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Letter to the Editor

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Response to "the Effectiveness of Dorsal Root Ganglion Neurostimulation for the Treatment of Chronic Pelvic Pain and Chronic Neuropathic Pain of the Lower Extremity: A Comprehensive Review of the Published Data"

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Dear Editor,

Literature reviews are a valuable tool for readers to obtain a global overview of a particular subject. A fair and balanced review and critique of the said matter is a prerequisite, moreover an absolute necessity for any non-biased review of literature; striving to treat all subject matter equally, using standards consistent with current practice. We are writing this letter in regard to the December 2020 publication "The Effectiveness of Dorsal Root Ganglion Neurostimulation for the Treatment of Chronic Pelvic Pain and Chronic Neuropathic Pain of the Lower Extremity: A Comprehensive Review of the Published Data" by Nagpal et al. [1], because we believe that the timing, tone, and methods selected to analyze were unfair and unbalanced, serving to misrepresent the current state of DRG-S.

Our first concern is regarding the comprehensiveness of this review. Although purporting to be a systematic review, the methods are not replicable as described and do not align with standard processes (e.g., PRISMA recommendations [2]). Furthermore, the number of articles presented in Figure 1 are surprisingly low. When we performed a simple keyword search for "dorsal root ganglion stimulation" (DRG-S) in PubMed, 4399 results were returned. Similarly, a 2019 systematic review of DRG stimulation reported 2133 results, and ultimately included 29 of these articles [3]. Even assuming some differences in inclusion/exclusion criteria for article inclusion, it is puzzling that the Nagpal article reported only 78 results despite using multiple databases and search strings and then included only 12 articles for their comprehensive review. We cannot be sure of the reasons for this, but one possibility may be time dependent. The range of publication dates of a literature review must be defined in the methods, particularly with new therapies, so to clearly define the relevance to the reader. DRG-S received Food and Drug Administration (FDA) approval in 2016, and the publication of this novel therapy's sentinel paper, the ACCURATE study [4], was published April 2017; thus a critical review 3.5 years later is warranted. However, this review lacked such a defined date range in the methods section. The seven DRG-S papers included after publication of the ACCURATE RCT had a most recent epub date in December 2018, and the average epub date of the seven papers was 29 months (873d) prior to the date of this paper. Such a comprehensive review clearly does not reflect the current state of this therapy and is outdated and irrelevant a year, at least, prior to its publication date.

Our second, and most serious, concern is with the authors' apparent "re-analysis" of the ACCURATE RCT's data as what the authors term a "true ITT (intent to treat)" analysis. Problematically, their methods are not clearly described. Inferring from sample sizes, it appears that the authors included all randomized subjects in their analysis. This means that they analyzed the neuromodulation outcomes of at least six people who were never implanted, which amounts to the invention of data. Next, the Nagpal team applied imputation for missing data (whether due to missed visits, subject withdrawal, or adverse events). Data imputation is employed in many clinical trials but is a complex statistical challenge [5]. Nagpal describes using "worst-case scenario" for the data imputation in their re-analysis, which would seem to indicate that all missing data, regardless of intervention, would be consistently interpreted as treatment failures. Instead, Nagpal imputed all missing DRG-S data as treatment failures and, conversely, all SCS data as

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treatment successes. Given this, it's not surprising that the study trends reversed: the Nagpal team specifically engineered their analysis to ensure it. To make a simple analogy, this would be competing in the 40 yard dash, except starting 10 yards behind the others; anyone can see that's not fair play.

Finally, the authors also presented their error-prone "ITT analysis" as if as if it were fact when applying the GRADE level of evidence assessment to arrive at a "very low" rating (instead of assessing the ACCURATE trial as written). This is simply a thought experiment and has no bearing on reality.

As described in its methods section, the ACCURATE trial was completed under an Investigational Device Exemption from the FDA, which means that the study's statistical analysis plan was submitted, reviewed, and approved by FDA prior to study start. Furthermore, the FDA granted approval for device sale after reviewing the data and analysis as written in the ACCURATE paper. Although it is certainly interesting to consider what might have happened if other statistical approaches had been applied, the fact of the matter is that ACCURATE used well-vetted and conventional methods. The same cannot be said for the Nagpal article.

In short, through highlighting and discrediting the ACCURATE study, ambiguous methodologies, and the incorrect application of an evidence grading criteria unfair to an SCS RCT, a lopsided perspective is painted. We must, as just practitioners, hold all therapies to the same standard, or we only inhibit progress.

Thank you for the time hear our divergent interpretation.

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