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Comprehensive Review

Therapeutic Role of Placebo: Evolution of a New Paradigm in Understanding Research and Clinical Practice

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Research into interventional techniques in managing chronic spinal pain continues to be challenging, mystifying, confusing, and biased. Insight, or lack thereof, into placebo and nocebo phenomena contributes mightily to these difficulties. Unfortunately, placebo-nocebo responses are the subject of numerous controversies and challenges from not only a research perspective, but also clinical perspective. While interventionalists consider the biggest threat to interventional pain management research is inappropriate and outdated interpretation of the data, a greater problem is the misuse of the placebo response in research, with the declaration that all and everything as a placebo effect: with a misinterpretation of the nature of the placebo the, associated conclusions can be inaccurate.

Researchers have been aware of placebo and nocebo effects for decades, even though misunderstandings and misgivings continue to be seen in scientific studies. In simplistic terms, placebo and nocebo had been understood to indicate improving or worsening of symptoms that occur during treatment with placebo/nocebo drugs or modalities. However, research has demonstrated that such terminology does not necessarily reflect "true" placebo effect or nocebo response. These effects are based on numerous factors, including natural course of a disease, spontaneous remission, regression to the mean, and a multitude of other conceptual, explanatory, and moral challenges. In modern clinical research, a neutral substance called placebo has been mainly used as a comparison factor rather than being studied itself, while the nocebo response has only been minimally studied.

A major misconception involves active placebo, a concept that has been extended beyond the administration of inert substances. The definition of active placebo of an active agent given to a patient, even though the pharmacologic action of the active agent is not known to be beneficial, has been converted to conveniently change many of the treatments which are effective on their own to be defined as placebos, often leading to conclusions that none of the interventions are effective.

This review focuses on a multitude of controversies surrounding placebo and nocebo phenomena in research and clinical applications. The discussion includes a focus on unsolved, forgotten, and ignored features of placebo responses in medicine, and provides an appropriate understanding of placebo and nocebo phenomena in interventional pain management. To that effect, this review also describes therapeutic placebos, research with open placebos, and improvements in understanding clinical applications of present interventional pain management research.

Keywords: Placebo effect, nocebo response, placebo analgesia, interventional techniques, active control trials, active placebos

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Interventional techniques in managing chronic spinal pain have faced numerous challenges with numerous authors frequently concluding that the effectiveness of procedures derived from contextual or nonspecific factors, commonly referred as placebo effects (1-8). However, interventional techniques are not alone in this aspect as the effectiveness of most medical interventions have been questioned related to placebo effects (2,3,8-21). Despite evidence for the effectiveness of interventional techniques, discordant conclusions have brought on multiple challenges related to the conduct of randomized controlled trials (RCTs) based on control design (active-control versus placebo-control) and outcomes assessments (absolute differences between 2 groups or minimum clinically important differences) with assessment of proportion of patients (4-7). The misunderstanding of the implications of placebo and nocebo effects and their role in interventional techniques is extensive and involves researchers, methodologists, and clinicians, despite overwhelming literature illustrating the role of placebo and nocebo to be different from active control. However, these concepts extend beyond honest differences of professional opinions, leading to intellectual bias, confluence of interest, and peer review bias (1,2,8,22-25). The Institute of Medicine (IOM) (22) succinctly described issues related to intellectual bias with conflicts of interest, which has led to replacing conflict of interest with confluence of interest to reflect the wider sources of bias and self-concern. (23). Misinterpretation of the literature by converting all active control trials utilizing local anesthetic as one of the treatment modalities to placebo control, with improper utilization of outcomes assessment, continues to raise questions in reference to intellectual bias and confluence of interest (4-21). Local anesthetics have overwhelming evidence with results in the range of 80% improvement in physical and functional status over 2-year follow-up as placebo effects, such that their use as a placebo is clearly inappropriate. The central theme of this manuscript is that setting public policy based on conclusions that are intellectually biased and derived from a confluence of interest, hinders not only the understanding of the research, but also diminishes the value of the research. In addition, it also leads to information bias, confirmation bias, outcomes bias, publication bias, and P-value bias (23,24). Ultimately, patients are prevented access to clinical and cost-effective therapies.

1.0 Historical Context

The history of placebo effects dates to 1811 when it was described by Robert Hooper in Quincy's Lexicon-Medicum as "an epithet given to any medicine adapted more to please than benefit the patient" (26). The word placebo, Latin for "I shall please" dates to a translation of the Bible by St. Jerome from Hebrew to Latin (27), and was first used in a medicinal context in the eighteenth century to describe an ineffective treatment (27). In 1955, Beecher proposed that placebo could have clinically important effects (28); however, this view was challenged in 2001 by Hrobjartsson et al (29), who concluded that there was no evidence of clinically important effects, except in the treatment of pain and continuous subjective outcomes. Subsequently, a Cochrane review also reached similar conclusions in 2010 (30), despite criticism from others (31). Even though substantial controversy regarding placebo continues, ongoing research continues on the subject (32). The use of placebo is considered an important methodological tool in medical research (33). One of the early concepts introduced about placebo is that patients who know they are receiving a placebo continue to report subjective improvement in their condition, specifically when they are told that the placebo can make them feel better (34). However, some studies may not have utilized true placebos, which is an inert substance into an inert structure rather than an active ingredient (34). Similarly, it has been demonstrated that if patients are informed about treatments, then these treatments are more effective, regardless of whether a placebo is involved or not (35,36).

This aspect of the placebo is the central hypothesis of this manuscript in the framework of misconstrued clinical research.

In contrast to placebo, the nocebo response has received less discussion and has been omitted from clinical assessments as an uncomfortable truth. Historically the term nocebo (Latin – I shall harm) was coined by Walter Kennedy in 1961 to denote the counterpart of the use of placebo (37). In short, a nocebo response is described as worsening of the symptoms or reduction of the beneficial effect by the administration of an inactive or active treatment. Kennedy also strongly emphasized that the specific usage of the term nocebo did not refer to "the iatrogenic action of drugs." (37). A key point was that nocebo responses should not be confused with true pharmaceutical side effects. Since then, the placebo-nocebo phenomenon has been the subject of an increasing and heated debate, and extensive research arriving at discordant opinions (38-40).

2.0 Mechanism and Clinical Context: Psychological Versus Physiological

Placebo has been defined as a "psychobiology phenomenon occurring in the patient's brain after the administration of an inert substance, or of a sham physical treatment such as sham surgery, along with verbal suggestions (or any other cue) of clinical benefit" (41,42). Others (43) have defined placebo response as "the reduction in symptoms as a result of factors related to patients' perception of the therapeutic intervention." Apart from describing nocebo effects and regardless of the nuances in definition of placebo, the common salient points are that there is no specific pharmaco-active ingredient in the medication or target physiologic mechanism when using a non-pharmacological intervention that accounts for the treatment response, and the improved outcome is principally related to a biopsychosocial response (44). Thus, in clinical trials without inclusion of a placebo group, but with the inclusion of a no treatment group, the so-called placebo effect is not measured. There are numerous challenges in research and in clinical practice in understanding the placebo-nocebo response and its implications on public policy and patient care (38-40,45-48).

The controversies start with the definition itself (40,46) along with multiple issues related to the physiologic mechanisms of placebo and nocebo (27,38-40,45-49). Kaptchuk and Miller (46) suggested that placebo effects rely on complex neurobiologic mechanisms involving neurotransmitters (e.g., endorphins, cannabinoids, dopamine) and activation of specific quantifiable and relevant areas of the brain (e.g., prefrontal cortex, anterior insula, rostral anterior cingulate cortex, and amygdala in placebo analgesia) (47,49). Further, some have identified genetic signatures of patients who are likely to respond to placebos (48). In addition, Rütgen et al (49) have shown the role of empathy may be associated with neural responses and neurotransmitter activity engaged during first-hand pain, and thus might indeed be grounded in our own pain experiences. Further, image-based and coordinate-based meta-analysis of functional magnetic resonance imaging (fMRI) studies have shown that sharing the pain of others consistently activates the bilateral anterior insular and anterior midcingular cortex (50).

