are the most common causes of nerve root pain and surgical interventions. The primary rationale for any form of surgery for disc prolapse is to relieve nerve root irritation or compression due to herniated disc material. The primary modality of treatment continues to be either open or microdiscectomy, although several alternative techniques are also utilized, including nucleoplasty, automated percutaneous discectomy and laser discectomy. There is a paucity of evidence for all decompression techniques, specifically alternative techniques including nucleoplasty.

Study Design: A systematic review of the literature of mechanical lumbar disc decompression with nucleoplasty.

Objective: To determine the effectiveness and update the effectiveness of mechanical lumbar disc decompression with nucleoplasty.

Methods: The available literature on mechanical lumbar disc decompression with nucleoplasty was reviewed. The quality assessment and clinical relevance criteria utilized were the Cochrane Musculoskeletal Review Group criteria as utilized for interventional techniques for randomized trials and the criteria developed by the Newcastle-Ottawa Scale criteria for observational studies.

The level of evidence was classified as good, fair, and limited or poor based on the quality of evidence developed by the U.S. Preventive Services Task Force (USPSTF).

Data sources included relevant literature identified through searches of PubMed and EMBASE from 1966 to September 2012, and manual searches of the bibliographies of known primary and review articles.

Outcome Measures: Pain relief and functional improvement were the primary outcome measures. Other outcome measures were improvement of psychological status, reduction in opioid intake, and return to work.

Short-term effectiveness was defined as one year or less, whereas long-term effectiveness was defined as greater than one year.

Results: For this systematic review, 37 studies were considered for inclusion. Of these, there was one randomized trial and 14 observational studies meeting inclusion criteria for methodological quality assessment.

Based on USPSTF criteria, the level of evidence for nucleoplasty is limited to fair in managing radicular pain due to contained disc herniation.

Limitations: A paucity of literature with randomized trials.

Conclusion: This systematic review illustrates limited to fair evidence for nucleoplasty in managing radicular pain due to contained disc herniation.

Key words: Intervertebral disc disease, chronic low back pain, disc herniation, disc protrusion, radiculitis, contained disc herniation, mechanical disc decompression, nucleoplasty, Coblation technology, nucleotomy.

Pain Physician 2013; 16:SE25-SE54

Due to the increasing incidence of chronic low back pain, the numerous modalities available for diagnosis and management, escalating costs and its impact on health care resources, our understanding of the causes of low back pain has evolved over the past century (1-50). Even then, in the majority of patients it is difficult to identify a definitive diagnosis, specifically when they do not present with disc herniation, physical findings, imaging, or electrodiagnostic findings (1,51-59). Kuslich et al (60) identified intervertebral discs, facet joints, ligaments, fascia, muscles, and nerve root dura as tissues capable of transmitting pain in the low back. Using controlled diagnostic techniques, the intervertebral discs, the zygapophysial (facet) joints, and sacroiliac joints have all been demonstrated to be common causes of chronic low back pain (1,54-59).

There has been a gradual shift towards less invasive treatments for disc herniation, including chymopapain, automated percutaneous disc decompression (PDD), laser disc decompression, and more recently, nucleoplasty. Nucleoplasty is defined as minimally invasive nuclear decompression using a bipolar radiofrequency device (61-67). Lumbar disc prolapse, protrusion, or herniation account for less than 5% of all low back problems, but are the most common causes of nerve root pain. Chemonucleolysis, percutaneous nucleotomy, percutaneous discectomy, and laser treatments incorporate different approaches to PDD, and all have been shown to reduce intradiscal pressure (68-77). In spite of emerging evidence for nonsurgical interventions of disc decompression, in reality each treatment is limited in its effectiveness in conjunction with associated complications (61-64,77-111).

Absolute indications for surgery, although rare, include altered bladder function and progressive muscle weakness (84). The usual goal of surgery is to provide for the rapid relief of pain and to address the possibility of impending disability in the minority of patients whose recovery is unacceptably low (84). The primary goal of surgical treatment of nerve root compression is the relief of compression by the removal of the herniated nuclear material. Historically, the primary modality of treatment has been open discectomy. However, disc herniation consists of both contained and non-contained types. While for non-contained disc herniations open discectomy is the approach of choice, partial removal of the nucleus pulposus in contained discs has been shown to decompress herniated discs and relieve pressure on nerve roots in a much less invasive and more cost-effective manner (61-64,77,81-85,112-114).

Nucleoplasty, a minimally invasive procedure, uses radiofrequency energy to remove nuclear material and to create small channels within the disc (61-63,68). With Coblation technology, radiofrequency energy is applied to a conductive medium, creating the formation a highly focused plasma field to form around the energized electrodes (61-63,68). The plasma field is composed of highly ionized particles (68). The created channel is thermally treated, producing a zone of thermal coagulation. Thus, nucleoplasty combines coagulation and tissue ablation (patented Coblation technology) to form channels in the nucleus and decompress the herniated disc. Claims have been made over the past few years that nucleoplasty can produce satisfactory results with fewer serious complications. However, these claims continue to be debated (9,61-64,77,86).

Gibson and Waddell (84) in the Cochrane Collaboration review presented the results from 40 randomized controlled trials (RCTs) and 2 quasi-randomized controlled trials (QRCTs) of surgical interventions for lumbar disc prolapse including 17 new trials since the first issue of the review. This review indicated that the place for alternative forms of discectomy other than traditional open discectomy is unresolved. They noted that as of January 2007 there were no RCTs examining Coblation as a treatment for disc prolapse.

Gibson and Waddell (84) concluded that there is considerable evidence that surgical discectomy provides effective clinical relief for carefully selected patients with sciatica due to lumbar disc prolapse that fails to resolve with conservative management. They noted that the choice of micro- or standard discectomy at present probably depends more on the training and expertise of the surgeon and the resources available than on scientific evidence of efficacy. In addition, they concluded that at present, unless or until better scientific evidence is available, multiple minimally invasive decompression techniques including Coblation therapy should be regarded as research techniques.

Mixter and Barr (115) reported on the open surgical treatment for rupture of the intervertebral disc in 1934. Less radical procedures started to appear as early as 1939 (116). In 1959, Smith (117) coined the term chemonucleolysis to describe the enzymatic dissolution of the nucleus pulposus as an alternative less invasive means of decompressing the bulging or herniated disc. Hijikata (118) described manual percutaneous lumbar discectomy in the 1970s. In 1985, Onik et al (119) described automated percutaneous lumbar discectomy, a minimally invasive method with aspiration of the

nucleus for treating contained disc herniations. More recently plasma nucleoplasty utilizing Coblation technology (61-64,120) has been described.

The Centers for Medicare and Medicaid Services (CMS) (121) has issued a non-certification for intradiscal procedures. The CMS (120) refers to multiple procedures collectively as thermal intradiscal procedures, including percutaneous or (plasma) disc decompression (PDD), or Coblation, along with other intradiscal therapies. However, in a systematic review of nucleoplasty for lumbar disc herniation (62), there was limited evidence in managing predominantly lower extremity pain due to contained disc herniation. In another evidence-based systematic review (61), it was concluded that based on the observational studies, nucleoplasty is a potentially effective, minimally invasive treatment for patients with symptomatic disc herniation who are refractory to conservative therapy. However, in another review (86), the authors showed that there were no published RCTs assessing Coblation or nucleoplasty. They also concluded that none of the minimally invasive techniques including automated percutaneous discectomy were effective. However, multiple other manuscripts have been published illustrating positive results (99,122-132), in addition to publications included in previous systematic reviews (61,62,117,118,120,128,133-147).

The purpose of this systematic review is to evaluate and update the current evidence described in a previous publication (62) supporting the use of percutaneous mechanical disc decompression with nucleoplasty to treat symptomatic disc protrusions.

1.0 Methods

The methodology utilized in this systematic review followed the review process derived from evidence-based systematic reviews and meta-analysis of randomized trials and observational studies (7,9,148-155), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (156-159), Standards for Reporting Observational Studies (STROBE) (160), Cochrane guidelines (7,152,153), Chou and Huffman's guidelines (9), and quality of reporting of analysis (149).

1.1 Criteria for Considering Studies for This Review

1.1.1 Types of Studies

Randomized controlled trials
Non-randomized observational studies
Case reports and reviews for adverse effects

1.1.2 Types of Participants

Participants of interest were adults aged at least 18 years old with chronic low back and lower extremity pain of at least 3 months duration.

Participants must have failed previous pharmacotherapy, exercise therapy, etc., prior to starting interventional pain management techniques.

1.1.3 Types of Interventions

The intervention was lumbar disc decompression with Coblation nucleoplasty appropriately performed with proper technique under fluoroscopic or CT guidance.

1.1.4 Types of Outcome Measures

- The primary outcome parameters were pain relief and functional status improvement.
- The secondary outcome measures were change in psychological status; return to work; reduction or elimination of opioid use, other drugs, or other interventions; and complications.
- At least 2 of the review authors independently, in an unblinded standardized manner, assessed the outcomes measures. Any disagreements between reviewers were resolved by a third author and consensus.

1.2 Literature Search

Searches were performed from the following sources without language restrictions:

1. PubMed from 1966
   www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
2. EMBASE from 1980
   www.embase.com/
3. Cochrane Library
   www.thecochranelibrary.com/view/0/index.html
4. U.S. National Guideline Clearinghouse (NGC)
   www.guideline.gov/
5. Previous systematic reviews and cross references
6. Clinical Trials
   clinicaltrials.gov/

The search period was from 1966 through September 2012.

1.3 Search Strategy

The search strategy emphasized chronic low back and lower extremity pain, disc herniation, and radiculitis treated with Coblation nucleoplasty.

Search terms included: chronic low back pain, disc herniation, radiculitis, percutaneous disc decompression, and Coblation nucleoplasty.

At least 2 of the review authors independently, in an unblinded standardized manner, performed each search. Accuracy was confirmed by a statistician. All searches were combined to obtain a unified search strategy. Any disagreements between reviewers were resolved by a third author and consensus.

1.4 Data Collection and Analysis

The review focused on randomized trials, observational studies, and reports of complications. The population of interest was patients suffering with chronic low back and lower extremity pain for at least 3 months. Only lumbar Coblation nucleoplasty studies were evaluated. All of the studies providing appropriate management and with outcome evaluations of 6 months or longer and statistical evaluations were reviewed. Reports without appropriate diagnosis, non-systematic reviews, book chapters, and case reports were excluded.

1.4.1 Selection of Studies

- In an unblinded standardized manner, 2 review authors screened the abstracts of all identified studies against the inclusion criteria.
- All articles with possible relevance were then retrieved in full text for comprehensive assessment of internal validity, quality, and adherence to inclusion criteria.

1.4.2 Inclusion and Exclusion Criteria

The following are the inclusion and exclusion criteria:

1. Are the patients described in sufficient detail to allow one to decide whether they are comparable to those who are treated in interventional pain management clinical practices?
   A. Setting – office, hospital, outpatient, inpatient
   B. Physician – interventional pain physician, general physician, anesthesiologist, physiatrist, neurologist, rheumatologist, orthopedic surgeon, neurosurgeon, etc.
   C. Patient characteristics - duration of pain
   D. Non-interventional techniques or surgical intervention in the past
2. Is the intervention described in sufficient detail to enable one to apply its use to patients in interventional pain management settings?
   A. Nature of intervention
   B. Frequency of intervention
   C. Duration of intervention
3. Were clinically relevant outcomes measured?
   A. Proportion of pain relief
   B. Disorder/specific disability
   C. Functional improvement
   D. Allocation of eligible and non-eligible patients to return to work
   E. Ability to work

1.4.3 Clinical Relevance

The clinical relevance of the included studies was evaluated according to 5 questions recommended by the Cochrane Back Review Group (Table 1) (151,161). Each question was scored as positive (+) if the clinical relevance item was met, negative (–) if the item was not met, and unclear (?) if data were not available to answer the question.

1.4.4 Methodological Quality or Validity Assessment

The methodological quality assessment was performed by 2 review authors who independently assessed, in an unblinded standardized manner, the internal validity of all the studies.

The methodological quality assessment was performed in such a manner as to avoid any discrepancies. Any discrepancies were evaluated by a third reviewer and settled by consensus.

The quality of each individual article used in this analysis was assessed using the Cochrane review criteria (Table 2) (156) for randomized trials, and the Newcas-

Table 1. *Clinical relevance questions*.

	P (+)	N (-)	U (unclear)
A) Are the patients described in detail so that one can decide whether they are comparable to those who are treated practice?			
B) Are the interventions and treatment settings described in sufficient detail to apply its use in clinical practice?			
C) Were clinically relevant outcomes measured and reported?			
D) Is the size of the effect clinically meaningful?			
E) Do the likely treatment benefits outweigh the potential harms?			

Scoring adapted and modified from Staal JB, et al. Injection therapy for subacute and chronic low back pain. *Cochrane Database Syst Rev* 2008; 3:CD001824 (161).

Table 2. ***Randomized controlled trials quality rating system.***

A	1. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a die (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments. Examples of inadequate methods are: alternation, birth date, social insurance/ security number, date in which they are invited to participate in the study, and hospital registration number.	Yes/No/ Unsure
B	2. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/ Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?		
	3. Was the patient blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/ Unsure
	4. Was the care provider blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/ Unsure
	5. Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: –for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes" –for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination –for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome –for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., co-interventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes" –for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data.	Yes/No/ Unsure
D	Were incomplete outcome data adequately addressed?		
	6. Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored. (N.B. these percentages are arbitrary, not supported by literature).	Yes/No/ Unsure
	7. Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.	Yes/No/ Unsure
E	8. Are reports of the study free of suggestion of selective outcome reporting?	In order to receive a "yes," the review author determines if all the results from all pre-specified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/ Unsure
F	Other sources of potential bias:		
	9. Were the groups similar at baseline regarding the most important prognostic indicators?	In order to receive a "yes," groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/ Unsure
	10. Were co-interventions avoided or similar?	This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.	Yes/No/ Unsure
	11. Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/ Unsure
	12. Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/ Unsure

Adapted and modified from Furlan AD et al; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941 (152).

tle-Ottawa Scale for observational studies (Tables 3 and 4) (162). For nonrandomized observational studies, the patient population should have had at least 50 total, or at least 25 in each group if they were comparison groups. Even though none of these instruments or criteria were systematically assessed, the advantages and disadvantages of each system were debated.

