In Response: From Manchikanti et al

We appreciate the lengthy letter by Chou entitled “Critiquing the Critiques.” At the outset, the letter reminded us of an exchange between Bogduk and Carragee in 2007 (1) criticizing each other – Bogduk claiming that Carragee et al utilized sophistry to discredit the study, whereas Carragee described Bogduk’s argument as “inflated albeit entertaining rhetoric”. Bogduk elaborated that the defense to sophistry is to inform the listeners of the fallacy of the argument, and to point out the opposite when it applies. In contrast, Carragee borrows Aristotle’s caution in The Art of Rhetoric, that when one hears bombastic and exaggerated styles of argument, the substance is likely deficient (2). Here, it appears that Chou’s argument could qualify for sophistry, and the art of rhetoric by rehashing the same arguments over and over again while leaving the substance out.

ASIPP rigorously supports peer-reviewed and bias free research including evidence synthesis, as well as government funding of such efforts. The criticism is extremely important, especially when the work is generously supported by taxpayer funds or even membership dues as in the case of the American Pain Society (APS). It appears that Chou, instead of aiming at imagined inappropriate issues should focus and concern himself with valid points raised in the critique. Further, it appears Chou is begging for shielding for funding from government grants as well as membership dues from the societies from open scientific critical reviews by concerned professional societies, which is grossly improper.

Physicians specializing in methodology, either working with the government or insurers or guideline developers, have a right to claim the supremacy of their methodology – at least in their own minds. However, they have a responsibility to understand the flaws in their vaunted methodology. Consequently, it is difficult to understand the wisdom of recommending or not recommending techniques without understanding them. Further, it has become quite a bit of a phenomenon and tradition for the experts who disagree with clinicians to act as victims. However, history shows it to be different. For example, if we look at the demise of Agency for Health Care Policy and Research (AHCPR) with its $75 million expenditures per guideline and proposed expenses of $200,000 to $300,000 for each systematic review, it would appear that this network
of specialists had as its major goal to show that nothing works (3, 4).

It is very perplexing to note that intricacies of evidence-based medicine (EBM) and methodology continues to change based on the philosophy of sponsoring agencies and insurers. We would welcome any type of proof that shows the evidence created by Chou and others is in fact based on evidence and that it improves patient care. It is extremely easy for methodologists to repeatedly tell clinicians that if they want to provide evidence that injection therapy is effective in specific subgroups of patients with subacute or chronic pain, they should conduct well-designed and randomized clinical trials (RCTs) with homogenous patient populations, a clear target condition, a clear-cut treatment rationale, and a sufficiently long follow-up period (5, 6). We clinicians then work hard to follow this, only to find that the methodologists then create criteria to discredit the same methodology they have been preaching.

With reference to West et al (7), we are at a loss as to why the Agency for Healthcare Research and Quality (AHRQ) would spend hundreds of thousands or even millions of dollars evaluating the quality criteria developed by others and then not provide guidance. Is it not appropriate to use the quality rating systems which have been appropriately looked at and summarized? Whether they are designed to be used to rate the study quality themselves or not, we fail to see the relevance and importance. Obviously this critical analysis should have done something and provided the readership with some guidance.

The next comment relates to the weighted scoring system for scoring the criteria included in the Cochrane Back Review Group (CRBG). Chou claims we said that a weighted methodology for rating RCTs is superior to unweighted methodologies. However, the word superior was never used in our manuscript. In addition, neither the weighted methodology nor unweighted methodologies have been supported by any empirical data or validation studies (8-15). Coincidentally, the overall quality of Cochrane systematic reviews was rated as fair to good (16). Further, to be uniform, we utilized the scoring system by Chou and Huffman (17-19), which has been used in multiple publications. They also chose to avoid citing manuscripts if they were favorable to clinicians, even one authored by Rubinstein and van Tulder (20). Rubinstein and van Tulder (20), in a best evidence review of diagnostic procedures for neck and low back pain, concluded that there was strong evidence for the diagnostic accuracy of facet joint blocks in evaluating spinal pain. Yet Chou and others claim that due to the lack of a gold standard, facet joint pain cannot be treated.

The next involves the methodologic quality assessment of systematic reviews. Again, Chou mentions that the final score is not based on simply adding the number of criteria that are met; rather it is based on the assessment of the type and severity of methodologic flaws. Once again, it is essential to mold the result as they would like to rather than follow a methodology. Then they provide the explanation that if a systematic review combined studies inappropriately, the scoring instructions are that it is likely to have major flaws. However, this has no relevance to the total scoring. Then they continue to bolster their argument by invoking in their methods section that their sole source of evidence for evaluating efficacy was randomized, placebo, or sham-controlled trials.