Researchers have demonstrated that there is compelling evidence that placebo effects are genuine biopsychosocial phenomena that represent more than simply the spontaneous remission, normal symptom fluctuations, and regression to the mean (47) which many researchers liberally apply to discredit almost all clinical interventions. However, Kaptuck and Miller (46) also state that placebo may provide relief, but rarely cure. They indicate that the therapeutic benefits associated with placebo effects do not alter the pathophysiology of diseases beyond their symptomatic manifestations, and placebo responses primarily address subjective and self-appraised symptomatology (46). They provide examples that there is no evidence that placebo can shrink tumors, even though experiments demonstrate that common symptoms of cancer and side effects of cancer treatment are responsive to placebo treatments. In addition, they also provide examples that an experiment in patients with bronchial asthma revealed that placebos do not effect forced expiratory volume in one second (FEV1), but can nonetheless dramatically relieve perceived symptoms (32,46). They also project these conclusions to many conditions, such as musculoskeletal, gastrointestinal, and urogenital disorders.

In contrast to the above assumptions, placebos have been shown to provide powerful and innate healing mechanisms (51-53). Multiple studies have demonstrated that placebo medication can improve objective measures such as: pulmonary function (54,55), white blood cell count (56), C-reactive protein (57), hepatic enzymes (58), dopamine (59), postprandial glucose (60), brain glucose metabolism (61), carbon dioxide partial pressure (pCO_2) levels (62), beta adrenergic activity of the heart (63), opioids (64), and cortisol levels (65).

3.0 Placebos in a Therapeutic Role

Intentional use of placebo has been recently documented in survey studies spanning across the globe, including the US (51,66-69), Canada (70,71), United Kingdom (72), Germany (73,74), and other countries. A systematic review performed with data from 12 countries reported that between 17% and 80% of clinicians interviewed have administered placebo treatments such as sugar pills or saline injection during their careers irrespective of health care systems and their complexities in these countries, specifically in the US (75-89).

Thus, placebos have become a form of evidence-based medicine, with appropriate assessment of inert substances into inert structures (1). Results of studies of placebos showed improvement in 56% of patients experiencing cancer related fatigue (90), 70% of women experienced menopausal hot flashes (91), and 75% to 80% of the patients with depression (92). More importantly, oral placebos have been associated with

decreased mortality, as demonstrated in a heart and estrogen-progestin replacement study with significantly lower mortality in patients who were adherent to placebo treatment compared with less adherent participants (93). Additionally, placebo vaginal cream was effective in eradicating human papilloma virus in 73% of the patients (94), whereas sham surgery was as effective as arthroscopy, lavage, or debridement for osteoarthritis of the knee (75) and ligation of the internal mammary artery (95) for angina. Evidence also has demonstrated increased effectiveness when the treatment is a procedure rather than a pill or a cream (30,96). Measured objective improvement was described in multiple studies (54-65).

4.0 Complex Role of Placebos in Research: Open vs. Hidden Placebo

Clinicians and researchers are focusing on open use of placebos for effective application in clinical medicine (2,8,44,51-53). Colloca et al (51) provided an analysis on using dose-extending placebos for pain relief. They described this provocative line of research as the use of placebos to enhance therapeutic outcomes through learning paradigms that produce behavioral and biological responses mirroring those induced by active drugs (97-99). Of interest are the findings indicating that placebos given after repeated administration of active treatment (i.e., morphine) acquire a drug-like effect (e.g., drug reduction) in both animals and humans (51). Further, it also has been demonstrated that the effect of this modality is greater than that obtainable through the use of placebo alone (100-104). Based on the results of several studies investigating non-deceptive placebos (105-112), Petkovic et al (52) designed a protocol for systematic review and meta-analysis of the effects of placebos without deception compared with no treatment. They conceptualized (53) that use of placebos in clinical practices may be a cost-effective option for enhancing the care of ailments such as mild pain and depression, since the use of placebos in clinical practice is widespread (51,66-74). Since placebos are suggested to work both by inducing positive expectations and through classical conditioning, it may be anticipated that open-label placebos, which cause the patient to expect an inert intervention, will not induce the same level of conscious expectations in a patient as a deceptive placebo. However, open-label placebos, when combined with an expectation of therapeutic benefit, may therefore improve health care outcomes via a range of downstream mechanisms, without the ethical worries inherent in deceptive placebos (113). The results of systematic review and meta-analysis of the effects of placebos without deception compared with no treatment (52,53) studying back pain, irritable bowel syndrome, depression, allergic rhinitis, and attention deficit hyperactivity disorder, showed a positive effect for non-deceptive placebos. They concluded that open-label placebos appear to have positive clinical effects compared to no treatment; however, larger definitive trials are warranted to explore the potential patient benefit of open-label placebos, to investigate the relative contributions of positive suggestions and ethical implications.

The prior research has demonstrated that hidden injections were significantly less effective and less variable compared with open injections in full view of the patient, suggesting that part of the response variability was due to nonspecific factors (placebo) (100,110,114-116). Levine and Gordon (117) showed that the method of drug administration can influence the analgesic response, since the placebo effect can be either eliminated by hidden injection (pre-programmed machine infusion) or enhanced by an open injection in full view of the patient. In the study of response variability to analgesics and the role for non-specific activation of endogenous opioids, Amanzio et al (114) demonstrated that when the placebo effect was not present, the effectiveness of the drug was reduced as well as the response variability to it. In addition, they also showed that when the opioid-mediated placebo component was blocked with naloxone, the same effects were observed. This reinforced the findings of Levine and Gordon (117) showing that the method of drug administration played a very important role in analgesic response, with a placebo as powerful as a hidden injection of 8 mg of morphine. Amanzio et al (114) showed that the dose necessary to reduce the pain by 50% had to be increased to compensate for the absence of the placebo. Therefore, they postulated that the difference between open and hidden pain reduction by 50% may be taken as a measure of the placebo effect. They also showed that in the clinical conditions studied, the placebo was as powerful as about 0.1 mg of buprenorphine or 31 mg of tramadol or 12 mg of ketorolac. Most importantly, the response variability to these drugs decreased dramatically in the hidden injection condition, thus reaffirming that factors other than pharmacokinetics and pharmacodynamics were involved. Amanzio and Benedetti (100) also showed in later investigations that if conditioning is performed

with opioids, placebo analgesia is mediated via opioid receptors, whereas, if conditioning is performed with non-opioid drugs, other non-opioid mechanisms are involved. Conditioning involving specific mechanisms of opioid conditioning may be reversed by naloxone, whereas, nonsteroidal anti-inflammatory drugs (NSAID) conditioning and conditioning with other drugs secondary to either cyclo-oxygenase inhibition or other mechanisms was naloxone insensitive (Fig. 1). In fact, Petrovic et al (115) concluded that placebo analgesia is qualitatively different from an opioid drug response during pain. In addition, they suggested that drugs directly interfere with the expectation pathway (118), indicating that a placebo response may not be interpreted as a passive control to a specific drug effect, but a highly active state in itself.