Each study was evaluated by at least 2 authors for stated criteria. Any disagreements were discussed with a third reviewer. Authors with a perceived conflict of interest for any manuscript were recused from reviewing the manuscript.

Table 3. *Newcastle-Ottawa quality assessment scale: Case control studies.*

Selection
1) Is the case definition adequate?
a) yes, with independent validation *
b) yes, e.g. record linkage or based on self reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated
3) Selection of Controls
a) community controls *
b) hospital controls
c) no description
4) Definition of Controls
a) no history of disease (endpoint) *
b) no description of source
Comparability
1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for disc herniation or radiculitis*
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Exposure
1) Ascertainment of exposure
a) secure record (eg surgical records) *
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes *
b) no
3) Non-Response rate
a) same rate for both groups *
b) non respondents described
c) rate different and no designation

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (162).

Table 4. *Newcastle-Ottawa quality assessment scale for cohort studies.*

Selection
1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community *
b) somewhat representative of the average _____ in the community *
c) selected group of users e.g. nurses, volunteers
d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
a) secure record (eg surgical records) *
b) structured interview *
c) written self report
d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes *
b) no
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for disc herniation or radiculitis*
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Outcome
1) Assessment of outcome
a) independent blind assessment *
b) record linkage *
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) *
b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (162).

For adverse effects, confounding factors, etc., it was not possible to use quality assessment criteria. Thus, these were considered based on the interpretation of published reports and critical analysis of the literature.

Only randomized trials meeting the inclusion criteria with at least 50% of applicable criteria were utilized for analysis. However, studies scoring lower were described and provided with an opinion and critical analysis.

Observational studies had to meet a minimum of 50% of the utilized criteria for cohort and case-control studies. Studies scoring less were also described and provided with an opinion and a critical analysis.

1.4.5 Data Extraction and Management

Two review authors independently, in an unblinded standardized manner, extracted the data from the included studies. Disagreements were resolved by discussion between the 2 reviewers; if no consensus could be reached, a third author was called in to break the impasse.

1.4.6 Clinical Effectiveness

The minimum amount of change in pain score to be clinically meaningful has been described as a 2-point change on a scale of 0 to 10 (or 20 percentage points), based on findings in commonly utilized trials studying general chronic pain (163), chronic musculoskeletal pain (164), and chronic low back pain (165,166). Recent descriptions of clinically meaningful improvement, however, showed either pain relief or functional status as 50% (87,90-98,167-179). Consequently, for this analysis, we utilize clinically meaningful pain relief of at least a 3-point change on an 11-point scale of 0 to 10, or 50% pain relief from the baseline, as clinically significant and a functional status improvement of 40% or more.

1.5 Summary Measures

Summary measures included a 50% or more reduction of pain in at least 40% of patients, or at least a 3-point decrease in pain scores and adverse events including side effects.

1.6 Analysis of Evidence

The analysis of the evidence was performed based on United States Preventive Services Task Force (USPSTF) criteria as illustrated in Table 5. This criteria has been utilized by multiple authors (9,77,90,96-98,176-181).

The analysis was conducted using 3 levels of evidence ranging from good, fair, and limited or poor.

At least 2 of the review authors independently, in an unblinded standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus. If there were any conflicts of interest (e.g., authorship), those reviewers were recused from assessment and analysis.

1.7 Outcome of the Studies

In the randomized trials, a study was judged to be positive if nucleoplasty was clinically relevant and effective, either with a placebo control or active control. This indicates that the difference in effect for primary outcome measure is statistically significant on the conventional 5% level. In a negative study, no difference between the study treatments or no improvement from baseline is identified. The outcomes were judged at the reference point with positive or negative results reported at 6 months, one year, and later.

For observational studies, a study was judged to be positive if nucleoplasty therapy was effective, with outcomes reported at the reference point with positive or negative results at 6 months, one year, and after.

For any study to be judged to be positive, at least 40% of patients must have shown significant improvement.

2.0 Results

Figure 1 shows a flow diagram of the study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 5. *Method for grading the overall strength of the evidence for an intervention.*

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least 2 consistent, higher-quality RCTs or studies of diagnostic test accuracy).
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least one higher-quality trial or study of diagnostic test accuracy of sufficient sample size; 2 or more higher-quality trials or studies of diagnostic test accuracy with some inconsistency; at least 2 consistent, lower-quality trials or studies of diagnostic test accuracy, or multiple consistent observational studies with no significant methodological flaws).
Limited or Poor	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Adapted and modified from methods developed by U.S. Preventive Services Task Force (9,77,90,180).

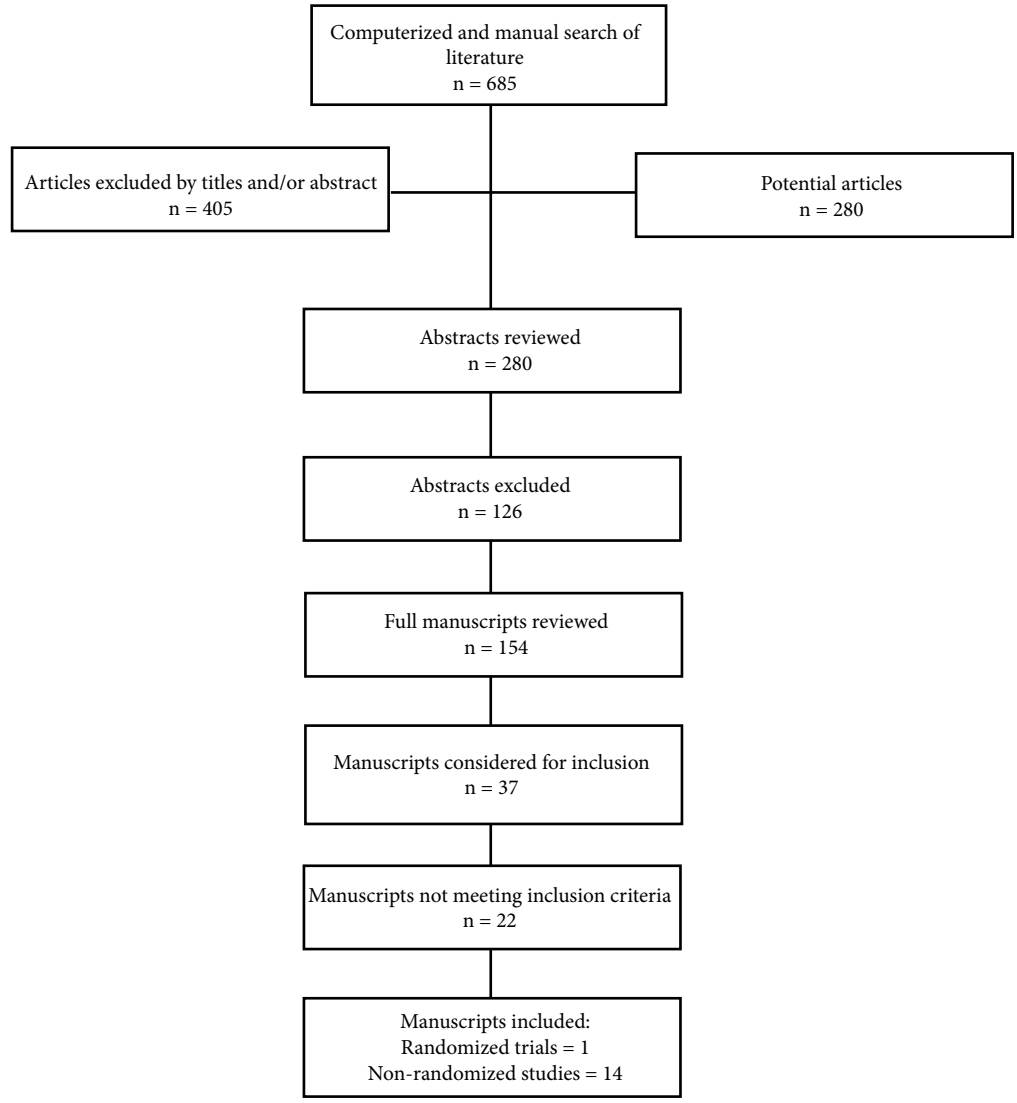

Fig. 1. *The flow diagram illustrating published literature evaluating mechanical lumbar disc decompression with nucleoplasty.*

(150). There were 37 studies considered for inclusion (68,74,75,99,120,122-147,182-187).

Of the 37 manuscripts identified, 22 were excluded (68,74,75,120,125,127,128,132,133,137,138,143-147,182-187). Table 6 shows the reasons for exclusion.

Table 7 illustrates the characteristics of the studies considered for inclusion (99,122-124,126,129-131,134-136,139-142). There was only one randomized trial (131). The remaining were observational reports (99,122-124,126,129,130,134-136,139-142). Follow-up of less than 6 months was considered as short-term whereas 6 months or longer was considered as long-term.

2.1 Methodological Quality Assessment

A methodological quality assessment of the RCTs meeting inclusion criteria was carried out utilizing Cochrane review criteria as shown in Table 8. Studies achieving Cochrane scores of 67% or higher were considered to be high quality, studies scoring 50% or higher were considered moderate quality, and studies scoring less than 50% were considered to be of poor quality and excluded.

Table 6. *List of excluded reports*.

Manuscript Author(s)	Reason for Exclusion
Chen et al, 2003 (68)	This was a study of intradiscal pressure of PDD with nucleoplasty in human cadavers.
Wang et al, 2005 (74)	This investigation reported the effect of uniform heating on the biomechanical properties of the intervertebral disc in a porcine model.
Welch & Gerszten, 2002 (75)	The authors described alternative strategies for lumbar discectomy including intradiscal electrothermal therapy and nucleoplasty. Nucleoplasty involved 25 patients with unpublished data.
Chen et al, 2003 (120)	The authors evaluated histologic findings of disc, endplate, and neural elements after Coblation of nucleus pulposus in an experimental study in cadavers. This was a case report of 3 patients with spinal stenosis treated with PDD with nucleoplasty.
Zhu et al, 2011 (125)	The effectiveness of Coblation nucleoplasty for protrusion of lumbar intervertebral disc was evaluated in 42 cases. Even though the results were positive with appropriate outcome parameters, the number of patients included in the study was 42 instead of at least 50.
Basaran & Topatan, 2008 (127)	The authors described a hypothetical minimally invasive treatment for herniated nucleus pulposus with a spinal balloon nucleoplasty.
Nau & Diederich, 2004 (128)	The authors evaluated the temperature distributions in cadaveric lumbar spine during nucleoplasty.
Kasch et al, 2012 (132)	The authors evaluated PDD with nucleoplasty-volumetry of the nucleus pulposus using ultrahigh-field MRI. The study was performed in 52 discs from 26 pigs and separated into thoracic and thoracolumbar discs. This is a basic science evaluation, but not a clinical study. In this evaluation, the authors demonstrated that nucleoplasty has a volume-reducing effect on the nucleus pulposus of the thoracic and thoracolumbar spine.
Yakovlev et al, 2007 (133)	This was a retrospective evaluation of 22 patients undergoing nucleoplasty.
Sharps & Isaac, 2002 (137)	The authors studied 49 patients in a prospective evaluation with positive results.
Singh et al, 2004 (138)	The authors studied 47 patients in a prospective, non-randomized observational study with positive results.
Bhagia et al, 2006 (143)	The authors evaluated side effects and complications after PDD using Coblation technology in 53 patients.
Calisaneller et al, 2007 (144)	The authors assessed percutaneous nucleoplasty for discogenic pain 6 months postoperative clinical, and 24-hour postoperative MRI examinations after nucleoplasty with radiofrequency energy in 29 patients. This observational report had only 29 patients.
Cohen et al, 2005 (145)	The authors evaluated nucleoplasty in an observational study consisting of only 9 patients.
Reddy et al, 2005 (146)	The authors evaluated 49 patients in a retrospective non-randomized study with Coblation nucleoplasty.
Lee et al, 2003 (147)	The authors evaluated histologic characterization of Coblation nucleoplasty performed on sheep intervertebral discs.
Puentedura et al, 2010 (182)	The manuscript described rehabilitation following lumbosacral percutaneous nucleoplasty in a single case report.
Smuck et al, 2007 (183)	The authors described epidural fibrosis following PDD with Coblation nucleoplasty in a single patient.
Theron et al, 2007 (184)	The authors evaluated percutaneous treatment of lumbar intervertebral disc herniation with radiopaque gelified ethanol.
Lee, 2012 (185)	The authors described in a review article various percutaneous intradiscal treatments.
Cuellar et al, 2010 (186)	The authors evaluated outcomes of PDD utilizing nucleoplasty in 22 patients in a retrospective case series. Authors analyzed factors that impact the result of nucleoplasty and attempted to validate the rational guidelines between minimally invasive treatments and open surgery.
Ruetten et al, 2008 (187)	This study evaluated full endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique. There was no Coblation technology utilized.

There was one randomized trial evaluating short and long-term relief (131), which scored 7 of 12 with moderate quality.

A methodological quality assessment of the observational studies meeting inclusion criteria was carried out utilizing Newcastle-Ottawa Scales as illustrated in Tables 9 and 10. For cohort studies, studies scoring 67% or higher were considered high quality, studies scoring 50% or higher were considered moderate quality, and studies scoring less than 50% were considered low quality and were excluded.