We do not doubt Chou’s extensive experience with the United States Preventive Services Task Force (USPSTF) methods, we only doubt the application of those methodologies to clinical situations. In fact, David Eddy and multiple other speakers utilized the criteria utilized in American Society of Interventional Pain Physicians’ (ASIPP) guidelines rather than those Chou has recommended. The issue is related to using them in an unbiased fashion rather than continuing to repeat them and using them with bias and subjectivity and calling everything else biased and subjective.

The above explanations address some of the issues, but the lack of transparency, accountability, consistency, and independence are still troubling. Leaving numerous deficiencies described in the critique aside, Chou jumps into a study by Mathews et al (21) which was always excluded in ASIPP reviews. Further, we have not claimed that lack of placebo control was poor quality; however, we did describe the short duration of follow-up and use of high volume injections as exclusion criteria or poor quality as Chou mentions. These might not be associated with bias per se in the methodological world, but they are associated with insurmountable clinical irrelevance in the clinical arena. It is important to understand that the study by Mathews et al (21) was included in 4 of the Cochrane reviews of injection therapy (8-10, 22), with a composite score of 67 of 100 for the manuscript which was published in 1987. By any criteria, 67 of 100 would be considered appropriate when 8 of the 11 criteria are met.
The next issue relates to caudal epidural injections (23). Chou ignores the fact that these patients, by selection criteria, already failed to improve with caudal epidural injections. Thus, if he wishes to utilize these for caudal epidural injections, he should mention the entire inclusion criteria, and also show that caudal epidural injections are not effective in patients who failed previously to respond to other caudal epidural injections. Then he provides a reinforcement tool, that “A basic principle of conducting systematic reviews is to follow the methods laid out for including and excluding studies, in order to remove subjective bias in selection of studies” Which applies to everyone, but, Chou and other methodologists. Chou and Huffman misinterpreted the evidence on adhesiolysis with lack of proper review of so-called placebo effect (23). If the reviewers would look carefully, this study did show placebo or positive effect at one month with significant pain relief of 50%.

Dashfield et al (24) compared caudal epidural injections with spinal endoscopic adhesiolysis, which is not indicated in patients without previous surgery or lumbar epidural fibrosis; yet Chou ignored or decided not to use this study for caudal epidural injections. This study was performed utilizing fluoroscopy and also had a rating of 7 of 11 by APS-AAPM methodologic quality assessment. Further, Chou also has not utilized Ackerman and Ahmad (25) in their evaluation of transforaminal epidural injections. However, they utilized a very low quality study by Zahaar (26). Chou and Huffman also missed the spinal endoscopic adhesiolysis manuscript which was published a long time before the review was conducted (27). It also appears that Chou and Huffman might have purposefully excluded the critical analysis of the American College of Occupational and Environmental Medicine (ACOEM) guidelines (28).

With regards to radiofrequency neurotomy, it is very clear that Chou does not understand clinical significance, as he does not think there is any value for properly positioning a radiofrequency cannula. For the record, the manuscript by Tekin et al (29) did not meet the inclusion criteria by ASIPP (30). Even then, when comparing 3 active control techniques, the authors showed significant decreases from the baseline in all 3 groups, including local anesthetic injection or control, pulsed radiofrequency, and conventional radiofrequency neurotomy. However, the differences were higher in the conventional radiofrequency group with baseline VAS of 6.5 ± 1.5 compared to at one year, 2.4 ± 1.1. None of the other groups showed 50% improvement. Certainly creative statistics can be presented to fit specific needs. With reference to Nath et al (31), Chou et al continued to refuse to admit the errors in their evaluation, now resorting to criticizing the randomization method, even though it was appropriate. Neither Bogduk (32), Nath et al (31), Datta et al (30), nor us, feel that has made any significant differences. Chou and Huffman (17) originally reported the final outcome scores in both groups were identical and there was no change in low back pain. This is in contrast to the manuscript which showed clear and distinct differences between both groups in all aspects of pain and quality of life variables. Chou and Huffman also missed the fundamental and basic fact that it was an active control study with needle placement, as well as local anesthetic injection over the nerve. The recent criticism from Chou has been that “the sham control group (which had higher baseline scores) had greater potential to experience improvement from baseline.” This criticism is not justified due to lack of a placebo group. Of the multiple other studies Chou and Huffman have included, Van Wijk et al (33), and multiple other studies did not meet inclusion criteria by others due to numerous deficiencies (29,33-37). Chou continues to deny the fact that these procedures were not performed appropriately. Of most interest is Leclaire et al (34) which invited criticism because it failed to define the study population and had inappropriate diagnostic criteria with a single intraarticular injection with inappropriate evaluation of response (50% relief for one day any time during the week) to identify patients for radiofrequency neurotomy. Finally, there was no placebo control. Interestingly enough, in response to Gauč’s (38) request, Leclaire et al (39) acknowledged multiple deficiencies. They described that their study used an invalidated and dated approach (30,40), and acknowledged the value of controlled local anesthetic blocks, false-positive results and technical aspects – which were all lacking (39). It is very interesting that Leclaire is the second author of the manuscript published by Carette et al (41), which is considered as a standard for negative response to treatment and also for positive response with sodium chloride solution injected into a closed space. Other studies including Van Wijk (33) also had multiple deficiencies (42) of their own results.