Multiple studies (44,119,120) have described the role of open label placebo treatment in chronic low back pain. Savvas et al (44) anticipated that additional benefits may be noted in the elderly with placebo treatments with reduction in existing or planned medication regimens and related comorbidities including adverse drug reactions and altered pharmacological response to drugs. Carvalho et al (119), in an RCT, investigated

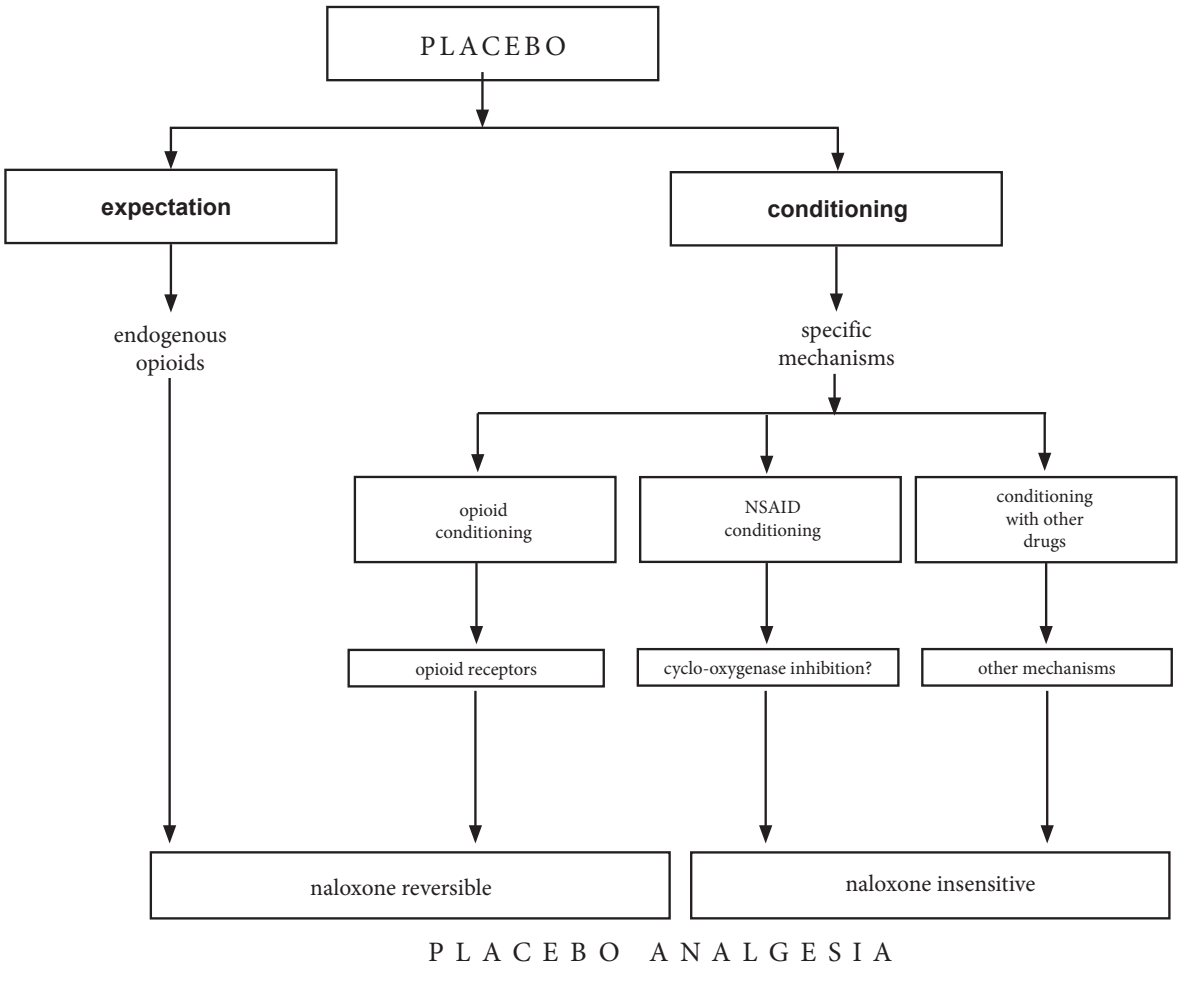

Fig. 1. *Schematic diagram of the mechanisms activating endogenous opioid systems and nonopioid systems in placebo analgesia.*

Source: Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci 1999; 19:484-494 (100).

whether placebo effects in chronic low back pain could be harnessed ethically by adding open label placebo treatment to treatment as usual for 3 weeks. In the trial, 83 adults reporting persistent low back pain for more than 3 months were assessed for pain severity and back-related dysfunction. All the patients continued their usual treatment and, with concealed allocation, 50% of the patients were given 2 placebo tablets, twice a day. They were provided with information that it was an inactive placebo that could still have a powerful effect, and the body can automatically respond to placebo, a positive attitude is helpful, but not necessary, and the placebo must be taken faithfully. Taking the open placebo significantly decreased reported pain (1.5 versus 0.2) and disability (2.9 versus 0.0) compared with usual therapy only. Of interest, of the 33 open label placebo participants responding to the question on the contents of the pills, 30 reported that "it was not an active substance, example sugar, flour, nothing in it, or what you said it would be." Only 3 participants reported that the pills were "painkillers." Further 21 of the 30 participants were initially skeptical and only 9 patients believed that it would work. Surprisingly with a crossover of patients receiving treatment as usual, participation in open label placebo showed significant pain reduction and improvement in back pain related disability. Multiple limitations of this study included a small number of patients and short-term follow-up. Even then, this provides a basis for activity of so-called placebos, even though they were not blinded, without deception.

5.0 Placebos in Interventional Pain Management: Debunking the Myths

Widespread misconceptions about placebo in interventional pain management and other interventions continue to escalate, leading to inappropriate conclusions and denial of coverage for multiple modalities, which have been shown to be effective in the literature though with discordant conclusions (4-21,121-143).

Even though the placebo and nocebo phenomena have been acknowledged for decades with extensive research, numerous controversies continue to exist in reference to the definition itself. There is the very fundamental question of whether it is more appropriate to talk about the "effect of" or "response to" the placebo. Numerous misinterpretations of placebo effect and nocebo response in research have led to a fantasy world of sham truth. The placebo-nocebo challenge includes a number of conceptual, explanatory, and moral questions and dilemmas as described specifically in interpretation of research (40). Jakovljevic (40) has described the state of placebo-nocebo research, mainly used as a comparison factor, rather than being studied in reference to placebo. There is a cacophony of conceptual questions regarding various definitions and meanings of terms such as placebo treatment, inert and active placebo, true and perceived placebo, pure and impure placebo, context effect and meaning responses. However, questions concerning the functions of neutral control treatment in research are very important from both ethical and methodological perspectives. Explanatory or epistemological questions are relevant to the mechanism underlying placebo-nocebo phenomenon related to treatment context, doctor-patient relationship, suggestion and auto-suggestion, deception, and self-fulfilling prophecies (40). The biggest threat for clinical research is the declaration of all and every research is a placebo effect, even ignoring intellectual bias and confluence of interest (40,144,145).

In clinical research, it is crucial that methodologists have an understanding of the literature, the procedural concepts, and ethical and moral aspects. Often research, just based on P values, is interpreted by non-clinicians without experience in clinical aspects of the research being reviewed, or even worse without experience in clinical research itself, nominally supported by senior authors without appropriate review of the available literature, leading to inappropriate conclusions (5-21,121-126,146-149). Understanding the study design is of paramount importance as shown in Table 1. Lack of understanding creates unsolved problems and consequences in interventional pain management.

One of the major issues related to interpretation of clinical research is the misunderstood concept of extension beyond the administration of inert substances of placebo (150,151). By definition, in a research setting, active placebos are pharmacologically active controls that are not considered to be effective for the index symptoms being treated (145). Thus, an active agent is given to a patient even though the pharmacologic action of the active agent is not known to be beneficial for treating the patient's diagnosed condition, typically to meet a patient's expectation that he or she will receive a treatment (145). However, this concept has been taken too far in interventional pain management by converting all local anesthetic injections and their known effects to placebo just based on misunderstanding and the pharmacological action of a local anesthetic in providing anesthesia in patients without chronic pain

Table 1. *Usefulness of specific control types in various situations.*

Trial Objective	Type of Control						
	Placebo Control	Active Control	Dose Response (D/R)	Placebo + Active	Placebo + D/R	Active + D/R	Placebo + Active + D/R
Measure Absolute effect size	Y	N	N	Y	Y	N	Y
Show existence of effect	Y	Y	Y	Y	Y	Y	Y
Show dose-response relationship	N	N	Y	N	Y	Y	Y
Compare therapies	N	Y	N	Y	N	P	Y

Y=Yes, N=No, P=Possible, depending on whether there is historical evidence of sensitivity to drug effects.