For case-control studies, 67% or higher was con-

Table 7. *Study characteristics of published reports of mechanical lumbar disc decompression with nucleoplasty.*

Study/Methods	Study Characteristics	Participants	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s) Short term relief ≤6 mos. Long-term relief >6 mos.
Gerszten et al, 2010 (131)	Randomized, active-control trial	90 patients associated with a single-level lumbar contained disc herniation were enrolled in a multicenter study.	Plasma disc decompression or nucleoplasty or transforaminal epidural steroid injections	VAS, ODI, SF-36	Patients in the plasma disc decompression or PDD group had significantly greater reduction in leg pain scores, ODI, and SF-36. During the 2-year follow-up, 56% of the patients in the PDD group and 28% of those in the transforaminal epidural group remained free from having a second procedure, following the study procedure.	Positive short-term and long-term results
Bokov et al, 2010 (99)	Prospective, non-randomized cohort study	138 participants were described with disc extrusion or sequestration undergoing microdiscectomy and 92 patients underwent nucleoplasty.	Coblation nucleoplasty	VAS, ODI	The overall success rate was 52% with total pain relief and satisfactory results in 74% of the patients. The size of the disc protrusion does not significantly affect the outcome with nucleoplasty.	Positive short-term and long-term results
Shabat et al, 2012 (122)	A prospective evaluation	87 patients with chronic low back pain, either mechanical back pain or radicular pain, were evaluated.	Nucleoplasty	VAS, ODI	After 6 months of follow-up 66% of the patients had pain relief and at 12 months follow-up 65% showed good results.	Positive short-term and long-term results
Azzazi et al, 2011 (123)	Observational study	50 patients with radicular pain due to contained disc herniation or focal protrusion were assessed.	Coblation nucleoplasty	VAS, ODI, reduction in analgesic treatment	This study reported complete resolution of symptoms in 40 of the 50 patients after one year.	Positive short-term and long-term results
Masala et al, 2007 (124)	Non-randomized evaluation	72 patients affected by lumbar disc herniation were treated with nucleoplasty Coblation from February 2004 to October 2005.	Nucleoplasty	VAS, Numeric pain scores, quality of relief	At one year evaluation 79% of the patients demonstrated a statistically significant improvement, whereas 17% were completely satisfied with complete resolution of symptoms and 62% obtained positive short-term and long-term improvement.	Positive short-term and long-term results
Karaman et al, 2011 (126)	Non-randomized evaluation	A total of 56 patients with chronic disc herniations having more significant radicular pain, who did not respond to non-invasive treatment methods and for whom open surgery was not an option, were selected for percutaneous nucleoplasty application.	Coblation nucleoplasty	VAS, ODI	Oswestry scores were 76.1 ± 10.2 in the beginning, which were reduced to 33.9 ± 14.9 at the end of 2 years. The proportion of patients stated good and excellent satisfaction was 66% at the 2 year follow-up.	Positive short-term and long-term results
Sinan et al, 2011 (129)	Prospective evaluation	82 patients, between ages 20 and 45, with established low back and/or leg pain of at least 3 months duration were treated with nucleoplasty.	Coblation nucleoplasty	VAS, Roland-Morris Disability Questionnaire, and subjective global rating of satisfaction	At 6 months and one year, 63 patients were considered as successful and 20 patients were considered as failed. The successful group showed significant improvement in VAS pain scales and Roland-Morris Disability Questionnaire.	Positive short-term and long-term results
Lemcke et al, 2010 (130)	Prospective comparative evaluation	128 patients with MRI-proven disc protrusion suffering from low back pain and/or radiating pain in the lower extremities were included.	Comparison of Coblation nucleoplasty with Dekompressor tool ; Nucleoplasty = 96; Disc dekompressor = 67	VAS, analgesic consumption, disability in daily life, ability to work	Statistical analysis was performed on 69 patients after nucleoplasty and 57 patients after disc decompressor after having completed the one-year follow-up. Significant improvement from pre-evaluation in both groups.	Positive short-term and long-term results

Table 7. (cont.) *Study characteristics of published reports of mechanical lumbar disc decompression with nucleoplasty.*

Study/Methods	Study Characteristics	Participants	Intervention(s)	Outcome(s)	Result(s)	Conclusion(s) Short term relief ≤6 mos. Long-term relief >6 mos.
Mirzai et al, 2007 (134)	A prospective evaluation	52 consecutive patients with leg pain and MRI evidence of small and medium-sized herniated discs correlating with the patients' symptoms (contained disc herniation less than 6 mm, with a disc height ≥ 50% in comparison to normal adjacent discs) were included.	Coblation nucleoplasty	VAS, ODI	Mean visual analog scale and mean Oswestry decreased significantly from 7.5 to 2.1 and 42.2 to 20.5. Analgesic consumption was stopped in 94% of the patients after one year. Overall, patient satisfaction was 88%.	Positive short-term and long-term results
Al-Zain et al, 2008 (135)	A prospective non-randomized evaluation	96 patients with established low back pain and/or radiating pain in the lower extremity underwent nucleoplasty from April 2005 to Dec. 2006.	Coblation nucleoplasty	VAS, analgesic consumption, disability and ability to work	61% of the patients showed improvement of 50% or greater at 6 months and 58% after one year.	Positive short-term and long-term results
Singh et al, 2002 (136)	Observational study	67 patients with contained disc herniation underwent PDD procedure using Coblation technology.	Coblation nucleoplasty	Pain relief and functional status improvement	At one year, 80% of the patients demonstrated statistically significant improvement in numeric pain scores. Statistically significant improvement was observed in 62%, 59%, and 60% of patients in sitting, standing, and walking ability at 12 months respectively.	Positive short-term and long term improvement
Singh et al, 2003 (139)	Observational report	80 patients with discogenic low back pain with or without radicular pain associated with contained disc herniation underwent PDD.	Coblation nucleoplasty	Numeric pain scores, ability to sit, stand, and walk	Overall, 75% of patients indicated a decrease in their numeric pain scores at 12 months with a statistically significant reduction. A total of 54% of patients indicated pain relief of 50% or more at 12 month follow-up. Significant improvement was reported by 54%, 44%, and 49% of patients in sitting, standing, and walking abilities, respectively, at one year follow-up.	Positive short-term and long-term results
Marin, 2005 (140)	Observational report	64 patients with contained disc herniation were treated with Coblation nucleoplasty.	Comparative evaluation of Coblation nucleoplasty and Coblation-assisted microdiscectomy	Pain relief and patient satisfaction	At 6 to 12 months 80% of the patients demonstrated an improvement in pain scores.	Positive short-term and long-term results
Gerszten et al, 2006 (141)	Observational study	67 patients with primarily radicular pain due to contained disc herniation underwent nucleoplasty-based decompression.	Coblation nucleoplasty with treatment	SF-36 health survey, EuroQol SD, and VAS	At 6 month follow-up with results available 36 patients continued to reflect improvement.	Positive short-term results
Alexandre et al, 2005 (142)	Observation study	1,390 patients with lumbar radiculitis or sciatica with disc pathology were included from February 2001 to May 2003.	Coblation nucleoplasty	Classified into excellent, good, scanty, and none. Excellent included total resolution of the clinical picture with full activity. Good included fairly total resolution of pain, with good quality of life	At one year follow-up, 55.8% showed excellent results and 24.9% showed good results with either total resolution or fairly total resolution of pain with full return to daily activities or good quality of life. MRI and/or CT performed 6 months after the procedure showed bulging was eliminated in 34%, significantly reduced in 48%, and unvaried in 18% of cases.	Positive short-term and long-term results in a large study

VAS = visual analog scale; ODI = Oswestry Disability Index; SF-36 = short-form 36; PDD = percutaneous disc decompression

sidered high quality, 50% or higher was considered moderate quality, and less than 50% was considered low quality. Those studies scoring less than 50% were excluded.

There were 14 observational studies (99,122-124,126,129,130,134-136,139-142) that were all considered moderate quality.

2.2 Clinical Relevance

Of the 14 studies assessed for clinical relevance, all of the studies met the criteria with a score of 3 out of 5 or greater (99,122-124,126,129-131,134-136,139-142). Table 11 illustrates the assessment of clinical relevance.

2.3 Meta-Analysis

No meta-analysis could be performed since there was only one randomized trial.

2.4 Analysis of Evidence

As shown in Table 12, based on the USPSTF criteria, the evidence is considered at 3 levels – good, fair, and limited or poor. Based on one randomized trial (131), which is of moderate quality, and 14 observational studies (99,122-124,126,129,130,134-136,139-142), which were all of moderate quality, the evidence for nucleoplasty is limited to fair.

Table 8. *Methodological quality assessment of randomized trial(s).*

	Gerszten et al, 2010 (131)
Randomization adequate	Y
Concealed treatment allocation	N
Patient blinded	N
Care provider blinded	N
Outcome assessor blinded	N
Drop-out rate described	Y
All randomized participants analyzed in the group	Y
Reports of the study free of suggestion of selective outcome reporting	Y
Groups similar at baseline regarding most important prognostic indicators	N
Co-interventions avoided or similar	Y
Compliance acceptable in all groups	Y
Time of outcome assessment in all groups similar	Y
Score	7/12

Y=yes; N=no; U=unclear

3.0 Complications

Rathmell et al (188) described the primary complications associated with nucleoplasty as those associated with the placement of the intradiscal introducer cannula and other complications resulting from the entry into the disc. These complications associated with intradiscal procedures included hematoma, superficial abscess, deep abscess, allergic reaction to radiographic contrast or antibiotic, direct needle trauma to the spinal nerve with transient or persistent paraesthesia, and spondylodiscitis. Rathmell et al (188) described that even though the introducer cannula used for nucleoplasty is larger in diameter than the typical #22 gauge spinal needle used to perform discography, there is no evidence to suggest that there is a higher complication rate associated with the use of this large bore introducer. Nevertheless, they cautioned that it stands to reason that use of a larger needle may well lead to a greater neural injury in the event of contact with a neural structure. A number of theoretical risks also have been described. The nucleoplasty results in marked temperature elevation and tissue destruction that is limited to the area immediately adjacent to the treatment tip of the probe. If the treatment tip is withdrawn too far and the active tip is pulled back into the metal introducer, this can theoretically cause heating of the entire length of the introducer cannula. Thus, it may produce a thermal injury. In addition, excessive extension of the treatment probe can lead to penetration of the anterior annulus fibrosis and extension into the retroperitoneal space, with potential damage to vascular structures in this area and a significant risk of infection.

Gerges et al (61) reported that the majority of reviewed studies reported no significant complications related to nucleoplasty (133,141,144). However, the study by Cohen et al (145) reported that 2 of 16 patients experienced new-onset "neurologic" symptoms following nucleoplasty. One patient complained of numbness in both feet and the other developed twitching symptoms in the leg and back. Bhagia et al (143) performed a quantitative analysis of the incidence of complications following nucleoplasty, specifically investigating short-term effects for up to a 2-week period. In their report, the most common side effects at 24 hours following nucleoplasty were soreness at the needle insertion site (76%), new numbness and tingling (26%), increased intensity of preprocedure back pain (15%), and new areas of back pain (15%). At 2 weeks following nucleoplasty, all patients had resolution of soreness at their needle insertion site and of pain in new areas of the back. However, new numbness and tingling was

Table 9. *Methodological quality assessment of case control studies of nucleoplasty utilizing Newcastle-Ottawa quality assessment scale.*

	Bokov et al (99)	Lemcke et al (130)
Selection		
1) Is the case definition adequate?		
a) yes, with independent validation *	X	X
b) yes, e.g. record linkage or based on self reports		
c) no description		
2) Representativeness of the cases		
a) consecutive or obviously representative series of cases *	X	X
b) potential for selection biases or not stated		
3) Selection of Controls		
a) community controls *	X	X
b) hospital controls		
c) no description		
4) Definition of Controls		
a) no history of disease (endpoint) *		
b) no description of source		
Comparability		
1) Comparability of cases and controls on the basis of the design or analysis		
a) study controls for disc herniation or radiculitis*	X	X
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)		
Exposure		
1) Ascertainment of exposure		
a) secure record (eg surgical records) *	X	X
b) structured interview where blind to case/control status *		
c) interview not blinded to case/control status		
d) written self report or medical record only		
e) no description		
2) Same method of ascertainment for cases and controls		
a) yes *	X	X
b) no		
3) Non-Response rate		
a) same rate for both groups	X	X
b) non respondents described		
c) rate different and no designation		
SCORE	7/12	7/12

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (162).

Table 10. *Methodological quality assessment of cohort studies of nucleoplasty utilizing Newcastle-Ottawa quality assessment scale.*

	Shabat et al (122)	Azzazi et al (123)	Masala et al (124)	Karaman et al (126)	Sinan et al (129)	Mirzai et al (134)	Al-Zain et al (135)	Singh et al (136)	Singh et al (139)	Marin (140)
Selection										
1) Representativeness of the exposed cohort										
a) truly representative of the average _____ (describe) in the community*	X	X	X	X	X	X	X	X	X	X
b) somewhat representative of the average pain patients in the community *										
c) selected group of users e.g. nurses, volunteers										
d) no description of the derivation of the cohort										
2) Selection of the non exposed cohort										
a) drawn from the same community as the exposed cohort *	X	X	X	X	X	X	X	X	X	X
b) drawn from a different source										
c) no description of the derivation of the non exposed cohort										
3) Ascertainment of exposure										
a) secure record (eg surgical records) *										
b) structured interview *	X	X	X	X	X	X	X	X	X	X
c) written self report										
d) no description										
4) Demonstration that outcome of interest was not present at start of study										
a) yes *	X	X	X	X	X	X	X	X	X	X
b) no										
Comparability										
1) Comparability of cohorts on the basis of the design or analysis										
a) study controls for disc herniation or radiculitis*										
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)										
Outcome (Exposure)										
1) Assessment of outcome										
a) independent blind assessment *										
b) record linkage *	X	X	X	X	X	X	X	X	X	X
c) self report										
d) no description										
2) Was follow-up long enough for outcomes to occur										
a) yes (select an adequate follow up period for outcome of interest) *	X	X	X	X	X	X	X	X	X	X
b) no										

Table 10 .(cont.) *Methodological quality assessment of cohort studies of nucleoplasty utilizing Newcastle-Ottawa quality assessment scale.*

	Shabat et al (122)	Azzazi et al (123)	Masala et al (124)	Karaman et al (126)	Sinan et al (129)	Mirzai et al (134)	Al-Zain et al (135)	Singh et al (136)	Singh et al (139)	Marin (140)
3) Adequacy of follow up of cohorts										
a) complete follow up - all subjects accounted for *	X	X	X	X	X	X	X	X	X	X
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *										
c) follow up rate < ____% (select an adequate %) and no description of those lost										
d) no statement										
SCORE	7/12	7/12	7/12	7/12	7/12	7/12	7/12	7/12	7/12	7/12

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.
Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (162).