On the diagnostic accuracy of invasive diagnostic techniques, we have provided in detail various criterion standards including long-term follow-up, which is...
utilized in diagnostic facet joint nerve blocks (43,44). Further, Chou does not mind misquoting us that we do not dispute that there is little evidence showing that provocative discography or facet joint blocks improve clinical outcomes. Further, he adds a very poorly performed study (45) which presents issues with regard to scientific methodology and the practice of interventional pain management. In fact, a reader would assume that double blocks are cost-effective, and recommended (45). Cohen et al (45) started with an inadequate sample and provided statements implying that repeat blocks continue to increase false-positives. This has not been shown to be true in multiple studies using the criterion standard of 80% pain relief with dual comparative blocks and the ability to perform previously painful movements, with a sustained diagnosis of facet joint pain after 2 years in 90% of the patients (43,44).

Chou and Huffman (17) also inappropriately included Birkenmaier's study (46) while excluding Rubinstein and van Tulder's best evidence review (20). The Birkenmaier study (46) is not only of poor quality, but has not met any inclusion criteria for a diagnostic accuracy study. It essentially compared 2 uncontrolled procedures. They utilized high concentrations of bupivacaine, 0.5%, and volumes higher than 1 mL. Even so, Birkenmaier et al (46) showed that patients who had been selected by medial branch blocks had better pain relief than did patients who had been diagnosed using pericapsular block with statistical significance noted at 6 weeks and 3 months. They also concluded that if serial controlled blocks cannot be used, lumbar facet joint pain remains a diagnostic dilemma.

The misunderstandings or lack of understanding of placebo continues to be a major issue. There are numerous difficulties related to placebo groups and interventional techniques. An active control study utilizing local anesthetic is not a placebo, even though Chou, Nelemans and Staal with their self-appointed authority arbitrarily converted it into a placebo (10,17,22).

By definition, the placebo effect is a physiological or psychological reaction to an inactive substance or an inactive procedure. Consequently, placebo effect represents a key interphase between physiology, psychology, and patient care (47-49). It has been shown that the magnitude of placebo analgesia is highly variable (50). Consequently, understanding predictors of placebo analgesia is important, as treatment for chronic pain can benefit from clinically meaningful placebo effects. Similarly, it is essential for clinicians and methodologists to understand nocebo effects.

In contrast to placebo, nocebo represents a phenomenon opposite that of placebo analgesia, characteristically considered to be a worsening or consistent lack of change of symptoms after the administration of some agent known to be effective – hyperalgesia (48,49). However, nocebo effects in interventional pain management have not been carefully distinguished from drug-induced hyperalgesia, tachyphylaxis, tolerance, and/or progression of the underlying organic pathology causing increased pain and diminished sensitivity to a particular pharmacologic agent or procedure.

It has been demonstrated that multiple personality variables, including optimism and pessimism of not only the patient desire for reduction of pain, but also the referring physician, family, and the investigators themselves, can produce or alter placebo analgesia, or even induce a nocebo effect (51-55). Thus, one can argue that a treatment's failure is a nocebo effect in a controlled situation, the opposite of the placebo effect. For example, in a study in patients undergoing interventional procedures, sodium chloride solution, midazolam, and fentanyl produced placebo effects in 13% to 15%, 15% to 20%, and 18% to 30% of the patients respectively (48). However, a nocebo effect was seen in 5% to 8% of the patients in the sodium chloride group, 8% of the patients in the midazolam group, and 3% to 8% of the patients in the fentanyl group. Consequently, it is essential to focus on not only the methodological aspects, but also other aspects, wherein positive and negative effects might be seen either with placebo or active agents in 13% to 30% of patients (48).