Source: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Choice of Control Group and Related Issues in Clinical Trials E10. July 20, 2000 (150).

(4-21,121-143). Authors have also misinterpreted the duration of action of steroids, expecting that it should last beyond its pharmacological action, similar to surgical interventions, but action of steroids may be of as little as one week or as long as 6 weeks (4-8,121).

The second issue is related to the assessment in placebo-controlled RCTs. Mean change in the primary outcome from baseline to treatment endpoint is commonly described as the placebo response (145). A highly significant and pervasive aspect in evidence assessment is the application of the primary outcome as the difference between 2 arms – namely the placebo (even if it is an active control trial with an active drug converted to placebo) and active arm of the RCT. For researchers investigating the placebo phenomenon itself or the effectiveness of a technique or a drug, experiments are tightly controlled to measure the response between the groups with P value without consideration of baseline to treatment values and failure to take into consideration the difference between active placebo or an active agent.

5.1 Present State of Evidence Assessment in Interventional Pain Management

In a systematic review with meta-analysis of randomized, sham control trials, Jonas et al (152) assessed 39 studies with 2,902 patients meeting inclusion criteria and providing sufficient data. They evaluated the extent of effectiveness of surgery and invasive procedures beyond a placebo response and concluded that the nonspecific effects of surgery and other invasive procedures were generally large, particularly in the field of pain-related conditions. Overall, there were 15 studies with inclusion of 1,584 patients included in the meta-analysis that investigated pain-related conditions, with the overall standardized mean non-significant difference at 0.13. They included 7 studies assessing the back pain related to radiofrequency neurotomy and vertebroplasty (153-159). However, they have not included multiple other techniques including epidural injections. They also have not considered the controversies in reference to interventional techniques (4-8).

The initial travesty of misinterpretation of interventional pain management trials originated with Chou and Huffman (121). These guidelines were basically prepared by Huffman, a non-physician, with assistance and supervision from Chou. Since then, multiple budding evidence-based medicine specialists (122,126,147-149) have expanded the philosophy, accepted by many others with political aspirations and confluence of interest, of converting active control trials into placebo control trials. Fundamentally, they have developed an alternate universe of misinterpretation without understanding the effect of placebo and nocebo, active placebo, inappropriateness of conversion of active trials to placebo trials, and the specific effects of healing rituals, doctor/patient relationship, and meaning response instead of response to placebo. Manchikanti et al (1,5-8,160) have repeatedly described the role of placebo and nocebo in interventional pain management, have demonstrated that sodium chloride solution, midazolam, and fentanyl produced placebo as well as nocebo effects in 13% to 18%, 15% to 20%, 18% to 30%; and 5% to 8%, 8% to 8%, 3% to 8% of patients, respectively, showing placebo and nocebo effects as shown in Figs. 2 and 3.

As shown in multiple publications, similar findings were also observed in general in reference to conflicts of interest and expertise of independent commenta-

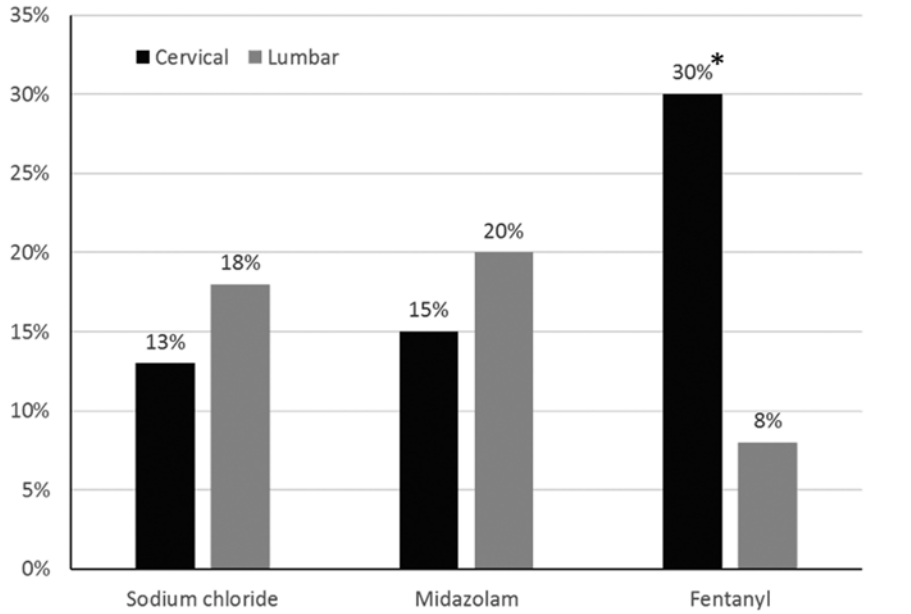

Fig. 2. *Effects of patients reporting relief and feeling better after administration of sodium chloride solution, midazolam, or fentanyl in the study groups in cervical and lumbar regions.*

Source: Manchikanti L, Pampati V, Damron KS. The role of placebo and nocebo effects of perioperative administration of sedatives and opioids in interventional pain management. *Pain Physician* 2005; 8:349-355 (160).

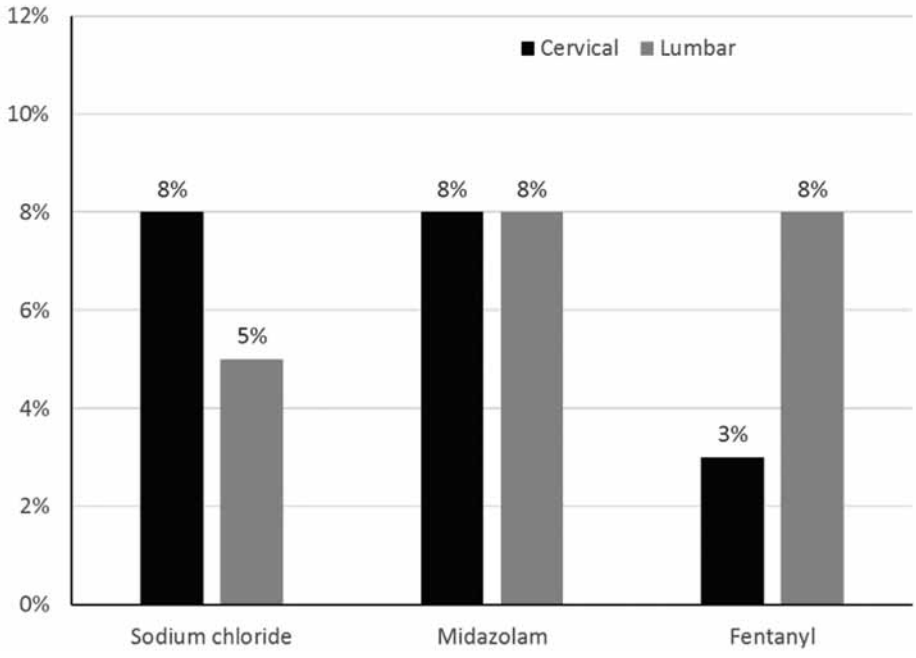

Fig. 3. *Nocebo response of patients reporting relief and feeling better after administration of sodium chloride solution, midazolam, or fentanyl in the study groups in cervical and lumbar regions.*

Source: Manchikanti L, Pampati V, Damron KS. The role of placebo and nocebo effects of perioperative administration of sedatives and opioids in interventional pain management. *Pain Physician* 2005; 8:349-355 (160).

tors in news stories about medical research, which also includes interventional pain management procedures (161). Wang et al (161) analyzed 104 independent comments and news stories on original clinical research published in high impact medical journals and 21 related journal editorials. The results showed the 5 of the 6 news stories failed to include independent comments. Overall 44% and 47% of the independent commentators were considered to lack clinical and academic expertise, whereas 14% and 52% of the editorialists lacked academic and clinical expertise. Overall, 25% of the independent commentators had neither academic nor clinical expertise, with academic or financial conflict of interest in 54% and 32%. When commentators' conflicts of interest were congruent with the findings of the source research, 97% and 93% of comments associated with academic and financial conflicts of interest, respectively, were favorably disposed toward the research (161).