Table 10 .(cont.) *Methodological quality assessment of cohort studies of nucleoplasty utilizing Newcastle-Ottawa quality assessment scale.*

	Gerszten et al (141)	Alexandre et al, 2005 (142)
Selection		
1) Representativeness of the exposed cohort		
a) truly representative of the average _____ (describe) in the community *	X	X
b) somewhat representative of the average pain patients in the community *		
c) selected group of users e.g. nurses, volunteers		
d) no description of the derivation of the cohort		
2) Selection of the non exposed cohort		
a) drawn from the same community as the exposed cohort *	X	X
b) drawn from a different source		
c) no description of the derivation of the non exposed cohort		
3) Ascertainment of exposure		
a) secure record (eg surgical records) *		
b) structured interview *	X	X
c) written self report		
d) no description		
4) Demonstration that outcome of interest was not present at start of study		
a) yes *	X	X
b) no		
Comparability		
1) Comparability of cohorts on the basis of the design or analysis		
a) study controls for disc herniation or radiculitis *		
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)		
Outcome (Exposure)		
1) Assessment of outcome		
a) independent blind assessment *		
b) record linkage *	X	X
c) self report		
d) no description		
2) Was follow-up long enough for outcomes to occur		
a) yes (select an adequate follow up period for outcome of interest) *	X	X
b) no		
3) Adequacy of follow up of cohorts		
a) complete follow up - all subjects accounted for *	X	X
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *		
c) follow up rate < ____% (select an adequate %) and no description of those lost		
d) no statement		
SCORE	7/12	7/12

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability
Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (162).

Table 11. *Clinical relevance of included studies.*

Manuscript Author(s)	A) Patient description	B) Description of interventions and treatment settings	C) Clinically relevant outcomes	D) Clinical importance	E) Benefits versus potential harms	Total Criteria Met
Bokov et al (99)	+	+	+	+	+	5/5
Shabat et al (122)	+	+	+	+	+	5/5
Azzazi et al (123)	+	+	+	+	+	5/5
Masala et al (124)	+	+	+	+	+	5/5
Karaman et al (126)	+	+	+	+	+	5/5
Sinan et al (129)	+	+	+	+	+	5/5
Lemcke et al (130)	+	+	+	+	+	5/5
Gerszten et al (131)	+	+	+	+	+	5/5
Mirzai et al (134)	+	+	+	+	+	5/5
Al-Zain et al (135)	+	+	+	+	+	5/5
Singh et al (136)	+	+	+	+	+	5/5
Singh et al (139)	+	+	+	+	+	5/5
Marin (140)	+	+	+	+	+	5/5
Gerszten et al (141)	+	+	+	+	+	5/5
Alexandre et al (142)	+	+	+	+	+	5/5

+ = positive; - = negative ; U = unclear

Scoring adapted from Staal JB, et al. Injection therapy for subacute and chronic low-back pain. Cochrane Database Syst Rev 2008; 3:CD001824 (161).

Table 12. *Summary results of eligible studies of mechanical lumbar disc decompression with nucleoplasty.*

Study	Methodological Quality Scoring	Number of Participants	Significant Pain Relief	Results
			> 12 mos.	Long-term > 12 mos.
Gerszten et al (131)	7/12	90	56%	P
Bokov et al (99)	7/12	138	74%	P
Shabat et al (122)	7/12	87	65%	P
Azzazi et al (123)	7/12	50	80%	P
Masala et al (124)	7/12	72	79%	P
Karaman et al (126)	7/12	56	66%	P
Sinan et al (129)	7/12	82	77%	P
Lemcke et al (130)	7/12	128	SI	P
Mirzai et al (134)	7/12	52	88%	P
Al-Zain et al (135)	7/12	96	58%	P
Singh et al (136)	7/12	67	80%	P
Singh et al (139)	7/12	80	75%	P
Marin (140)	7/12	64	80%	P
Gerszten et al (141)	7/12	67	54%	P
Alexandre et al (142)	7/12	1,390	55.8%	P
	TOTAL	2,519	62%*	P

P = positive; SI = significant improvement

*Lemcke et al (130) was not included as data was not available

present in 15% of patients and 4% of patients had an increased intensity of preprocedure back pain (143). This was not functionally limiting in any of the patients. In each instance, the leg symptoms were non-dermatomal in distribution, suggesting a somatic referral mechanism (56). Symptoms were attributed to provocation of the nerve fibers supplying the posterolateral aspect of the intervertebral disc. One case report of epidural fibrosis following nucleoplasty was reported (186).

Gerszten et al (131) in a randomized trial of 90 patients, of which 45 underwent nucleoplasty, reported procedure-related adverse events in 5, or 11% of patients. These adverse events included pain at the injection site, increased radicular pain, increased weakness, increased back pain, light-headedness, muscle tightness or spasms, and acute low back pain with muscle spasms. These adverse-related events were higher in the transforaminal group than in the nucleoplasty group. Chen et al (120), in an experimental nucleoplasty study of histologic findings of disc, end plate, and neural elements after Coblation of nucleus pulposus, suggested that the nucleoplasty achieves volumetric removal of target disc tissue without overt thermal or structural damage to the adjacent tissues. Histologic examination revealed no evidence of direct mechanical or thermal damage of the surrounding tissues. There was clear evidence of Coblation channels with clean coagulation borders of the nucleus pulposus. They also found normal histologic findings of the annulus and end plate, with normal neural elements of the spinal cord and nerve roots at the level of the procedure.

4.0 Discussion

This systematic review evaluated the role of lumbar disc decompression with nucleoplasty. The evidence appeared to be superior to other intradiscal therapies even though nucleoplasty is included with other intradiscal therapies (77). The present evidence for nucleoplasty is limited to fair in managing radicular pain due to contained disc herniation. This is a change in the evidence from previous evaluations (61,62) due to the subsequent publication of a randomized trial (131) and a total of 14 positive observational studies (99,122-124,126,129,130,134-136,139-142).

Nucleoplasty utilizing Coblation technology dissolves the nuclear material through molecular dissociation, and is thought to lower nuclear pressure, thereby reducing the nerve root tension and allowing a protrusion to implode inward. There is a lack of systematic reviews for nucleoplasty. However, Derby et al (63) evaluated the evidence-informed management of chronic low back pain with minimally invasive nuclear decompression and concluded that nucleoplasty does not support the treatment of back pain alone, but is better suited for the improvement of referred extremity pain in patients with protrusion of less than 4 to 6 mm, minimal stenosis, and relatively well-maintained disc heights. Gibson and Waddell (84) in their systematic review concluded that there are no RCTs examining Coblation as a treatment for disc prolapse. The present review found multiple observational manuscripts evaluating the effectiveness of nucleoplasty, with 14 of them (99,122-124,126,129,130,134-136,139-142) meeting methodological quality assessment criteria for inclusion. In general, all the studies showed positive results. A total of 2,429 patients were evaluated in these studies, each with at least 50 patients and one-year follow-up where and relief ranged from 54% to 88%, with an average of 62% of patients showing improvement, based on 14 studies.

Derby et al (63) summarized the evidence, stating that we have yet to discover the cure for chronic low back pain. Relying on the published literature, they concluded that for chronic low back pain caused by a disrupted and mildly protruding disc, there is no treatment that stands head and shoulders above the rest. Nucleoplasty and other minimally invasive nuclear decompression devices are trying to bridge the gap between non-invasive treatment modalities and surgical fusion. The techniques are only a first iteration. They added that the scientific rationale for these procedures is wanting but not hopeless. They postulated that the targeted removal of a herniated nucleus behind a protrusion is a more logical strategy for achieving the desired effect of removing the source of inflammation and relieving tension on the adjacent irritated annulus than open discectomy, fusion, or disc arthroplasty. Furthermore, they described that future designs will allow better navigation into protrusions and incorporate enhanced methods to safely remove herniated nuclear material.

In spite of variable results, nucleoplasty is appealing because it is simple, relatively safe, and destroys minimal tissue. Disc height should therefore be maintained or collapse more slowly and allow the body time to adapt. In addition, the 17-gauge introducer needle should cause significantly less collateral damage to normal annulus when compared with surgical arthroscopic decompression techniques that remove herniations from inside the disc (63). Because the surgical decom-

pression outcomes for small protrusions is inconsistent, and because patients often prefer fusion or arthroplasty to be the last resort, nuclear decompression using a minimally invasive technique would seem to be a reasonable next option for hydrated discs with relatively well-maintained disc heights (63). Thus, for patients with chronic low back pain and referred leg pain, nucleoplasty may be an option. Derby et al (63) stated that comparing nucleoplasty to fusion surgery, the reported median decreases in pain scores including both leg and back pain after nucleoplasty are 54% and median improvement in back-specific impairment scores is 42% after fusion. Moreover, nucleoplasty is generally safer than fusion. Finally, once an artificial disc or fusion instrumentation is inserted, there is no turning back (63). However, there is a risk that epidural fibrosis may develop with nucleoplasty (186).

Manchikanti et al (62) in a systematic review of the literature of disc decompression with nucleoplasty published in 2009 showed that there was a paucity of literature, both observational and randomized. They also showed that only 5 observational studies met inclusion criteria (134-136,139,140). Based on these 5 observational studies, they concluded that the evidence was rather limited in managing PDD with nucleoplasty for the treatment of leg pain. They also concluded that there was no evidence available in managing axial low back pain.

In a systematic review published in 2010, Gerges et al (61) with the inclusion of all the relevant literature for nucleoplasty, included 14 studies. All of them were observational. They reached a similar conclusion as Manchikanti et al (62) with limited evidence.

Contrary to previous evaluations, in this evaluation we were able to assess one randomized trial (131) and 14 observational studies (99,122-124,126,129,130,134-136,139-142) meeting methodological quality assessment criteria. This shows significant progress in the evidence. Among these, the only available randomized trial by Gerszten et al (131), published in 2010, evaluated clinical outcomes with PDD compared with standard care using fluoroscopically-guided transforaminal epidural steroid injection over the course of 2 years. They concluded that among patients who had radicular pain associated with a contained lumbar disc herniation, treated with PDD had significantly reduced pain and better quality of life scores than those treated using repeated transforaminal epidural steroid injection. In addition, significantly more PDD patients than transforaminal epidural steroid injection patients avoided having to undergo a secondary procedure during the 2-year study follow-up. Furthermore, a significantly higher percentage of patients in the PDD group showed a minimum of clinically important changes. This is the best study thus far assessing nucleoplasty in a randomized fashion. This is, however, not a true placebo-control study. It is an active-control study with transforaminal epidural steroid injection procedures and PDD . Some may consider that the sample size as too small; however, the sample size calculations were appropriate. The authors utilized extensive outcomes assessment. The major disadvantage is that the randomized, controlled portion of the trial was limited to a 6-month follow-up. There is also criticism that transforaminal epidural is not really comparable to disc decompression as one is known to provide short-term relief and the other one is expected to provide long-term relief of greater than one year or so. Overall, the study is considered moderate quality.

Among the other studies, which are noteworthy, is the study by Alexandre et al (142). In this study, they evaluated 1,390 patients with chronic lumbar pain with or without radicular pain, lasting more than 3 months after the failure of medically and physically conservative treatments. In addition, inclusion criteria also included a positive provocative discography level and a negative control level. Contraindications included the presence of neurological deficit, infection, and coagulopathies. They utilized rather strict outcome measures with results being classified as excellent with total resolution of the clinical picture and full re-uptake of daily activities; good with total resolution of pain and relatively good quality of life; scanty with insignificant pain resolution and inability to take up normal daily activities; and none with no results both on pain and clinical field. They showed striking results with over 80% of patients, with 55.8% with excellent results and 24.9% with good results. They also illustrated that MRI and/or CT performed 6 months after the procedure showed that bulging discs were eliminated in 34%, significantly reduced in 48%, and unvaried in 18% of cases.

In a cadaveric study, Kasch et al (132) assessed 52 discs from T8 to L1 from 26 pigs separated into thoracic T8-T11 and thoracolumbar T12-L1. In this assessment of volumetry, they found that average preinterventional nucleus volume was 0.799 mL, whereas postinterventional volume reduction in the nucleoplasty group was significant at 0.052 mL, or 6.3% in thoracic discs, and 0.082 mL, or 7.25%, in thoracolumbar discs. They concluded that nucleoplasty achieved volume reductions of

14.72% in thoracic and 11.6% in thoracolumbar compared to the placebo group. Consequently, nucleoplasty seems to demonstrate a pathophysiologic, clinical, and biologic basis for disc decompression.

Limitations of this systematic review include scant literature. There was only one randomized trial, which was of moderate quality (131), although with positive results. The remaining evidence is dependent on observational studies. The number of observational studies meeting inclusion criteria has increased to 14 with one large study including 1,390 patients (142). Inclusion criteria were rather strict, in that at least 50 patients and one-year follow-up was required. Thus, multiple studies were excluded even though these have been included in other systematic reviews. However, placebo-control is an extremely difficult issue with interventional trials as demonstrated by Gerszten et al (131). Furthermore, there is a great deal of misunderstanding in relation to active-control trials and placebo-control trials. This misunderstanding continues to emerge in interventional pain management, resulting in inappropriate analysis of the evidence. In fact, multiple studies that have considered themselves as placebo-controlled in interventional pain management settings (9,18,189-196) have utilized local anesthetic injection, in essence producing a facet joint nerve block. As the literature illustrates, a facet joint nerve block can provide on average 13 to 16 weeks of prolonged relief (103,169-171). This may have been problematic in interpretation in many placebo controlled interventional trials (197-203). Consequently, these studies could be construed as active-control trials even though sham treatment was utilized. Similarly, multiple studies in the evaluation of epidural treatment have utilized local anesthetic and called them placebo studies. Proper terminology may be that these are sham-controlled but not placebo-controlled. It is not always feasible to perform placebo-controlled studies in an interventional setting, and the absence of these studies has led to some third party payers denying payment for effective therapies.

