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LETTER

Rebuttal Letter to the Editor: Defending Evidence-Based Practices in Interventional Pain Medicine [Letter]

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Dear editor

We read with great interest the recent editorial by D'Souza et al titled "A Call for Reckoning and Reform in Interventional Pain Medicine and Neuromodulation Research".[1] While we appreciate the authors' commitment to advancing scientific rigor in our field, we respectfully disagree with several assertions that appear to oversimplify complex therapeutic mechanisms and unfairly dismiss established methodological frameworks. We wish to provide a balanced perspective on two key issues raised in the editorial.

The Case for "Targeted Drug Delivery" in Intrathecal Therapy

The editorial's critique of the term "targeted drug delivery" for intrathecal drug delivery (ITDD) demonstrates a fundamental misunderstanding of cerebrospinal fluid (CSF) dynamics and the sophisticated mechanisms underlying this therapeutic approach. The authors argue that intrathecal delivery lacks anatomical specificity compared to peripheral nerve blocks, citing widespread CNS distribution of hydrophilic and lipophilic agents. This argument fails to acknowledge the extensive body of literature demonstrating that intrathecal delivery is indeed highly targeted through multiple mechanisms.

First, **CSF flow dynamics create predictable drug distribution patterns** that enable precise targeting of specific spinal segments. Research consistently demonstrates that intrathecal drugs establish steep rostral-caudal concentration gradients from the catheter tip, with morphine concentrations decreasing 5–10 fold over distances of only 5–10 cm.[2,3] This gradient is not a limitation but rather a feature that enables targeted delivery to specific dermatomal distributions corresponding to the patient's pain pattern.

Second, **catheter tip position critically determines therapeutic outcomes**. Studies have shown that cervical catheter placement is significantly more effective for upper extremity spasticity due to faster CSF flow in the cervical region, leading to higher drug concentrations at greater distances from the catheter tip.[4,5] Furthermore, catheter position can alter drug spread rates by up to 86%, demonstrating the precision achievable through proper catheter tip placement.[6] The ability to position catheters at specific spinal levels to target relevant neural pathways represents a level of anatomical targeting that systemic therapies cannot achieve.

Third, **pharmacokinetic properties enable selective targeting**. Hydrophilic drugs like morphine demonstrate longer half-lives, deeper spinal cord penetration, and more rostral diffusion, while lipophilic drugs like fentanyl provide limited diffusion for greater medication density at specific locations.[7,8] This differential pharmacokinetic behavior allows clinicians to select agents based on desired targeting characteristics – a foundational element of targeted therapy.

The editorial's comparison to peripheral nerve blocks misses the fundamental point that intrathecal delivery targets the dorsal horn of the spinal cord – the precise anatomical location where nociceptive processing occurs. The fact that intrathecal morphine provides equivalent analgesia to systemic morphine at 1/100th of the dose while minimizing

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systemic side effects exemplifies the targeting precision achieved.[9,10] This dramatic dose reduction would be impossible without anatomical and functional targeting.

Rather than representing marketing terminology, "targeted drug delivery" accurately describes a sophisticated therapeutic approach that leverages CSF dynamics, catheter positioning, and drug pharmacokinetics to achieve precise delivery to specific neural targets. The extensive literature supporting catheter tip positioning guidelines, drug selection algorithms, and dosing protocols demonstrates the scientific foundation underlying this terminology.

Methodological Diversity in Guideline Development

The editorial's criticism of guidelines that fail to meet AMSTAR-2, AGREE, and RIGHT standards reflects an unnecessarily restrictive view of evidence assessment methodologies.[1] While these tools provide valuable frameworks, the assertion that guidelines should exclusively rely on these specific instruments ignores the diversity of validated methodological approaches available to guideline developers.

The **GRADE (Grading of Recommendations Assessment, Development and Evaluation) system**, adopted by over 70 organizations including the CDC, NICE, and Cochrane Collaboration, provides a robust alternative framework that many consider superior to AMSTAR-2 for guideline development.[11,12] GRADE's structured approach to evidence assessment, explicit consideration of values and preferences, and transparent recommendation grading has been successfully applied across multiple medical specialties, including interventional pain management.

Several **alternative methodologies** have demonstrated equivalent rigor to the authors' preferred tools. The NHMRC (National Health and Medical Research Council) hierarchy, developed in Australia, provides a comprehensive evidence assessment framework that assigns levels based on research question types, recognizing that different clinical questions require different study designs.[13] The SIGN (Scottish Intercollegiate Guidelines Network) methodology, with over 25 years of successful implementation, offers a proven approach to evidence-based guideline development that has produced high-quality recommendations across numerous medical fields.[14]

For specialized fields like interventional pain medicine, the **IDSA-ESMO (Infectious Diseases Society-European Society Medical Oncology) framework** offers particular advantages for lower-resourced guideline developers, providing an intuitive typology with the ability to categorize tiers of evidence without requiring extensive methodological expertise.[15] The **ADAPTE framework** enables systematic adaptation of existing high-quality guidelines to specific clinical contexts, reducing duplication of effort while maintaining scientific rigor.[16]

Risk of bias assessment tools extend far beyond AMSTAR-2. The ROB 2 (Risk of Bias 2) tool, specifically designed for randomized trials, provides superior assessment capabilities compared to older instruments.[17] ROBINS-I V2, recently updated in 2024, offers comprehensive bias assessment for non-randomized studies with enhanced algorithmic mapping between signaling questions and bias judgments.[18]

The editorial's implicit suggestion that guidelines failing to meet these three specific criteria are inherently flawed ignores the reality that **methodological quality depends on appropriate tool selection** for the specific clinical question, available evidence, and target audience. A guideline developed using GRADE methodology with ROB 2 bias assessment may be methodologically superior to one mechanically applying AMSTAR-2 criteria to inappropriate study designs.

Conclusion

While we share the authors' commitment and sentiment to advancing scientific rigor in interventional pain medicine, we believe their critique of "targeted drug delivery" terminology and methodological frameworks reflects an oversimplified view of complex therapeutic and methodological concepts. The extensive literature supporting intrathecal therapy as a targeted intervention, combined with the diversity of validated guideline development methodologies, suggests that the field's current practices may be more scientifically sound than the editorial suggests.

Increasingly, editorials and even guidelines are being authored by academicians who do not actively practice clinical medicine, introducing a biased, theoretical perspective that further widens the gap the authors seek to address. Journals also carry a moral and ethical responsibility to promote the publication of clinically grounded an ethically conducted research.

Rather than wholesale rejection of established terminology and methodological approaches, we advocate for continued refinement of evidence-based practices through constructive dialogue that recognizes both the achievements and limitations

of current interventional pain medicine research. The path forward requires balanced assessment of our field's strengths and weaknesses, not dismissal and criticism of evidence-based practices that have improved patient outcomes for decades.

Disclosure

Dr Hemant Kalia reports consulting for Abbott, Curonix, Averitas, Nalu, other from spr therapeutics, other from saluda, during the conduct of the study; other from Abbott, other from Nalu, Curonix, SPR, Averitas, Saluda, outside the submitted work. Tolga Suvar is an educator and consultant for Medtronic. Dr Matthew Chung reports consulting for Saluda Medical, outside the submitted work. Dr Amitabh Gulati reports consulting for from Medtronic, AIS healthcare, Neurovasis, Hinge health, SPR therapeutics, Nalu medical and Menda health, during the conduct of the study. The authors report no other conflicts of interest in this communication.

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