A wide discrepancy in the results with discordance has been demonstrated in multiple assessments, more recently in the assessment of evidence published by Chou et al with public funding from the Agency for Healthcare Research and Quality (AHRQ) and subsequently in the Annals of Internal Medicine (4,125). The commercial interests of many of the authors sponsored by AHRQ and benefitting from industry are enormous (5-7,125). Manchikanti et al (5), in a comparative systematic review and meta-analysis of epidural injections for lumbar radiculopathy and spinal stenosis, demonstrated these differences and biases. They utilized extensive quality assessment criteria and did not convert active control trials into placebo control trials (162,163). They also utilized modified grading of qualitative evidence (164). They considered 39 RCTs (165-203) to meet inclusion criteria from 80 manuscripts considered for inclusion. Manchikanti et al (5) considered analysis based on each modality of treatment (caudal, interlaminar, and transforaminal) and the solution injected (lidocaine, bupivacaine, and steroid). Further, short-term improvement was defined as any improvement of 3 months, and long-term improvement was described as greater than 6 months. The effectiveness of repeat injections was considered rather than focusing on a single injection. Instead of utilizing 20% as acceptable improvement, Manchikanti et al (5) utilized 50% improvement in pain and functional status as appropriate. Table 2 shows vast differences between the methodological quality assessment of the 2 systematic reviews. Chou et al (4,125) rated many of the high quality trials as poor quality trials indicating their bias in interpretation. Appendix Tables 1 through 4 show the results of meta-analysis with pain relief and functional status at 3 months and 6 months. This not only highlighted the wrong assumptions about active control trials and active placebos, but also highlighted Chou et al's and a multitude of other authors' philosophy that the therapeutic effects in epidural steroids are primarily related to the corticosteroid and inflammation (4,125). Essentially, there is overwhelming literature showing the experimental evidence and clinical effectiveness of local anesthetics alone, which is similar or occasionally superior to steroids (5,8-21,132-135,141,167,179,181,186,189,193,204-217). In the analysis by Manchikanti et al (5), there were 7 trials assessing lidocaine as a sole agent or lidocaine with steroids (167,168,172,179,181,189,193) and only 3 trials assessing bupivacaine alone in comparison to bupivacaine with steroid (198-200). Manchikanti et al (5) discussed extensively the role of placebo effect and managing bias and conflict of interest. In addition, there is an abundance of literature illustrating even the inert substances producing therapeutic effects when injected into an active structure (165,195,218-225) underscoring the effect of inert substances (true placebos) into pain generating structures.

In addition, there is an abundance of literature in reference to the misinterpretation of trials in managing facet joint pain, sacroiliac joint pain, and vertebral augmentation procedures (4,8,11,13,14,18,19,20,121,128-130,204-206,226-235). Despite this negative literature, overall, interventional techniques have been used frequently in managing chronic pain (236-240). Further, as shown earlier, placebos have been utilized as therapeutic agents (51,66-89,241).

6.0 Unsolved Problems and Controversies of Placebos in Research

Chavarria et al (242), in assessing the role of placebo and nocebo phenomenon in clinical management and their impact on treatment outcomes, found that placebo/nocebo effects are difficult to disentangle from the natural course of illness or the actual effects of a new drug in a clinical trial. They proposed that physicians should recognize these phenomena and master tactics on how to manage these effects to enhance the quality of clinical practice. Corsi and Colloca (243) also described the advantage of measuring expectations and psychological factors in assessing placebo and nocebo effects. They showed that simple linear regression analysis showed that placebo responses were

Table 2. *Methodological quality assessment of epidural injections with caudal, interlaminar, and transforaminal approaches in managing pain of disc herniation/radiculitis and spinal stenosis.*

Trial	Present Analysis			Concordance and Discordance of Results	
	Cochrane Criteria	IPM-QRB Criteria	Quality Grading (high, moderate, low) Cochrane/IPM-QRB	Based on Cochrane Review Criteria by Chou et al	Present Analysis Compared with Chou et al's Analysis
Carette et al (165)	11/12	27/48	High/Moderate	Fair	3
Iversen et al (166)	7/12	28/48	Moderate	Good	2
Manchikanti et al (167)	10/12	44/48	High	Fair	3
Sayegh et al (168)	10/12	28/48	High/Moderate	Fair	3
Ackerman & Ahmad (169)	7/12	25/48	Moderate	Fair	1
Dashfield et al (170)	9/12	33/48	High	NA	NA
Murakibhavi & Khemka (171)	7/12	27/48	Moderate	NA	NA
Manchikanti et al (172)	11/12	44/48	High	Fair	3
Park et al (173)	10/12	33/48	High	Fair	3
Huda et al (174)	8/12	23/48	High/Moderate	Fair	3
Béliveau (175)	6/12	15/48	Moderate/Low	Poor	3
Datta & Upadhyay (176)	7/12	20/48	Moderate	Poor	3
Dilke et al (177)	8/12	28/48	High/Moderate	Fair	3
Arden et al (178)	9/12	31/48	High/Moderate	Fair	3
Manchikanti et al (179)	10/12	44/48	High	Poor	4
Lee et al (180)	6/12	28/48	Moderate	NA	NA
Ghai et al (181)	9/12	39/48	High	NA	NA
Rados et al (182)	8/12	30/48	High/Moderate	Fair	3
Park et al (183)	10/12	34/48	High	NA	NA
Amr (184)	11/12	38/48	High	NA	NA
Pirbudak et al (185)	12/12	35/48	High	NA	NA
Ghai et al (186)	9/12	42/48	High	Good	1
Wilson-MacDonald et al (187)	10/12	31/48	High/Moderate	Fair	3
Candido et al (188)	9/12	37/48	High	Fair	3
Manchikanti et al (189)	10/12	43/48	High	NA	NA
Fukusaki et al (190)	5/12	18/48	Moderate	Poor	3
Friedly et al (191)	9/12	30/48	High/Moderate	Good	1
Vad et al (192)	4/12	16/48	Moderate	NA	NA
Manchikanti et al (193)	10/12	44/48	High	Poor	4
Koh et al (194)	9/12	32/48	High	NA	NA
Ghahreman et al (195)	11/12	37/48	High	Good	1
Jeong et al (196)	9/12	31/48	High/Moderate	Fair	3
Karppinen et al (197)	12/12	34/48	High	Good	1
Riew et al (198)	8/12	32/48	High	Fair	3
Tafazal et al (199)	10/12	32/48	High	Fair	3
Ng et al (200)	11/12	37/48	High	Fair	3
Cohen et al (201)	5/12	26/48	Moderate	NA	NA
Becker et al (202)	6/12	26/48	Moderate	Fair	3
Kennedy et al (203)	9/12	30/48	High	Fair	3

1 = Correlation of present criteria with Chou et al's analysis; 2 = Discordance with Chou et al's criteria being higher; 3 = Discordance with Chou et al's criteria being lower; 4 = Discordance with Chou et al's criteria being poor from high.

negatively correlated with anxiety severity and different aspects of fear of pain; whereas, nocebo responses were positively correlated with anxiety, sensitivity, and physiological suggestibility with a trend towards catastrophizing. However, step-wise regression analysis indicated that an aggregate score of motivation (value/utility and pressure/tense subscales) and suggestibility (physiological reactivity and persuadability subscales), accounted for the 51% of the variance in the placebo responsiveness. In addition, anxiety severity Neuroticism-Extraversion-Openness to experience (NEO) openness-extraversion and depression accounted for the 49.1% of the variance of the nocebo response. Surprisingly, psychological factors and personality factors did not influence expectations.