It has been widely reported by Cochrane reviewers and others that placebo effect studies are susceptible to response bias and to other types of biases. Hróbjartsson et al (204) reviewed the pervasive and complex connection between the placebo effect and bias. Ever since the concept of the placebo was brought to the attention of the medical community by Beecher (205) in his classic 1955 JAMA article, "The Powerful Placebo," in which he presented a review of assorted placebo-control trials, and argued that the substantial improvement in the condition of patients receiving placebo was caused by the placebo intervention. Nevertheless, Beecher's analysis committed the very fallacy that underlies the need for controlled trials. The observed response to placebo in randomized trials does not itself provide any reliable, unbiased, evidence of a placebo effect —an outcome caused by receiving a sham treatment disguised to be indistinguishable from an active medical intervention. Further, unbiased assessment of the placebo effect requires comparison of placebo interventions with a suitable control group in order to distinguish an effect of the placebo intervention from confounding factors, for example the natural history of the condition under investigation or regression to the mean (206). Even though Beecher's approach were clearly recognized as flawed in the late 1990's (207), by that time the notion of 'powerful placebo' became deeply rooted. Meanwhile methodologists haven't started anchoring to every study results to the natural history of the condition under investigation or regression to the mean. However, Krogsbøll et al in (208) reference to spontaneous improvement in randomized clinical trials and metaanalysis of 3-armed trials comparing no treatment, placebo, and active intervention, dispelled these myths. They showed that the conditions that had most pronounced spontaneous improvement were nausea 45%, smoking 40%, depression 35%, phobia 34%, and acute pain 25%. They also showed that overall, across all conditions and interventions there was a statistically significant change from baseline in all 3 arms. However, for chronic pain no treatment contributed to very small improvement and placebo response was also less than 30%, whereas active treatment showed effect of 60%. Assessment of standardized mean difference for changes from baseline group by acute or chronic conditions showed no change in the no treatment group. Consequently, authors concluded that spontaneous improvement and effect of placebo contributed importantly to the observed treatment effect in actively treated patients, but the relative importance of these factors differed according to clinical condition and intervention. Further, in 2001, in sharp contrast, the power of placebo was challenged by a systematic review published in the New England Journal of Medicine (209). This review identified 114 randomized clinical trials including placebo and no treatment groups, and reported no evidence of overall effects of placebo for objective and binary outcomes and a small, and doubtfully clinically relevant, effect for continuous subjective outcomes,

such as pain. These findings are clearly incompatible with Beecher's classic position and present methodologists view of spontaneous improvement of the disorder or disease. While some academic commentators either pointed out that worthwhile effects could still exist in some settings (210), or saw the review as a necessary scientific correction to set the bar differently for claims concerning placebo (211), some media commentators interpreted the result as demonstrating the placebo effect to be a myth (212). Even though review which was updated in 2004 showed similar findings (213), the latest update from 2010 reported more multifaceted results (214). The recent systematic review showed that large analgesic effects of placebo interventions were found in several well conducted trials and a considerable variation in effect could in part be explained by differences in trial design, for example, effect of placebo was larger when the intervention was a device as compared with pill placebo. Overall popular fascination with the placebo effect, specifically methodologists who do not like any type of interventions in medicine, fueled fascination with the placebo effect with unrealistic assessments of its therapeutic effects to rule out any treatment effects. On the same token, some have suggested the therapeutic potential of placebos (215). However, all the metaanalysis (211,213,214) involving progressively larger number of studies and subjects, performed for Cochrane review, challenges the belief that in general that the placebo is powerful. Consequently, estimating the size of the effect of placebo is not only subject to considerable uncertainty, but seems to be almost impossible. Hróbjartsson et al (204) in their methodological analysis and discussion of placebo effect studies and their susceptibility to response bias and to other types of biases, showed that the difference between placebo and no-treatment remains an approximately and fairly crude reflection of the true effect of placebo intervention. They showed that a main problem is response bias in trials with outcomes that are based on patient's reports. Other biases involve differential co-intervention and patient drop-outs, publication bias, and outcome reporting bias, however, they have ignored the bias of the methodologists and improper analysis, and lack of consideration of injection of an inactive solution into active structure. Consequently, extrapolation of results to clinical settings are challenging because of lack of clear identification of the causal factors in many clinical trials, and the non-clinical settings and short duration of most laboratory experiments. They (204) concluded that creative experimental efforts are needed to assess rigorously the clinical significance of placebo interventions and investigate the component elements that may contribute to therapeutic benefit. In fact, nonanalgesic solutions (e.g., saline) injected into painful structures have been reported to result in significant activity or even pain relief not only for spinal pain, but also for other chronic pain conditions (216-226). The placebo and nocebo effects, and decisions to consider all local anesthetic injections as placebo, are due to a lack of understanding about the scientific basis for placebo and nocebo (218,219,227-243). Further, the hazards of evidence-based medicine have been well described in the literature. Thus, it is essential to understand not only the study design but placebo and nocebo influences on the outcomes.

In summary, this systematic evaluation, which was performed with strict standards, shows nucleoplasty may provide appropriate relief in properly selected patients with contained disc herniation with determined evidence, which is fair.

5.0 Conclusion

This systematic review illustrates limited to fair evidence for nucleoplasty in managing radicular pain due to contained disc herniation. Nucleoplasty may provide appropriate relief in properly selected patients with contained disc herniation without significant complications and minimal morbidity.

Acknowledgments

The authors wish to thank Vidyasagar Pampati, MSc, for statistical assistance; Sekar Edem for assistance in the search of the literature, Alvaro F. Gómez, MA, and Laurie Swick, BS, for manuscript review; and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript. The authors also thank *Pain Physician* for permission to reproduce Manchikanti et al's manuscript from 2009 (62). We would like to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript.

Author Affiliations

Dr. Manchikanti is Medical Director of the Pain Management Center of Paducah, Paducah, KY, and Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY.

Dr. Falco is Medical Director of Mid Atlantic Spine & Pain Physicians, Newark, DE; Director, Pain Medicine

Fellowship Program, Temple University Hospital, Philadelphia, PA; and Associate Professor, Department of PM&R, Temple University Medical School, Philadelphia, PA.

Dr. Benyamin is Medical Director, Millennium Pain Center, Bloomington, IL, and Clinical Assistant Professor of Surgery, College of Medicine, University of Illinois, Urbana-Champaign, IL.

Dr. Caraway, St. Mary's Pain Relief Center, Huntington, WV.

Dr. Deer is Medical Director, Center for Pain Relief, and Clinical Professor, Anesthesiology, West Virginia University School of Medicine, Charleston, WV.

Dr. Singh is Medical Director, Spine Pain Diagnostics Associates, Niagara, WI.

Dr. Hameed is with Mid Atlantic Spine & Pain Physicians, , DE.

Dr. Hirsch is Vice Chief of Interventional Care, Chief of Minimally Invasive Spine Surgery, Service Line Chief of Interventional Radiology, Director of Endovascular Neurosurgery and Neuroendovascular Program, Massachusetts General Hospital; and Associate Professor, Harvard Medical School, Boston, MA.

Conflict of Interest:

Dr. Falco is a Consultant for St. Jude Medical Inc. and Joimax Inc.

Dr. Benyamin is a consultant with Bioness and Nevro, serves on the advisory boards of Vertos Medical and Nuvo Pharma, teaches/lectures for Vertos Medical, Boston Scientific, Neurotherm, and Bioness, and receives research/grants from Alfred Mann Foundation, Teknon Foundation, Spinal Restoration, Inc., Bioness, Boston Scientific, Vertos Medical, Medtronic, Kimberly Clarke, Epimed, BioDelivery Sciences International, Inc., Theravance, Mundipharma Research, Cephalon/Teva, AstraZeneca, and Purdue Pharma, LP.

Dr. Caraway is a consultant for Medtronic, Inc., Spinal Modulation, Inc., and Vertos, Inc.

Dr. Deer is a consultant and research advisor for Bioness, Medtronic, St. Jude, Spinal Modulation, and Vertos.

References

1. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, Buenaventura RM, Conn A, Datta S, Derby R, Falco FJE, Erhart S, Diwan S, Hayek SM, Helm S, Parr AT, Schultz DM, Smith HS, Wolfer LR, Hirsch JA. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician* 2009; 12:699-802.
2. Ivanova JI, Birnbaum HG, Schiller M, Kantor E, Johnstone BM, Swindle RW. Real-world practice patterns, healthcare utilization, and costs in patients with low back pain: The long road to guideline-concordant care. *Spine J* 2011; 11:622-632.
3. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251-258.
4. Luo X, Pietrobon R, Sun SX, Liu GG, Hey L. Estimates and patterns of direct health care expenditures among individuals with back pain in the United States. *Spine (Phila Pa 1976)* 2004; 29:79-86.
5. Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: Time to back off? *J Am Board Fam Med* 2009; 22:62-68.
6. Manchikanti L, Falco FJE, Singh V, Pampati V, Parr AT, Benyamin RM, Fellows B, Hirsch JA. Utilization of interventional techniques in managing chronic pain in the Medicare population: Analysis of growth patterns from 2000 to 2011. *Pain Physician* 2012; 15:E969-E982.
7. Staal JB, de Bie RA, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low back pain: An updated Cochrane review. *Spine (Phila Pa 1976)* 2009; 34:49-59.
8. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain: An update of a Cochrane review. *Spine (Phila Pa 1976)* 2011; 36:E825-E846.
9. Chou R, Huffman L. *Guideline for the Evaluation and Management of Low Back Pain: Evidence Review*. American Pain Society, Glenview, IL, 2009.
   www.americanpainsociety.org/uploads/pdfs/LBPEvidRev.pdf
10. Abbott ZI, Nair KV, Allen RR, Akuthota VR. Utilization characteristics of spinal interventions. *Spine J* 2012; 1:35-43.
11. Jacobs WC, van Tulder M, Arts M, Rubinstein SM, van Middelkoop M, Ostelo R, Verhagen A, Koes B, Peul WC. Surgery versus conservative management of sciatica due to a lumbar herniated disc: A systematic review. *Eur Spine J* 2011; 20:513-522.
12. Kovacs FM, Urrútia G, Alarcón JD. Surgery versus conservative treatment for symptomatic lumbar spinal stenosis: A systematic review of randomized controlled trials. *Spine (Phila Pa 1976)* 2011; 36:E1335-E1351.
13. Manchikanti L, Pampati V, Hirsch JA. Analysis of utilization patterns of vertebroplasty and kyphoplasty in the Medicare population. *J Neurointervent Surg* 2012; Published Online July 7, 2012.
14. Manchikanti L, Pampati V, Falco FJE, Hirsch JA. Growth of spinal interventional pain management techniques: Analysis of utilization trends and medicare expenditures 2000 to 2008. *Spine (Phila Pa 1976)* 2013; 38:157-168.
15. Manchikanti L, Helm II S, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV. Opioid epidemic in the United States. *Pain Physician* 2012; 15:ES9-ES38.

