

A Reaffirmation to Our Call for Reform: Response to Rebuttal Letter Regarding “A Call for Reckoning and Reform in Interventional Pain Medicine and Neuromodulation Research” [Response to Letter]

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Dear editor

We thank Kalia et al for their letter¹ to our editorial “A Call for Reckoning and Reform in Interventional Pain Medicine and Neuromodulation Research”.² Such exchanges are essential to advance our field. While we appreciate their engagement, we would like to clarify several assertions.

On the Use of the Term “Targeted Drug Delivery”

First, the authors note that the terminology “targeted drug delivery” is accurate in the context of intrathecal drug delivery systems (IDDS); however, we would like to highlight that lipophilic opioids such as fentanyl actually have a large volume of distribution and readily crosses the blood-brain barrier. Preclinical and clinical studies highlight that fentanyl rapidly distributes away from the intrathecal space and into the epidural space and fat.³ This can result in systemic distribution, even when delivered intrathecally. In contrast, hydrophilic agents such as morphine demonstrate expansive rostral-caudal migration within the intrathecal space, and their clinical use can be associated with systemic-type effects such as sedation and respiratory depression. The presence of steep concentration gradients does not negate the fact that spread occurs and systemic side effects persist. Thus, we believe the term “targeted” is a misnomer and not an accurate representation of the pharmacokinetic profiles of opioids included in IDDS.

In relation to this, “targeted drug delivery” is not entirely a scientific or generic descriptor. Nomenclature describing a therapy should be clear and direct. For instance, when referring to neurostimulation of the dorsal spinal cord, this is synonymous with “spinal cord stimulation”. Similar to IDDS, spinal cord stimulation can be tailored in ways that enhance precision. Clinicians can determine the appropriate anatomical level for lead placement, optimize stimulation parameters (amplitude, pulse width, frequency, dipole configuration), and alter waveform paradigms (eg, conventional stimulation versus newer waveform paradigms). Yet despite this ability to refine therapy delivery, we call it what it is —“spinal cord stimulation”, as opposed to inappropriate terms like “targeted stimulation delivery”. This same concept can be applied to other pain therapies, such as “steroid injection” (instead of “targeted anti-inflammatory delivery”). We implore physicians to use standardized phrases that describe the therapy itself, avoiding ambiguous labels that could confuse patients or imply superiority over other established precise and targeted interventions (eg, peripheral nerve stimulation or regional nerve blocks/catheters).

On Methodological Rigor and Evidence Appraisal

Second, the letter misinterprets our discussion of evidence appraisal frameworks. We never state that A Measurement Tool to Assess Systematic Reviews, version 2 (AMSTAR-2) should be used for guideline development, nor do we prescribe any specific tool for evidence appraisal for guidelines. Our aim was to highlight that many systematic reviews and guidelines do not meet certain benchmarks of methodological and reporting quality.⁴⁻⁶ Our call is not for rigidity, but for rigor and transparency.

The conflation of AMSTAR-2 along with other checklists by the authors represents a critical misunderstanding that warrants clarification:

- Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluates the certainty of evidence within a systematic review with extensions proposed for other designs (eg, scoping reviews, network meta-analyses).
- AMSTAR-2 assesses the methodological rigor of the review itself (not the level of evidence within a review, guideline, etc).
- Reporting Items for Practice Guidelines in Healthcare (RIGHT) and Appraisal of Guidelines for Research and Evaluation (AGREE) checklists evaluate the quality of reporting and development of guidelines.

The above checklists are not interchangeable and misapplying them is inappropriate and dilutes their utility.

In relation to this, Kalia et al¹ proceed to outline the GRADE framework and its advantages. We are, of course, very familiar with this methodology and fully support its use when applied appropriately. Indeed, two of our authors (RSD, NS) have directly collaborated with one of GRADE's original developers, and co-developed derivative frameworks tailored to other evidence types.^{7,8} Our group has also authored guidelines specifically addressing evidence appraisal and the proper implementation of the GRADE framework.⁹⁻¹² Beyond methodological development, we have applied GRADE extensively in systematic reviews and meta-analyses of neuromodulation therapies, evaluating outcomes across domains such as pain relief, physical function, and emotional health.¹³⁻¹⁶ These efforts consistently demonstrate that the certainty of evidence remains very low to low, reflecting the current state of neuromodulation research.

On Clinician Perspective and Authorship

Third, we would caution the letter writers regarding their broad statements on the qualifications of authors of editorials and guidelines within pain medicine. As the field of pain medicine continues to grow, we encourage all clinicians and researchers at all stages of their career to engage in objective discourse, high-quality research, and healthy debate. The field of pain is advanced not only by clinicians, but also scientists, engineers, epidemiologists, and other disciplines.

While the authors bring up the issue of bias, it is important to acknowledge that a substantial portion of interventional pain medicine literature is authored by individuals with direct financial conflicts of interest (COI).^{17,18} The response by Kalia et al¹ is no exception, as it includes two co-authors with direct financial ties to an IDDS manufacturer.

Conclusion

Constructive dialogue is necessary and should not minimize deficiencies in the field. Our patients deserve clear terminology, rigorous science, transparent reporting, and representation from all professionals dedicated to the advancement of pain medicine. Only then can we advance into a discipline that is scientifically mature, patient-centered, and credible to the broader medical community.

Disclosure

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