Koog (244) described the effect of placebo acupuncture over no-treatment with a model incorporating the placebo and nocebo effects. Koog (244) based this model on the concept that conventionally in controlled trials of drugs or modalities the placebo and nocebo effects have been determined separately and understood to be the difference between the placebo and no-treatment groups. Based on this consensus, a series of studies have investigated placebo and nocebo effects in acupuncture (245-250).

Interestingly enough, Kaptchuk et al (251) showed that the placebo acupuncture had larger effects on pain outcomes compared with the placebo pill and almost equal effects of adverse events for the placebo acupuncture and placebo pill. Accordingly, placebo and nocebo effects may not be separable in acupuncture as described (252) or even any of the other interventions. Consequently, Koog (244) postulated that the effect of placebo acupuncture over no-treatment may not be the pure placebo or nocebo effects. Thus, Koog (244) postulated that it is necessary to consider the effect of placebo acupuncture over no-treatment in relation to these 2 effects. In addition, they Koog (244) also discussed Moerman's hypothesis (253) indicating that the placebo effect is a flawed notion, because participants in a trial do not actually respond to the placebo's mean. Some argue that, even though, "meaning response" is different from the current model, their concepts correspond with each other (244). In addition, Kaptchuk et al (34,46,245,254), widely published in placebo literature, also perceived the placebo effect to be, "the specific effect of healing ritual," similar to doctor-patient relationship and physical examination. Consequently, the healing ritual and meaning response may be more appropriate concepts to assess the efficacy of an intervention. Koog (244) provided a simple mathematical model incorporating both the placebo and nocebo effects to see how the efficacy of acupuncture is affected. The results were based on the difference in the proportions of participants who respond to the placebo and nocebo effects. Consequently, this model and the debate continue and further research is warranted to understand these effects more completely (244).

In the lines of thinking of open label placebo and emerging literature, Gerdesmeyer et al (255) performed a unique trial with a novel design of a randomized, placebo trial to determine the placebo effect size. They evaluated patients with plantar fasciitis and provided nonsurgical treatment with extracorporeal shock wave therapy (ESWT) with a 6-week follow-up. ESWT has been reported as the most promising nonsurgical treatment, with the highest quality evidence supporting its use, in managing plantar fasciitis (256-260). Describing the design as inverse placebo RCT, they included 2 groups of patients randomized to receive either a blinded placebo shock wave treatment or an unblinded placebo shock wave treatment. The primary outcome measure was the differences in percent change of visual analog scale scores 6 weeks after the intervention. The study included a total of 106 patients. All patients received the same sham ESWT with a different explanation, one with blind placebo and other one with unblinded or open placebo. In this assessment after 6 weeks, patients receiving the blinded placebo treatment reported less heel pain, with significantly higher changes in pain ratings in the blinded placebo group than in the unblinded placebo group. They concluded that the results indicate the true placebo effect sizes, which can be analyzed through a proper inverse placebo control RCT design. They also concluded that instead of treating a large number of patients with placebos in an RCT, which increases the risk for patients not receiving the treatment, the inverse placebo RCT technique seems to be much more appropriate to analyze effect sizes or any effective treatment in accordance to the good clinical practice guidelines and Declarations of Helsinki. Thus, Gerdesmeyer et al (255) proposed that placebo studies can improve their conclusions by making the placebo and its control condition as similar as possible by solely varying the information about treatment. Further, they also hypothesized that in a similar fashion, active treatment studies can also benefit from this actual placebo effect. Figure 4 and Table 3 show the results of the inverse placebo trial by Gerdesmeyer et al (255). These results are similar to open treatment with

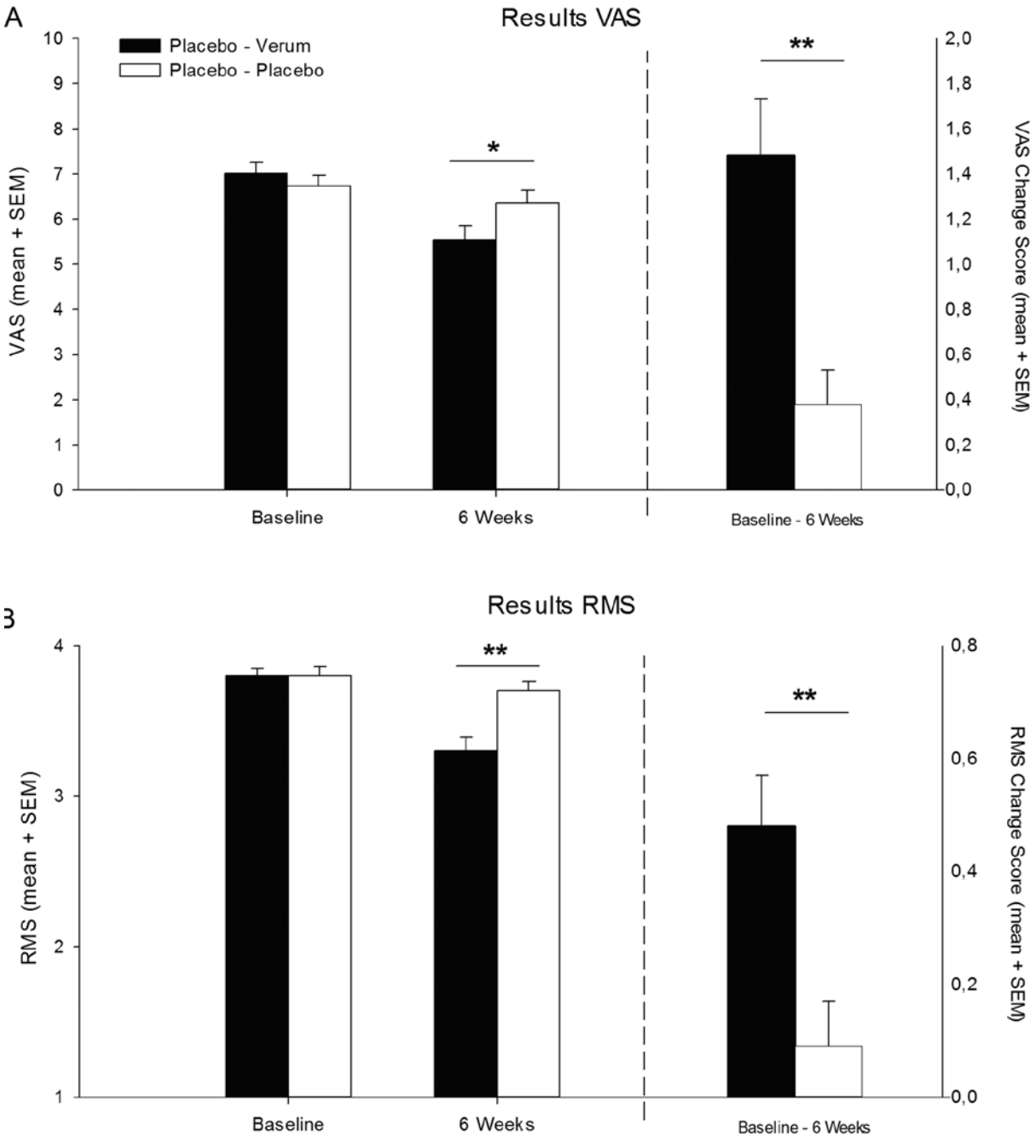

Fig. 4. *Results and Roles-Maudsley Score (RMS) with placebo-verum and placebo-placebo treatments.*

opioids compared to blinded treatment where patients are not aware that they are receiving any type of treatment. Thus, true placebo effect is significantly less than placebo effect secondary to expectation and multiple modulatory effects at 6-week follow-up.