16. Manchikanti L, Singh V, Caraway DL, Benyamin RM, Hirsch JA. Medicare physician payment systems: Impact of 2011 schedule on interventional pain management. *Pain Physician* 2011; 14:E5-E33.
17. Manchikanti L, Hirsch JA. Medicare physician payment rules for 2011: A primer for the neurointerventionalist. *AJNR Am J Neuroradiol* 2011; 32:E101-E104.
18. Manchikanti L, Datta S, Gupta S, Munglani R, Bryce DA, Ward SP, Benyamin RM, Sharma ML, Helm II S, Fellows B, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 2. Therapeutic interventions. *Pain Physician* 2010; 13:E215-E264.
19. Manchikanti L, Singh V, Caraway DL, Benyamin RM, Falco FJE, Hirsch JA. Proposed physician payment schedule for 2013: Guarded prognosis for interventional pain management. *Pain Physician* 2012; 15:E615-E627.
20. Manchikanti L, Singh V, Hirsch JA. Saga of payment systems of ambulatory surgery centers for interventional techniques: An update. *Pain Physician* 2012; 15:109-130.
21. Manchikanti L, Parr AT, Singh V, Fellows B. Ambulatory surgery centers and interventional techniques: A look at long-term survival. *Pain Physician* 2011; 14:E177-E215.
22. Manchikanti L, Falco FJ, Benyamin RM, Helm S 2nd, Parr AT, Hirsch JA. The impact of comparative effectiveness research on interventional pain management: Evolution from Medicare Modernization Act to Patient Protection and Affordable Care Act and the Patient-Centered Outcomes Research Institute. *Pain Physician* 2011; 14:E249-E282.
23. Manchikanti L, Hirsch JA. Medicare physician payment rules for 2011: A primer for the neurointerventionalist. *J Neurointervent Surg* 2011; 3:399-402.
24. Park CH, Lee SH, Jung JY. Dural sac cross-sectional area does not correlate with efficacy of percutaneous adhesiolysis in single level lumbar spinal stenosis. *Pain Physician* 2011; 14:377-382.
25. Newmark JL, Mehra A, Singla AK. Radiocontrast media allergic reactions and interventional pain practice - A review. *Pain Physician* 2012; 15:E665-E675.
26. Manchikanti L, Caraway DL, Parr AT, Fellows B, Hirsch JA. Patient Protection and Affordable Care Act of 2010: Reforming health care reform for the new decade. *Pain Physician* 2011; 14:E35-E67.
27. Atluri S, Akbik H, Sudarshan G. Prevention of opioid abuse in chronic non-cancer pain: An algorithmic, evidence based approach. *Pain Physician* 2012; 15:ES177-ES189.
28. Duarte RV, Raphael JH, Haque MS, Southall JL, Ashford RL. A predictive model for intrathecal opioid dose escalation for chronic non-cancer pain. *Pain Physician* 2012; 15:363-369.
29. Goodin A, Blumenschein K, Freeman PR, Talbert J. Consumer/patient encounters with prescription drug monitoring programs: Evidence from a Medicaid population. *Pain Physician* 2012; 15:ES169-ES175.
30. Krashin DL, Merrill JO, Trescot AM. Opioids in the management of HIV-related pain. *Pain Physician* 2012; 15:ES157-ES168.
31. Owen GT, Burton AW, Schade CM, Passik S. Urine drug testing: Current recommendations and best practices. *Pain Physician* 2012; 15:ES119-ES133.
32. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: A review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician* 2012; 15:ES67-ES92.
33. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, Brown KR, Bruel BM, Bryce DA, Burks PA, Burton AW, Calodney AK, Caraway DL, Cash KA, Christo PJ, Damron KS, Datta S, Deer TR, Diwan S, Eriator I, Falco FJE, Fellows F, Geffert S, Gharibo CG, Glaser SE, Grider JS, Hameed H, Hameed M, Hansen H, Harned ME, Hayek SM, Helm II S, Hirsch JA, Janata JW, Kaye AD, Kaye AM, Kloth DS, Koyyalagunta D, Lee M, Malla Y, Manchikanti KN, McManus CD, Pampati V, Parr AT, Pasupuleti R, Patel VB, Sehgal N, Silverman SM, Singh V, Smith HS, Snook LT, Solanki DR, Tracy DH, Vallejo R, Wargo BW. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2 – Guidance. *Pain Physician* 2012; 15:S67-S116.
34. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, Brown KR, Bruel BM, Bryce DA, Burks PA, Burton AW, Calodney AK, Caraway DL, Cash KA, Christo PJ, Damron KS, Datta S, Deer TR, Diwan S, Eriator I, Falco FJE, Fellows F, Geffert S, Gharibo CG, Glaser SE, Grider JS, Hameed H, Hameed M, Hansen H, Harned ME, Hayek SM, Helm II S, Hirsch JA, Janata JW, Kaye AD, Kaye AM, Kloth DS, Koyyalagunta D, Lee M, Malla Y, Manchikanti KN, McManus CD, Pampati V, Parr AT, Pasupuleti R, Patel VB, Sehgal N, Silverman SM, Singh V, Smith HS, Snook LT, Solanki DR, Tracy DH, Vallejo R, Wargo BW. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I – Evidence assessment. *Pain Physician* 2012; 15:S1-S66.
35. Lee JH, Lee SH. Clinical effectiveness of percutaneous adhesiolysis using Navicath for the management of chronic pain due to lumbosacral disc herniation. *Pain Physician* 2012; 15:213-221.
36. Wewalka M, Abdelrahimsai A, Wiesinger G, Uher EM. CT-guided transforaminal epidural injections with local anesthetic, steroid, and tramadol for the treatment of persistent lumbar radicular pain. *Pain Physician* 2012; 15:153-159.
37. Magalhaes FN, Dotta L, Sasse A, Teixera MJ, Fonoff ET. Ozone therapy as a treatment for low back pain secondary to herniated disc: A systematic review and meta-analysis of randomized controlled trials. *Pain Physician* 2012; 15:E115-E129.
38. Schultz DM, Webster LR, Kosek P, Dar U, Tan Y, Sun M. Sensor-driven position-adaptive spinal cord stimulation for chronic pain. *Pain Physician* 2012; 15:1-12.
39. Boogaard S, Heymans MW, Patijn J, de Vet HC, Faber CG, Peters ML, Loer SA, Zuurmond WW, Perez R. Predictors for persistent neuropathic pain--a Delphi survey. *Pain Physician* 2011; 14:559-568.
40. Gupta A, Patton C, Diskina D, Cheatle M. Retrospective review of physician opioid prescribing practices in patients with aberrant behaviors. *Pain Physician* 2011; 14:383-389.
41. Solanki DR, Koyyalagunta D, Shah RV, Silverman SM, Manchikanti L. Monitoring opioid adherence in chronic pain patients: Assessment of risk of substance misuse. *Pain Physician* 2011; 14:E119-E131.
42. Gentile DA, Woodhouse J, Lynch PJ, Maier J, McJunkin TL. Reliability and validity of the Global Pain Scale with chronic pain sufferers. *Pain Physician*

2011; 14:61-70.

43. Raffaeli W, Sarti D, Demartini L, Sotgiu A, Bonezzi C; Italian Ziconotide Group. Italian registry on long-term intrathecal ziconotide treatment. *Pain Physician* 2011; 14:15-24.
44. Gupta S, Gupta M, Nath S, Hess GM. Survey of European pain medicine practice. *Pain Physician* 2012; 15:E983-E994.
45. Deer TR, Kim C, Bowman R, Ranson MT, Yee BS. Study of percutaneous lumbar decompression and treatment algorithm for patients suffering from neurogenic claudication. *Pain Physician* 2012; 15:451-460.
46. Shui YU, Tao W, Huang D, Li Y, Fan B. Spinal cord stimulation for chronic pain originating from Lyme disease. *Pain Physician* 2012; 15:511-514.
47. Chang-Chien GC, Candido KD, Knezevic NN. Digital subtraction angiography does not reliably prevent paraplegia associated with lumbar transforaminal epidural steroid injection. *Pain Physician* 2012; 15:515-523.
48. Wang W, Mei XP, Chen L, Tang J, Li JL, Wu SX, Xu LX, Li YQ. Triptolide prevents and attenuates neuropathic pain via inhibiting central immune response. *Pain Physician* 2012; 15:E995-E1006.
49. Manchikanti L, Benyamin RM, Swicegood JR, Falco FJE, Datta S, Pampati V, Fellows B, Hirsch JA. Assessment of practice patterns of perioperative management of antiplatelet and anticoagulant therapy in interventional pain management. *Pain Physician* 2012; 15:E955-E968.
50. Pizzo PA, Clark NM. Alleviating suffering 101 – pain relief in the United States. *N Engl J Med* 2012; 366:197-199.
51. Pang WW, Mok MS, Lin ML, Chang DP, Hwang MH. Application of spinal pain mapping in the diagnosis of low back pain—analysis of 104 cases. *Acta Anaesthesiol Sin* 1998; 36:71-74.
52. Manchikanti L, Singh V, Pampati V, Damron K, Barnhill R, Beyer C, Cash K. Evaluation of the relative contributions of various structures in chronic low back pain. *Pain Physician* 2001; 4:308-316.
53. Bogduk N. Low back pain. *Clinical Anatomy of Lumbar Spine and Sacrum*. 4th edition. Churchill Livingstone, New York, 2005, pp 183-216.
54. Manchikanti L, Benyamin RM, Singh V, Falco FJE, Hameed H, Derby R, Wolfer LR, Helm II S, Calodney AK, Datta S, Snook LT, Caraway DL, Hirsch JA, Cohen SP. An update of the systematic appraisal of the accuracy of utility of lumbar discography in chronic low back pain. *Pain Physician* 2013; 16:SE55-SE95.
55. Wolfer L, Derby R, Lee JE, Lee SH. Systematic review of lumbar provocation discography in asymptomatic subjects with a meta-analysis of false-positive rates. *Pain Physician* 2008; 11:513-538.
56. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. *Spine (Phila Pa 1976)* 1995; 20:1878-1883.
57. Falco FJE, Manchikanti L, Datta S, Sehgal N, Geffert S, Onyewu O, Singh V, Bryce DA, Benyamin RM, Simopoulos TT, Vallejo R, Gupta S, Ward SP, Hirsch JA. An update of the systematic assessment of the diagnostic accuracy of lumbar facet joint nerve blocks. *Pain Physician* 2012; 15:E869-E907.
58. Simopoulos TT, Manchikanti L, Singh V, Gupta S, Hameed H, Diwan S, Cohen SP. A systematic evaluation of prevalence and diagnostic accuracy of sacroiliac joint interventions. *Pain Physician* 2012; 15:E305-E344.
59. Hancock MJ, Maher CG, Latimer J, Spindler MF, McAuley JH, Laslett M, Bogduk N. Systematic review of tests to identify the disc, SIJ or facet joint as the source of low back pain. *Eur Spine J* 2007; 16:1539-1550.
60. Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: A report of pain response to tissue stimulation during operation on the lumbar spine using local anesthesia. *Orthop Clin North Am* 1991; 22:181-187.
61. Gerges FJ, Lipsitz SR, Nedeljkovic SS. A systematic review on the effectiveness of the Nucleoplasty procedure for discogenic pain. *Pain Physician* 2010; 13:117-132.
62. Manchikanti L, Derby R, Benyamin RM, Helm S, Hirsch JA. A systematic review of mechanical lumbar disc decompression with nucleoplasty. *Pain Physician* 2009; 12:561-572.
63. Derby R, Baker RM, Lee CH. Evidence-informed management of chronic low back pain with minimally invasive nuclear decompression. *Spine J* 2008; 8:150-159.
64. Bokov A, Isrelov A, Skorodumov A, Aleynik A, Simonov A, Mlyavykh S. An analysis of reasons for failed back surgery syndrome and partial results after different types of surgical lumbar nerve root decompression. *Pain Physician* 2011; 14:545-557.
65. Freidenstein J, Aldrete JA, Ness T. Minimally invasive interventional therapy for Tarlov cysts causing symptoms of interstitial cystitis. *Pain Physician* 2012; 15:141-146.
66. Harned ME, Salles SS, Grider JS. An introduction to trialing intrathecal baclofen in patients with hemiparetic spasticity: A description of 3 cases. *Pain Physician* 2011; 14:483-489.
67. Graybill J, Conermann T, Kabazie AJ, Chandy S. Spinal cord stimulation for treatment of pain in a patient with post thoracotomy pain syndrome. *Pain Physician* 2011; 14:441-445.
68. Chen YC, Lee SH, Chen D. Intradiscal pressure study of percutaneous disc decompression with nucleoplasty in human cadavers. *Spine (Phila Pa 1976)* 2003; 28:661-665.
69. Kambin P, Brager MD. Percutaneous posterolateral discectomy. Anatomy and mechanism. *Clin Orthop Relat Res* 1987; 223:145-154.
70. Kambin P, Schaffer JL. Percutaneous lumbar discectomy. Review of 100 patients and current practice. *Clin Orthop Relat Res* 1989; 238:24-34.
71. Karasek M, Bogduk N. Twelve-month follow-up of a controlled trial of intradiscal thermal anuloplasty for back pain due to internal disc disruption. *Spine (Phila Pa 1976)* 2000; 25:2601-2607.
72. Nerubay J, Caspi I, Levinkopf M, Tadmor A, Bubis JJ. Percutaneous laser nucleolysis of the intervertebral lumbar disc. An experimental study. *Clin Orthop Relat Res* 1997; 337:42-44.
73. Sasaki M, Takahashi T, Miyahara K, Hirose T. Effects of chondroitinase ABC on intradiscal pressure in sheep: An *in vivo* study. *Spine (Phila Pa 1976)* 2001; 26:463-468.
74. Wang JC, Kabo JM, Tsou PM, Halevi L, Shamie AN. The effect of uniform heating on the biomechanical properties of the intervertebral disc in a porcine model. *Spine J* 2005; 5:64-70.
75. Welch WC, Gerszten PC. Alternative strategies for lumbar discectomy: Intradiscal electrothermy and nucleoplasty. *Neurosurg Focus* 2002; 13:E7.