Designing a placebo study in interventional techniques is an extremely difficult venture. Many believe that comparing the impact of an intervention with the natural course of the disease in a randomized, blinded fashion can only be achieved when the comparator group receives a placebo. This placebo, in the case of interventional treatment, would be a sham intervention, and represents the first obstacle for RCTs in interventional pain management. Considering that interventional pain management techniques are only offered when conservative treatment fails, researchers face a patient population that has a highly pronounced wish for improvement and is often reluctant to accept the potential receipt of a placebo therapy. This results in a high rate of patients' refusal to par-
ticipate in a study and subsequent withdrawals if they do participate – an apparent nocebo effect. The placebo effect will not actually reveal the true effect of the lack of treatment since all patients who are suffering with chronic pain are not enrolled in the study, and are not receiving the same attention, evaluation, explanation, and so-called placebo treatment. Finally, one must design a TRUE placebo study.

Very few studies have applied true placebo or so-called sham interventions. Many of those claiming to be placebo-controlled are actually active interventions. True placebo would only be injection of an inactive agent into an inactive location away from the epidural space or facet joint nerves, or facet joints themselves. Even the injections of sodium chloride solution and dextrose have been shown to yield different results (56). The experimental and clinical findings from the investigations of the electrophysiological effects of 0.9% sodium chloride and dextrose 5% in water solution have illustrated multiple variations of neural stimulation. The potential inaccuracy created by 0.9% sodium chloride solution versus 5% dextrose has been described in the literature (56-58). Further, injection of sodium chloride either into the disc, facet joint, or paraspinal muscles produces similar, yet variable results (58,59). There are also studies showing the lack of inertness of sodium chloride solution when injected into a closed space, and sodium chloride has been injected to treat low back pain and sciatica (60).

In addition to the injection of placebo, placement of the needle itself and injection of any solution with adhesiolysis effects in addition to the neurolytic effects of the needle and various solutions injected, along with mechanical pressure, and dilution of inflammatory substances, also play a substantial role in understanding the placebo effect or its lack thereof.

Clinical aspects, as well as placebo and nocebo, have to be taken into consideration if local anesthetic is considered to be a placebo, or even if the placebo actually helps. Is it worthwhile to provide patients with such a placebo treatment for them to improve? Otherwise, the patients with long-term chronic pain might continue to suffer. Also, when evaluating a placebo effect, one should consider the role of repeat interventions over a period of as long a time as 2 years or so with continued positive results in a high percentage of the patients similar to the other intervention.

Local anesthetics also have been described and proven to provide short and long-term symptomatic relief based on various mechanisms (61-68), including suppression of nociceptive discharge, the block of axonal transport, the blockade of the sympathetic reflex arc, blockade of sensitization, anti-inflammatory effect, and axonal transport blockade of nerve fibers. Further, no additional benefit was demonstrated by using corticosteroids in rat experimentation with nerve root infiltration with either local anesthetic alone, or with local anesthetic and steroids (68).

Chou states that we question the integrity of the APS review and guideline which is unjustified and uncalled for. We believe that it is for the public to decide. We still need clarification as to why so many errors are present as per Chou’s explanation with the inclusion of the American Academy of Pain Medicine (AAPM) and the American College of Physicians (ACP). The second issue relates to the funding — why is it so secretive, how much funding was provided, and of that funding, how much was received by Chou and Huffman? It seems that these are the only 2 who have received funding and worked on the manuscript. Chou has failed to show who was in the working group, how many of them left, and the reasons why they left.

Finally, doing serious work that Dr. Chou claims to do for better patient care and the health and welfare of the public in a cost effective manner should earn him respect by the recipients of such care and the providers but the result of his involvement raises serious questions about his intentions, and agenda in secrecy. The bottom line is just don’t love the truth and hate the facts. Once again using Carragee’s approach, we are also reminded of the American legal aphorism: “When you have the facts on your side, pound the facts; when you have the law on your side, pound the law; if you have neither the facts nor the law, pound the table.”

We believe Dr. Chou is pounding the table.

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