7.0 Conclusion

The emerging literature on placebos, confluence of interest, and intellectual bias provides overwhelming evidence of irregularities in interpretation of review of

Table 3. *Results of subjective pain ratings.*

Subjective pain rating	Placebo-Verum	Placebo-Placebo	Placebo-Verum vs. Placebo-Placebo	Effect size	Confidence interval of effect size
	M (SEM)	M (SEM)	p	MW	95 % CI
VAS					
Baseline	7.0 (.24)	6.7 (.24)	.476	.460	.352 to .569
After 6 weeks	5.5 (.31)	6.3 (.28)	.031	.621	.513 to .729
Change score	1.5 (.25)	0.4 (.15)	.002	.668	.566 to .770
RMS					
Baseline	3.8 (.05)	3.8 (.06)	.810	.491	.414 to .567
After six weeks	3.3 (.09)	3.7 (.06)	.004	.644	.549 to .738
Change score	0.5 (.09)	0.1 (.08)	.002	.645	.559 to .731

Note: ESWT, Extracorporeal shock wave therapy; M, mean; SEM, standard error of means; VAS, Visual analogue scale; RMS, Roles & Maudsley Score; *P* -values refer to results of two-tailed Mann-Whitney-U test; effect sizes in terms of Mann-Whitney estimator (MW) with 95 % CI.

scientific literature based on the placebo effects. The majority of the literature in interventional pain management has omitted the nocebo phenomenon. While it is considered that there are numerous unsolved problems related to placebo and nocebo phenomena, they continue to be problematic for scientific analysis and conclusions for clinical practice based on confluence of interest and lack of understanding related to lack of clinical experience and, at times, to lack of experience of the researchers. It is crucial that the importance of active placebos is recognized and active drugs, which are used in treatments, not be considered as placebos.

The emerging literature, specifically the results of the trial provided by Gerdesmeyer et al (255), provides the basis for future research with a design to assess true placebo effect sizes through a proper inverse placebo control RCT design. Thus, instead of treating large numbers of patients with placebos in an RCT, which increases the risk of patients not receiving the treatment, the inverse placebo RCT technique seems to be much more appropriate to analyze effect sizes of any active treatment in accordance to good clinical practice guidelines.

More importantly, this review hopes to resolve questions about the placebo and nocebo phenomena in interventional techniques and their interpretation. Essentially, this review should provide a basis for the provision of care even through placebo treatments rather than without any treatment, if there is significant improvement results from placebo treatments. This review also provides future policy implications to discard biased literature based on misunderstandings that calls for the elimination of all types of interventions.

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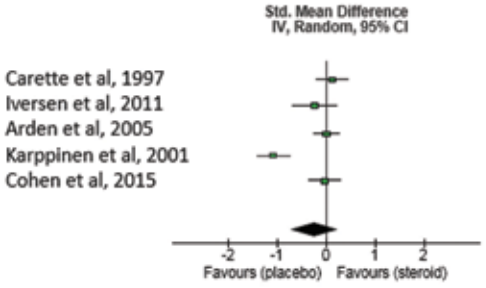
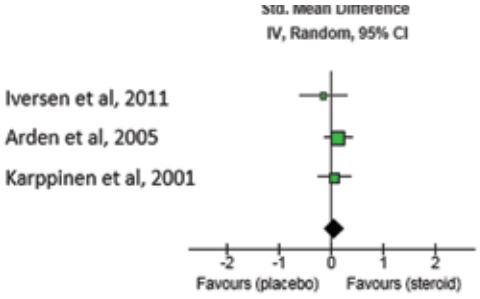
Appendix 1. Results of pain relief of placebo-controlled trials of epidural steroids with saline or bupivacaine.

Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Carette et al, 1997 (165) Saline with steroid	2.6	3.6	77	2.3	3.4	79	20.40%	0.11(-0.20,0.43)
Iversen et al, 2011 (166) Saline with steroid	6.6	5	37	7.8	5	39	18.30%	-0.24 (-0.69, 0.21)
Arden et al, 2005 (178) Steroid with bupivacaine	4.7	5	120	4.7	5	108	21.10%	0.00 (-0.26, 0.26)
Karppinen et al, 2001 (197) Steroid with bupivacaine	2.6	1	79	3.7	1	79	20.10%	-1.09 (-1.43, -0.76)
Cohen et al, 2015 (201) Steroid with bupivacaine	1	2.5	72	1.1	2.7	73	20.20%	-0.04 (-0.36, 0.29)
Total (95% CI)			385			378	100.00%	-0.25 (-0.68,0.18)
Heterogeneity: Chi² = 34.45, df = 4 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 1.13 (P = 0.26)								



A. *Short term follow-up minimum 3 months of pain relief.*

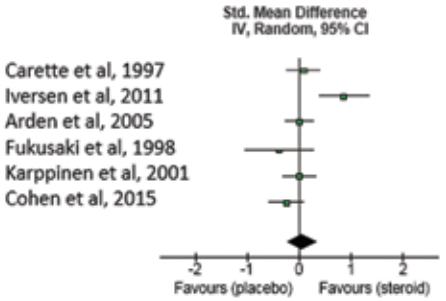
Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Iversen et al, 2011 (166)	0	12	37	2	14	39	16.40%	-0.15 (-0.60, 0.30)
Arden et al, 2005 (178)	4.9	5	120	4.3	5	108	49.30%	0.12 (-0.14, 0.38)
Karppinen et al, 2001 (197)	2.3	5	78	2	5	80	34.30%	0.06 (-0.25, 0.37)
Total (95% CI)			235			227	100.00%	0.05 (-0.13, 0.24)
Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%								
Test for overall effect: Z = 0.58 (P = 0.56)								



B. *Long-term follow-up of 6 months of pain relief.*

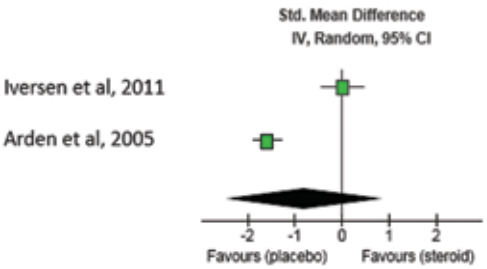
Appendix 2. Results of functional status improvement of placebo control trials of epidural steroids with saline or bupivacaine.

Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Carette et al, 1997 (165)	17.3	20.6	77	15.4	25.5	79	18.60%	0.08(-0.23, 0.40)
Iversen et al, 2011 (166)	4	3	37	1.4	3	39	14.00%	0.86 (0.39, 1.33)
Arden et al, 2005 (178)	32	5	120	32	5	108	20.30%	0.00 (-0.26, 0.26)
Fukusaki et al, 1998 (190)	10	8	19	13	7	18	10.00%	-0.39 (-0.04, 0.26)
Karppinen et al, 2001 (197)	20	5	80	20	5	80	18.80%	0.00 (-0.31, 0.31)
Cohen et al, 2015 (201)	6.2	15.8	73	10.2	16.7	72	18.20%	-0.24 (-0.57, 0.08)
Total (95% CI)			406			396	100.00%	0.05 (-0.21, 0.32)
Heterogeneity: Chi² = 14.89, df = 5 (P = 0.007); I² = 68%								
Test for overall effect: Z = 0.39 (P = 0.70)								