76. Ohnmeiss DD, Guyer RD, Hochschuler SH. Laser disc decompression. The importance of proper patient selection. *Spine (Phila Pa 1976)* 1994; 19:2054-2058.
77. Helm S 2nd, Deer TR, Manchikanti L, Datta S, Chopra P, Singh V, Hirsch JA. Effectiveness of thermal annular procedures in treating discogenic low back pain. *Pain Physician* 2012; 15:E279-E304.
78. Postacchini F. Management of herniation of the lumbar disc. *J Bone Joint Surg Br* 1999; 81:567-576.
79. Saal JS, Saal JA. Management of chronic discogenic low back pain with a thermal intradiscal catheter. A preliminary report. *Spine (Phila Pa 1976)* 2000; 25:382-388.
80. Stolke D, Sollmann WP, Seifert V. Intra- and postoperative complications in lumbar disc surgery. *Spine (Phila Pa 1976)* 1989; 14:56-59.
81. Manchikanti L, Singh V, Falco, FJE, Calodney AK, Onyewu O, Helm S, Benyamin R, Hirsch JA. An updated review of automated percutaneous mechanical lumbar discectomy for the contained herniated lumbar disc. *Pain Physician* 2013; in press.
82. Singh V, Manchikanti L, Calodney AK, Staats PS, Falco FJE, Caraway DL, Hirsch JA, Cohen SP. Percutaneous lumbar laser disc decompression: An update of current evidence. *Pain Physician* 2013; in press.
83. Manchikanti L, Singh V, Calodney AK, Helm II S, Deer TR, Benyamin RM, Falco FJE, , Hirsch JA. Percutaneous lumbar mechanical disc decompression utilizing Dekompressor®: An update of current evidence. *Pain Physician* 2013; in press.
84. Gibson JNA, Waddell G. Surgical interventions for lumbar disc prolapse. *Cochrane Database Syst Rev* 2009; (1):CD001350.
85. Percutaneous Discectomy. Washington State Department of Labor and Industries, Office of Medical Director; February 24, 2004.
86. Freeman BJ, Mehdian R. Intradiscal electrothermal therapy, percutaneous discectomy, and nucleoplasty: What is the current evidence? *Curr Pain Headache Rep* 2008; 12:14-21.
87. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Fluoroscopic caudal epidural injections in managing post lumbar surgery syndrome: Two-year results of a randomized, double-blind, active-control trial. *Int J Med Sci* 2012; 9:582-591.
88. Robaina Padrón FJ. Lumbar post-laminectomy syndrome I. Pain management using interventionist techniques. *Neurocirugia (Astur)* 2007; 18:468-477.
89. Rodrigues FF, Dozza DC, de Oliveira CR, de Castro RG. Failed back surgery syndrome: Casuistic and etiology. *Arq Neuropsiquiat* 2006; 64:757-761.
90. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. A randomized, controlled, double-blind trial of fluoroscopic caudal epidural injections in the treatment of lumbar disc herniation and radiculitis. *Spine (Phila Pa 1976)* 2011; 36:1897-1905.
91. Manchikanti L, Cash RA, McManus CD, Pampati V, Fellows B. Fluoroscopic caudal epidural injections with or without steroids in managing pain of lumbar spinal stenosis: One year results of randomized, double-blind, active-controlled trial. *J Spinal Disord* 2012; 25:226-234.
92. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJE. Lumbar interlaminar epidural injections in central spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:51-63.
93. Manchikanti L, Singh V, Cash KA, Pampati V, Falco FJE. Fluoroscopic caudal epidural injections in managing chronic axial low back pain without disc herniation, radiculitis or facet joint pain. *J Pain Res* 2012; 5:381-390.
94. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin R. Fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar axial or discogenic pain. *J Pain Res* 2012; 5:301-311.
95. Manchikanti L, Cash KA, McManus CD, Pampati V, Fellows B. Results of 2-year follow-up of a randomized, double-blind, controlled trial of fluoroscopic caudal epidural injections in central spinal stenosis. *Pain Physician* 2012; 15: 371-384.
96. Parr AT, Manchikanti L, Hameed H, Conn A, Manchikanti KN, Benyamin RM, Diwan S, Singh V, Abdi S. Caudal epidural injections in the management of chronic low back pain: A systematic appraisal of the literature. *Pain Physician* 2012; 15:E159-E198.
97. Manchikanti L, Buenaventura RM, Manchikanti KN, Ruan X, Gupta S, Smith HS, Christo PJ, Ward SP. Effectiveness of therapeutic lumbar transforaminal epidural steroid injections in managing lumbar spinal pain. *Pain Physician* 2012; 15:E199-E245.
98. Benyamin RM, Manchikanti L, Parr AT, Diwan SA, Singh V, Falco FJE, Datta S, Abdi S, Hirsch JA. The effectiveness of lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain. *Pain Physician* 2012; 15:E363-E404.
99. Bokov A, Skorodumov A, Isrelov A, Stupak Y, Kukarin A. Differential treatment of nerve root compression pain caused by lumbar disc herniation applying nucleoplasty. *Pain Physician* 2010; 13:469-480.
100. Kim CH, Issa MA, Vaglienti RM. Use of observational mechanical gateway connector in spinal cord stimulation trials. *Pain Physician* 2011; 14:525-530.
101. Helm S II, Benyamin RM, Chopra P, Deer TR, Justiz R. Percutaneous adhesiolysis in the management of chronic low back pain in post lumbar surgery syndrome and spinal stenosis: A systematic review. *Pain Physician* 2012; 15:E435-E462.
102. Hansen H, Manchikanti L, Simopoulous TT, Christo PJ, Gupta S, Smith HS, Hameed H, Cohen SP. A systematic evaluation of the therapeutic effectiveness of sacroiliac joint interventions. *Pain Physician* 2012; 15:E247-E278.
103. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of lumbar facet joint nerve blocks in managing chronic low back pain: A randomized, double-blind, controlled trial with a 2-year follow-up. *Int J Med Sci* 2010; 7:124-135.
104. Hayek SM, Deer TR, Pope JE, Panchal SJ, Patel VB. Intrathecal therapy for cancer and non-cancer pain. *Pain Physician* 2011; 14:219-248.
105. Deer TR, Smith HS, Burton AW, Pope JE, Doleys DM, Levy RM, Staats PS, Wallace MS, Webster LR, Rauck RL, Cousins M. Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. *Pain Physician* 2011; 14:E283-E312.
106. Anderson PA, Rouleau JP. Intervertebral disc arthroplasty. *Spine (Phila Pa 1976)* 2004; 29:2779-2786.
107. Skorodumov A, Istrelov A, Liang H, Eristavi M. Outcomes of percutaneous disc decompression utilizing nucleoplasty for the treatment of chron-

ic discogenic pain. *Pain Physician* 2007; 10:319-328.

108. Schaufele MK. Single level lumbar disc herniations resulting in radicular pain: Pain and functional outcomes after treatment with targeted disc decompression. *Pain Med* 2008; 9:835-843.
109. Manchikanti L, Malla Y, Wargo BW, Fellows B. Infection control practices (safe injection and medication vial utilization) for interventional techniques: Are they based on relative risk management or evidence? *Pain Physician* 2011; 14:425-434.
110. Manchikanti L, Malla Y, Wargo BW, Cash KA, McManus CD, Damron KS, Jackson SD, Pampati V, Fellows B. A prospective evaluation of bleeding risk of interventional techniques in chronic pain. *Pain Physician* 2011; 14:317-329.
111. Manchikanti L, Falco FJE, Benyamin RM, Caraway DL, Helm II, S, Wargo BW, Hansen H, Parr AT, Singh S, Hirsch JA. Assessment of infection control practices for interventional techniques: A best evidence synthesis of safe injection practices and use of single-dose medication vials. *Pain Physician* 2012; 15:E573-E614.
112. Brown MD. Update on chemonucleolysis. *Spine (Phila Pa 1976)* 1996; 21:62S-68S.
113. Mayer HM. Spine update: Percutaneous lumbar disc surgery. *Spine (Phila Pa 1976)* 1994; 19:2719-2723.
114. Lucio JC, VanConia RB, DeLuzio KJ, Lehmen JA, Rodgers JA, Rodgers WB. Economics of less invasive spinal surgery: An analysis of hospital cost differences between open and minimally invasive instrumented spinal fusion procedures during the perioperative period. *Risk Manag Healthc Policy* 2012; 5:65-74.
115. Mixter W, Barr J. Rupture of the intervertebral disc with involvement of the spinal canal. *N Engl J Med* 1934; 211:210-215.
116. Love JG. Removal of the protruded intervertebral discs without laminectomy [editorial]. *Proc Mayo Clin* 1939; 14:1800.
117. Smith L. Enzyme dissolution of the nucleus pulposus in humans. *JAMA* 1964; 187:137-140.
118. Hijikata S. Percutaneous nucleotomy: A method of percutaneous nuclear extraction. *J Toden Hospital* 1975; 5:39-44.
119. Onik G, Helms C, Ginsburg L, Hoaglund FT, Morris J. Percutaneous lumbar diskectomy using a new aspiration probe. *AJNR* 1985; 6:290-293.
120. Chen YC, Lee SH, Saenz Y, Lehman NL. Histologic findings of disc, end plate and neural elements after coblation of nucleus pulposus: An experimental nucleoplasty study. *Spine J* 2003; 3:466-470.
121. Phurrough S, Salive M, O'Connor D, Schafer J. *Decision Memo for Thermal Intradiscal Procedures.* 2008 [cited September 30, 2008]. www.cms.hhs.gov/mcd/viewdecisionmemo.asp?from2=viewdecisionmemo.asp&id=215&
122. Shabat S, David R, Folman Y. Nucleoplasty is effective in reducing both mechanical and radicular low back pain: A prospective study in 87 patients. *J Spinal Disord Tech* 2012; 25:329-332.
123. Azzazi A, Al-Mekawi S, Zein M. Lumbar disc nucleoplasty using coblation technology: Clinical outcome. *J Neurointerv Surg* 2011; 3:288-292.
124. Masala S, Massari F, Fabiano S, Ursone A, Fiori R, Pastore F, Simonetti G. Nucleoplasty in the treatment of lumbar diskogenic back pain: One year follow-up. *Cardiovasc Intervent Radiol* 2007; 30:426-432.
125. Zhu H, Zhou XZ, Cheng MH, Shen YX, Dong QR. The efficacy of coblation nucleoplasty for protrusion of lumbar intervertebral disc at a two-year follow-up. *Int Orthop* 2011; 35:1677-1682.
126. Karaman H, Tüfek A, Ölmez Kavak G, Yildirim ZB, Temel V, Çelik F, Akdemir MS, Kaya S. Effectiveness of nucleoplasty applied for chronic radicular pain. *Med Sci Monit* 2011; 17:CR461-CR466.
127. Basaran A, Topatan S. Spinal balloon nucleoplasty: A hypothetical minimally invasive treatment for herniated nucleus pulposus. *Med Hypotheses* 2008; 70:1201-1206.
128. Nau WH, Diederich CJ. Evaluation of temperature distributions in cadaveric lumbar spine during nucleoplasty. *Phys Med Biol* 2004; 49:1583-1594.
129. Sinan T, Sheikh M, Buric J, Dashti K, Al-Mukhaimi A. Percutaneous coblation nucleoplasty in patients with contained lumbar disc prolapse: 1 year follow-up in a prospective case series. *Acta Neurochir Suppl* 2011; 108:107-112.
130. Lemcke J, Al-Zain F, Mutze S, Meier U. Minimally invasive spinal surgery using nucleoplasty and the Dekompressor tool: A comparison of two methods in a one year follow-up. *Minim Invasive Neurosurg* 2010; 53:236-242.
131. Gerszten PC, Smuck M, Rathmell JP, Simopoulos TT, Bhagia SM, Mocek CK, Crabtree T, Bloch DA; SPINE Study Group. Plasma disc decompression compared with fluoroscopy-guided transforaminal epidural steroid injections for symptomatic contained lumbar disc herniation: A prospective, randomized, controlled trial. *J Neurosurg Spine* 2010; 12:357-371.
132. Kasch R, Mensel B, Schmidt F, Drescher W, Pfuhl R, Ruetten S, Merk HR, Kayser R. Percutaneous disc decompression with nucleoplasty-volumetry of the nucleus pulposus using ultrahigh-field MRI. *PLoS One* 2012; 7:e41497.
133. Yakovlev A, Tamimi MA, Liang H, Eristavi M. Outcomes of percutaneous disc decompression utilizing nucleoplasty for the treatment of chronic discogenic pain. *Pain Physician* 2007; 10:319-327.
134. Mirzai H, Tekin I, Yaman O, Bursali A. The results of nucleoplasty in patients with lumbar herniated disc: A prospective clinical study of 52 consecutive patients. *Spine J* 2007; 7:88-92.
135. Al-Zain F, Lemcke J, Killeen T, Meier U, Eisenschenk A. Minimally invasive spinal surgery using nucleoplasty: A 1-year follow-up study. *Acta Neurochir (Wien)* 2008; 150:1257-1262.
136. Singh V, Piryani C, Liao K, Nieschultz S. Percutaneous disc decompression using coblation (nucleoplasty) in the treatment of chronic discogenic pain. *Pain Physician* 2002; 5:250-259.
137. Sharps LS, Isaac Z. Percutaneous disc decompression using Nucleoplasty. *Pain Physician* 2002; 5:121-126.
138. Singh V, Piryani C, Liao K. Role of percutaneous disc decompression using coblation in managing chronic discogenic low back pain: A prospective, observational study. *Pain Physician* 2004; 7:419-425.
139. Singh V, Piryani C, Liao K. Evaluation of percutaneous disc decompression using coblation in chronic back pain with or without leg pain. *Pain Physician* 2003; 6:273-280.
140. Marin FZ. CAM versus nucleoplasty. *Acta Neurochir Suppl* 2005; 92:111-114.
141. Gerszten PC, Welch WC, King JT. Quality of life assessment in patients un-

dergoing nucleoplasty-based percutaneous discectomy. *J Neurosurg Spine* 2006; 4:36-42.

142. Alexandre A, Coro L, Azuelos A, Pellone M. Percutaneous nucleoplasty for discoradicular conflict. *Acta Neurochir Suppl* 2005; 92:83-86.
143. Bhagia SM, Slipman CW, Nirschl M, Isaac Z, El-Abd O, Sharps LS, Garvin C. Side effects and complications after percutaneous disc decompression using coblation technology. *Am J Phys Med Rehabil* 2006; 85:6-13.
144. Calisaneller T, Ozdemir O, Karadeli E, Altinors N. Six months post-operative clinical and 24 hour post-operative MRI examinations after nucleoplasty with radiofrequency energy. *Acta Neurochir (Wien)* 2007; 149:495-500.
145. Cohen SP, Williams S, Kurihara C, Griffith S, Larkin TM. Nucleoplasty with or without intradiscal electrothermal therapy (IDET) as a treatment for lumbar herniated disc. *J Spinal Disord Tech* 2005; 18:S119-S124.
146. Reddy AS, Loh S, Cutts J, Rachlin J, Hirsch JA. New approach to the management of acute disc herniation. *Pain Physician* 2005; 8:385-390.
147. Lee MS, Cooper G, Lutz GE, Doty SB. Histologic characterization of coblation nucleoplasty performed on sheep intervertebral discs. *Pain Physician* 2003; 6:439-442.
148. Manchikanti L, Benyamin RM, Helm S, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 3: Systematic reviews and meta-analysis of randomized trials. *Pain Physician* 2009; 12:35-72.
149. 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.
150. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Ann Intern Med* 2009; 151:W65-W94.
151. van Tulder M, Furlan A, Bombardier C, Bouter L; Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. *Spine (Phila Pa 1976)* 2003; 28:1290-1299.
152. Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941.
153. van Tulder MW, Suttorp M, Morton S, Bouter LM, Shekelle P. Empirical evidence of an association between internal validity and effect size in randomized controlled trials of low-back pain. *Spine (Phila Pa 1976)* 2009; 34:1685-1692.
154. Manchikanti L, Datta S, Smith HS, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 6. Systematic reviews and meta-analyses of observational studies. *Pain Physician* 2009; 12:819-850.
155. 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. *JAMA* 2000; 283:2008-2012.
156. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T; CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Ann Intern Med* 2001; 134:663-694.
157. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340:c869.
158. Moher D, Schulz KF, Altman DG; CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *J Am Podiatr Med Assoc* 2001; 91:437-442.
159. Moher D, Schulz KF, Altman DG; CONSORT. The CONSORT statement: Revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Med Res Methodol* 2001; 1:2.
160. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *Ann Intern Med* 2007; 147:W163-W194.
161. Staal JB, de Bie R, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev* 2008; 3:CD001824.
162. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp
163. Farrar JT. What is clinically meaningful: Outcome measures in pain clinical trials. *Clin J Pain* 2000; 16:S106-S112.
164. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain* 2004; 8:283-291.
165. Bombardier C. Outcome assessments in the evaluation of treatment of spinal disorders: Summary and general recommendations. *Spine (Phila Pa 1976)* 2000; 25:3100-3103.
166. Hagg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J* 2003; 12:12-20.
167. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Assessment of effectiveness of percutaneous adhesiolysis and caudal epidural injections in managing lumbar post surgery syndrome: A 2-year follow-up of randomized, controlled trial. *J Pain Res* 2012; in submission.
168. Manchikanti L, Cash KA, McManus CD, Pampati V. Assessment of effectiveness of percutaneous adhesiolysis in managing chronic low back pain secondary to lumbar central spinal canal stenosis. *Int J Med Sci* 2012; in press.
169. Manchikanti L, Singh V, Falco FJE, Cash KA, Fellows B. Comparative outcomes of a 2-year follow-up of cervical medial branch blocks in management of chronic neck pain: A randomized, double-blind controlled trial. *Pain Physician*

2010; 13:437-450.

170. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V, Fellows B. The role of thoracic medial branch blocks in managing chronic mid and upper back pain: A randomized, double-blind, active-control trial with a 2-year follow-up. *Anesthesiol Res Pract* 2012; 2012:585806.
171. Manchikanti L, Singh V, Falco FJ, Cash KA, Fellows B. Cervical medial branch blocks for chronic cervical facet joint pain: A randomized double-blind, controlled trial with one-year follow-up. *Spine (Phila Pa 1976)* 2008; 33:1813-1820.
172. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic epidural injections in cervical spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:E59-E70.
173. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic cervical interlaminar epidural injections in managing chronic pain of cervical post-surgery syndrome: Preliminary results of a randomized, double-blind active control trial. *Pain Physician* 2012; 15:13-26.
174. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. Management of chronic pain of cervical disc herniation and radiculitis with fluoroscopic cervical interlaminar epidural injections. *Int J Med Sci* 2012; 9:424-434.
175. Manchikanti L, Cash KA, Pampati V, Malla Y. Fluoroscopic cervical epidural injections in chronic axial or disc-related neck pain without disc herniation, facet joint pain, or radiculitis. *J Pain Res* 2012; 5:227-236.
176. Benyamin RM, Wang VC, Vallejo R, Singh V, Helm S II. A systematic evaluation of thoracic interlaminar epidural injections. *Pain Physician* 2012; 15:E497-E514.
177. Diwan SA, Manchikant L, Benyamin RM, Bryce DA, Geffert S, Hameed H, Sharma ML, Abdi S, Falco FJE. Effectiveness of cervical epidural injections in the management of chronic neck and upper extremity pain. *Pain Physician* 2012; 15:E405-E434.
178. Falco FJE, Manchikanti L, Datta S, Wargo BW, Geffert S, Bryce DA, Atluri S, Singh V, Benyamin RM, Sehgal N, Ward S, Helm II S, Gupta S, Boswell MV. Systematic review of therapeutic effectiveness of cervical facet joint interventions: An update. *Pain Physician* 2012; 15:E839-E868.
179. Manchikanti KN, Atluri S, Singh V, Geffert S, Sehgal N, Falco FJE. An update of evaluation of therapeutic thoracic facet joint interventions. *Pain Physician* 2012; 15:E463-E481.
180. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D; Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force. *Am J Prevent Med* 2001; 20:21-35.
181. Atluri S, Singh V, Datta S, Geffert S, Sehgal N, Falco FJE. Diagnostic accuracy of thoracic facet joint nerve blocks: An update of the assessment of evidence. *Pain Physician* 2012; 15:E483-E496.
182. Puentedura EJ, Brooksby CL, Wallmann HW, Landers MR. Rehabilitation following lumbosacral percutaneous nucleoplasty: A case report. *J Orthop Sports Phys Ther* 2010; 40:214-224.
183. Smuck M, Benny B, Han A, Levin J. Epidural fibrosis following percutaneous disc decompression with coblation technology. *Pain Physician* 2007; 10:691-696.
184. Theron J, Guimaraens L, Casasco A, Sola T, Cuellar H, Courtheoux P. Percutaneous treatment of lumbar intervertebral disk hernias with radiopaque gelified ethanol: A preliminary study. *J Spinal Disord Tech* 2007; 20:526-532.
185. Lee SC. Percutaneous intradiscal treatments for discogenic pain. *Acta Anaesthesiol Taiwan* 2012; 50:25-28.
186. Cuellar VG, Cuellar JM, Vaccaro AR, Carragee EJ, Scuderi GJ. Accelerated degeneration after failed cervical and lumbar nucleoplasty. *J Spinal Disord Tech* 2010; 23:521-524.
187. Ruetten S, Komp M, Merk H, Godolias G. Full-endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique: A prospective, randomized, controlled study. *Spine (Phila Pa 1976)* 2008; 33:931-939.
188. Rathmell JP, Saal JS, Saal J. Discography, IDET, percutaneous discectomy, and nucleoplasty: Complications and their prevention. *Pain Med* 2008; 9:S73-S81.
189. Nath S, Nath CA, Pettersson K. Percutaneous lumbar zygapophysial (facet) joint neurotomy using radiofrequency current, in the management of chronic low back pain. A randomized double-blind trial. *Spine (Phila Pa 1976)* 2008; 33:1291-1297.
190. 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 (Phila Pa 1976)* 1999; 24:1937-1942.
191. 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.
192. Manchikanti L, Benyamin RM, Falco FJE, Caraway DL, Datta S, Hirsch JA. Guidelines warfare over interventional techniques: Is there a lack of discourse or straw man? *Pain Physician* 2012; 15:E1-E26.
193. 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.
194. McDonald GJ, Lord SM, Bogduk N. Long-term follow-up of patients treated with cervical radiofrequency neurotomy for chronic neck pain. *Neurosurgery* 1999; 45:61-68.
195. 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 (Phila Pa 1976)* 2000; 25:1270-1277.
196. Barnsley L. Percutaneous radiofrequency neurotomy for chronic neck pain: Outcomes in a series of consecutive patients. *Pain Med* 2005; 6:282-286.
197. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009; 361:557-568.
198. Kallmes DF, Cornstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, Hollingworth W, Ghdoke B, Annesley-Williams DJ, Ralston SH, Jarvik JG. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009; 361:569-579.
199. Ploeg WT, Veldhuizen AG, The B, Sietsma MS. Percutaneous vertebroplasty as a treatment for osteoporotic vertebral compression fractures: A systematic review. *Eur Spine J* 2006; 15:1749-1758.
200. Lotz JC. Trials of vertebroplasty for ver-

tebral fractures. *N Engl J Med* 2009; 361:2098.

201. Grey A, Bolland M. Trials of vertebroplasty for vertebral fractures. *N Engl J Med* 2009; 361:2098-2099.
202. Clark W, Lyon S, Burnes J. Trials of vertebroplasty for vertebral fractures. *N Engl J Med* 2009; 361:2097-2098.
203. Baerlocker MO, Munk PL, Liu DM. Trials of vertebroplasty for vertebral fractures. *N Engl J Med* 2009; 361:2098.
204. Hróbjartsson A, Kaptchuk TJ, Miller FG. Placebo effect studies are susceptible to response bias and to other types of biases. *J Clin Epidemiol* 2011; 64:1223-1229.
205. Beecher HK. The powerful placebo. *J Am Med Assoc* 1955; 159:1602-1606.
206. Hróbjartsson A. What are the main methodological problems in the estimation of placebo effects. *J Clin Epidemiol* 2002; 55:430-435.
207. Kienle GS, Kiene H. The powerful placebo effect: Fact or fiction? *J Clin Epidemiol* 1997; 50:1311-1318.
208. Krogsbøll LT, Hróbjartsson A, Gøtzsche PC. Spontaneous improvement in randomised clinical trials: Meta-analysis of three-armed trials comparing no treatment, placebo and active intervention. *BMC Med Res Methodol* 2009; 9:1.
209. Hróbjartson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Eng J Med* 2001; 344:1594-1602.
210. Brody H, Weismantel D. A challenge to core beliefs. *Adv Mind Body Med* 2001; 17:296-298.
211. Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: Illness and interpersonal healing. *Perspectives Bio Med* 2009; 52:518-539.
212. Kolata G. Placebo effect is more myth than science, study says. *The New York Times* May 24, 2001. www.nytimes.com/2001/05/24/us/placebo-effect-is-more-myth-than-science-study-says.html
213. Hróbjartson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J Intern Med* 2004; 256:91-100.
214. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010; 1:CD003974.
215. Meissner K, Höfner L, Fässler M, Linde K. Widespread use of pure and impure placebo interventions by GPs in Germany. *Fam Pract* 2012; 29:79-85.
216. 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.
217. 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.
218. Karppinen J, Malmivaara A, Kurunlahti M, Kyllonen E, Pienimaki T, Nieminen P, Ohinmaa A, Tervonen O, Vanharanta H. Periradicular infiltration for sciatica: A randomized controlled trial. *Spine (Phila Pa 1976)* 2001; 26:1059-1067.
219. Manchikanti L, Giordano J, Fellows B, Hirsch JA. Placebo and nocebo in interventional pain management: A friend or a foe - or simply foes? *Pain Physician* 2011; 14:E157-E175.
220. Kang YM, Choi WS, Pickar JG. Electrophysiologic evidence for an intersegmental reflex pathway between lumbar paraspinal tissues. *Spine (Phila Pa 1976)* 2002; 27:E56-E63.
221. Pham Dang C, Lelong A, Guilley J, Nguyen JM, Volteau C, Venet G, Perrier C, Lejus C, Blanloeil Y. Effect on neurostimulation of injectates used for perineural space expansion before placement of a stimulating catheter: Normal saline versus dextrose 5% in water. *Reg Anesth Pain Med* 2009; 34:398-403.
222. Tsui BC, Kropelin B, Ganapathy S, Finucane B. Dextrose 5% in water: Fluid medium maintaining electrical stimulation of peripheral nerve during stimulating catheter placement. *Acta Anaesthesiol Scand* 2005; 49:1562-1565.
223. Indahl A, Kaigle AM, Reikeras O, Holm SH. Interaction between the porcine lumbar intervertebral disc, zygapophysial joints, and paraspinal muscles. *Spine (Phila Pa 1976)* 1997; 22:2834-2840.
224. Indahl A, Kaigle A, Reikeras O, Holm S. Electromyographic response of the porcine multifidus musculature after nerve stimulation. *Spine (Phila Pa 1976)* 1995; 20:2652-2658.
225. Bhatia MT, Parikh LCJ. Epidural saline therapy in lumbo-sciatic syndrome. *J Indian Med Assoc* 1966; 47:537-542.
226. Gupta AK, Mital VK, Azmi RU. Observations of the management of lumbosciatic syndromes (sciatica) by epidural saline. *J Indian Med Assoc* 1970; 54:194-196.
227. Smuck M, Levin JH. RE: Manchikanti L, Singh V, Falco FJE, Cash KA, Fellows B. Cervical medial branch blocks for chronic cervical facet joint pain: A randomized double-blind, controlled trial with one-year follow-up. *Spine (Phila Pa 1976)* 2008; 33:1813-1820. *Spine (Phila Pa 1976)* 2009; 34:1116-1117.
228. Levin JH. Prospective, double-blind, randomized placebo-controlled trials in interventional spine: What the highest quality literature tells us. *Spine J* 2009; 9:690-703.
229. Manchikanti L, Shah RV, Datta S, Singh V. Critical evaluation of interventional pain management literature provides inaccurate conclusions. *Spine J* 2009; 9:706-708.
230. Nelemans PJ, Debie RA, DeVet HC, Sturmans F. Injection therapy for subacute and chronic benign low back pain. *Spine (Phila Pa 1976)* 2001; 26:501-515.
231. Egsmose C, Lund B, Bach Andersen R. Hip joint distension in osteoarthrosis. A triple-blind controlled study comparing the effect of intra-articular indoprofen with placebo. *Scand J Rheumatol* 1984; 13:238-242.
232. Häuser W, Bartram C, Bartram-Wunn E, Tölle T. Adverse events attributable to nocebo in randomized controlled drug trials in fibromyalgia syndrome and painful diabetic peripheral neuropathy: Systematic review. *Clin J Pain* 2012; 28:437-451.
233. Lyby PS, Forsberg JT, Asli O, Flaten MA. Induced fear reduces the effectiveness of a placebo intervention on pain. *Pain* 2012; 153:1114-1121.
234. Louhiala P, Puustinen R. Rethinking the placebo effect. *J Med Ethics* 2008; 34:107-109.
235. Louhiala P. The ethics of the placebo in clinical practice revisited. *J Med Ethics* 2009; 35:407-409.
236. Concato J. When to randomize, or "Evidence-based medicine needs medicine-based evidence." *Pharmacoepidemiol Drug Saf* 2012; 21:6-12.
237. Manchikanti L, Pampati V, Damron KS. The role of placebo and nocebo effects of perioperative administration of sed-

atives and opioids in interventional pain management. *Pain Physician* 2005; 8:349-355.

238. Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. *Clin J Pain* 2012; 28:567-572.
239. Gelijns AC, Gabriel SE. Looking beyond translation--integrating clinical research with medical practice. *N Engl J Med* 2012; 366:1659-1661.
240. Quill TE, Holloway RG. Evidence, preferences, recommendations--finding the right balance in patient care. *N Engl J Med* 2012; 366:1653-1655.
241. Blease C. The principle of parity: The "placebo effect" and physician communication. *J Med Ethics* 2012; 38:199-203.
242. Bisby MA. Inhibition of axonal transport in nerves chronically treated with local anesthetics. *Exp Neurol* 1975; 47:481-489.
243. Livingston EH, McNutt RA. The hazards of evidence-based medicine: Assessing variations in care. *JAMA* 2011; 306:762-763.