A. *Long-term follow-up of 3 months of functional status.*

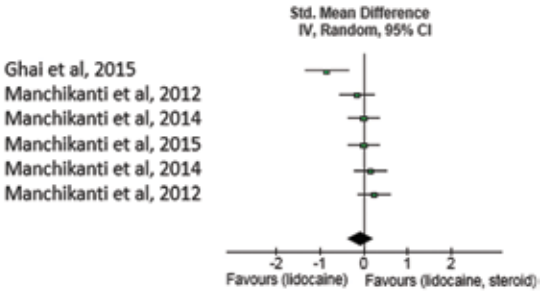
Study	Steroid with Sodium Chloride Solution or Bupivacaine			Placebo			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Iversen et al, 2011 (166)	1.9	8.2	39	1.9	4.2	37	49.40%	0.00 (-0.45, 0.45)
Arden et al, 2005 (178)	31	5	108	39	5	120	50.60%	-1.59 (-1.89, 1.30)
Total (95% CI)			147			157	100.00%	-0.81 (-2.37, 0.76)
Heterogeneity: Chi² = 24.24, df = 1 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.01 (P < 0.31)								



B. *Long-term follow-up of 6 months of functional status.*

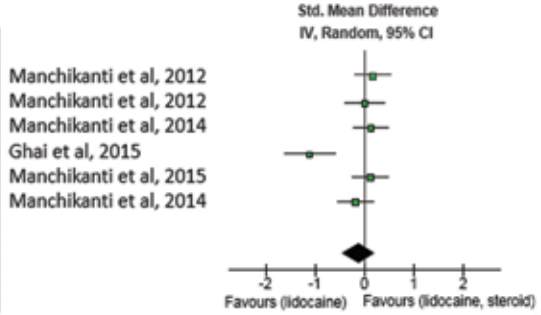
Appendix 3. Results of pain relief improvement of active-control trials of epidural lidocaine compared with epidural lidocaine with steroids.

Study	Lidocaine, steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Manchikanti et al, 2012 (167)	4.4	1.7	60	4	1.8	60	17.50%	0.23 (-0.13, 0.59)
Manchikanti et al, 2012 (172)	3.5	1.9	50	3.8	1.8	50	16.40%	-0.16 (-0.55, 0.23)
Manchikanti et al, 2014 (179)	4.5	1	60	4.3	1.6	60	17.50%	0.15 (-0.21, 0.51)
Ghai et al, 2015 (181)	3.5	1.6	35	4.8	1.4	34	13.50%	-0.86 (-1.35, -0.36)
Manchikanti et al, 2015 (189)	4.3	1.5	60	4.3	1.3	60	17.50%	0.00 (-0.36, 0.36)
Manchikanti et al, 2014 (193)	4.2	1.5	60	4.2	1.8	60	17.50%	0.00 (-0.36, 0.36)
Total (95% CI)			325			324	100.00%	-0.08 (-0.34, 0.19)
Heterogeneity: Chi² = 14.12, df = 5 (P = 0.01); I² = 65%								
Test for overall effect: Z = 0.57 (P = 0.57)								



A. *Follow-up minimum of 3 months -- pain relief.*

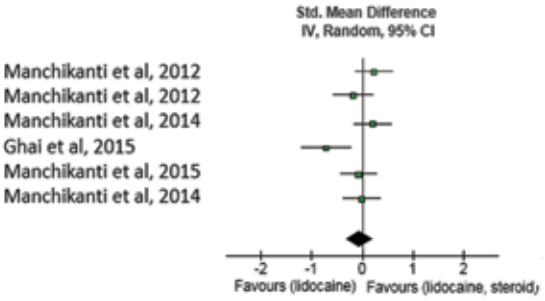
Study	Lidocaine, steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Manchikanti et al, 2012 (167)	4.2	1.8	60	3.9	1.8	60	17.30%	0.17 (-0.19, 0.52)
Manchikanti et al, 2012 (172)	3.4	2	50	3.4	1.8	50	16.60%	0.00 (-0.39, 0.39)
Manchikanti et al, 2014 (179)	4.3	1.4	60	4.1	1.7	60	17.30%	0.13 (-0.23, 0.41)
Ghai et al, 2015 (181)	3.6	1.6	35	5.3	1.4	34	14.10%	-1.12 (-1.63, -0.61)
Manchikanti et al, 2015 (189)	4.4	1.7	60	4.2	1.8	60	17.30%	0.11 (-0.24, 0.47)
Manchikanti et al, 2014 (193)	4	1.6	60	4.3	1.6	60	17.30%	-0.19 (-0.54, 0.17)
Total (95% CI)			325			324	100.00%	-0.12 (-0.44, 0.20)
Heterogeneity: Chi² = 23.37, df = 5 (P = 0.0003); I² = 79%								
Test for overall effect: Z = 0.74 (P = 0.46)								



B. *Long-term follow-up of 12 months -- pain relief.*

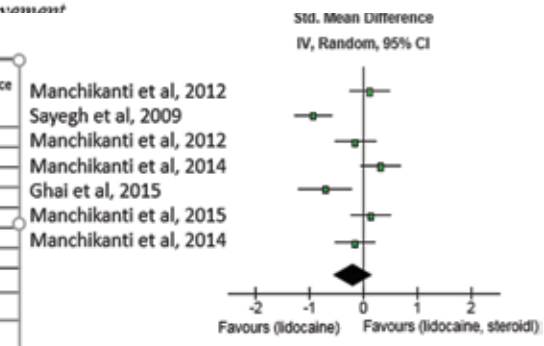
Appendix 4. Results of functional status improvement of active control trials of epidural lidocaine compared with epidural lidocaine with steroids.

Study	Lidocaine, steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Manchikanti et al, 2012 (167)	14.3	6.5	60	12.7	7.2	60	17.60%	0.23 (-0.13, 0.59)
Manchikanti et al, 2012 (172)	11.3	7.4	50	12.6	6.8	50	16.30%	-0.18 (-0.57, 0.21)
Manchikanti et al, 2014 (179)	15.6	4.2	60	14.5	6.3	60	17.60%	0.20(-0.15, 0.56)
Ghai et al, 2015 (181)	18.8	14.3	35	28.6	12.8	34	13.20%	-0.71(-1.20, 0..23)
Manchikanti et al, 2015 (189)	15.3	6.2	60	15.7	5.3	60	17.60%	-0.07 (-0.43, 0.29)
Manchikanti et al, 2014 (193)	13.3	6.4	60	13.4	7.2	60	17.60%	-0.01 (-0.37, 0.34)
Total (95% CI)			325			324	100.00%	0.06 (-0.30, 0.18)
Heterogeneity: Chi² = 12.89, df = 5 (P = 0.02); I² = 61%								
Test for overall effect: Z = 0.51 (P = 0.61)								



A. *Short-term follow-up minimum 3 months - functional status improvement*

Study	Lidocaine, steroid with Sodium Chloride Solution or Bupivacaine			Lidocaine only			Weight	Std. Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Manchikanti et al, 2012 (167)	14.4	7.2	60	13.6	7.3	60	14.50%	0.11 (-0.25, 0.47)
Sayegh et al, 2009 (168)	4.9	7.1	81	13	10.1	70	14.80%	-0.93 (-1.27, -0.60)
Manchikanti et al, 2012 (172)	11.1	7.6	50	12.3	7.3	60	14.30%	-0.16 (-0.54, 0.22)
Manchikanti et al, 2014 (179)	16.1	4.8	60	14.2	6.8	60	14.50%	0.33 (-0.04, 0.68)
Ghai et al, 2015 (181)	19.8	14.3	35	29.6	12.8	34	12.80%	-0.71 (-1.20, -0.23)
Manchikanti et al, 2015 (189)	16.8	6.4	60	15.9	7.2	60	14.50%	0.13 (-0.23, 0.49)
Manchikanti et al, 2014 (193)	13.9	6.5	60	15	6.9	60	14.50%	-0.16 (-0.52, 0.20)
Total (95% CI)			406			404	100.00%	-0.19 (-0.54, 0.15)
Heterogeneity: Chi² = 42.96, df = 6 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 1.10 (P = 0.27)								



B. *Long-term follow-up of 12 months - functional status improvement.*

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