Title

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Journal

Regional Anesthesia & Pain Medicine, 48(9)

ISSN

1098-7339

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Publication Date

2023-09-01

DOI

10.1136/rapm-2023-104389

OPEN ACCESS

Patient-centered results from a multicenter study of continuous peripheral nerve blocks and postamputation phantom and residual limb pain: secondary outcomes from a randomized, clinical trial

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rapm-2023-104389).

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Received 30 January 2023
Accepted 27 February 2023

To cite: Ilfeld BM, Khatibi B, Maheshwari K, *et al*. *Reg Anesth Pain Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/rapm-2023-104389

ABSTRACT

Introduction We previously reported that a 6-day continuous peripheral nerve block reduces established postamputation phantom pain. To provide patients and providers with the information to best inform treatment decisions, here we reanalyze the data and present the results in a more patient-centered format. We also provide information on patient-defined clinically relevant benefits to facilitate evaluation of available studies and guide future trial design.

Methods The original trial enrolled participants with a limb amputation and phantom pain who were randomized to receive a 6-day continuous peripheral nerve block(s) of either ropivacaine (n=71) or saline (n=73) in a double-masked fashion. Here we calculate the percentage of each treatment group that experienced a clinically relevant improvement as defined by previous studies as well as present what the participants of our study defined as small, medium, and large analgesic improvements using the 7-point ordinal Patient Global Impression of Change scale.

Results Among patients who were given a 6-day ropivacaine infusion, 57% experienced at least a 2-point improvement on the 11-point numeric rating scale in their average and worst phantom pain 4 weeks postbaseline as compared with 26% (p<0.001) for average and 25% (p<0.001) for worst pain in patients given a placebo infusion. At 4 weeks, the percentage of participants rating their pain as improved was 53% for the active vs 30% for the placebo groups (95% CI 1.7 (1.1, 2.7), p=0.008). For all patients combined, the median (IQR) phantom pain Numeric Rating Scale improvements at 4 weeks considered small, medium, and large were 2 (0–2), 3 (2–5), and 5 (3–7), respectively. The median improvements in the Brief Pain Inventory interference subscale (0–70) associated with small, medium, and large analgesic changes were 8 (1–18), 22 (14–31), and 39 (26–47).

Conclusions Among patients with postamputation phantom pain, a continuous peripheral nerve block more than doubles the chance of a clinically relevant improvement in pain intensity. Amputees with phantom and/or residual limb pain rate analgesic improvements as clinically relevant similarly to other chronic pain etiologies, although their smallest relevant improvement in the Brief Pain Inventory was significantly larger than previously published values.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ We previously reported that a 6-day continuous peripheral nerve block reduces established postamputation phantom pain and presented the data in a format best used to test a hypothesis

⇒ However, this physician–scientist focus does not adequately reflect the patient's perspective, leaving essential questions for consumers of the research—both future patients and their providers—unanswered.

WHAT THIS STUDY ADDS

⇒ Among patients with postamputation phantom pain, a continuous peripheral nerve block more than doubles the chance of a clinically relevant improvement in pain intensity.

⇒ We also provide amputee-specific values for the improvements in pain scores and pain's interference with functioning that patients find to be small, medium and large.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future patients and their caretakers will be able to make more-informed decisions regarding possible treatment of postamputation limb pain with continuous peripheral nerve blocks.

⇒ This information can facilitate evaluation of currently-published research, and enable future clinical researchers to improve study design and analysis.

Trial registration number NCT01824082.

INTRODUCTION

Traditional outcome measures are frequently chosen to test a hypothesis, with the presentation of the results reflecting this physician–scientist focus. However, these often do not adequately reflect the patient's perspective, leaving essential questions for consumers of the research—both future

patients and their providers—unanswered.[1] Consequently, published randomized, controlled trials often fail to maximize their ostensible purpose: to provide actionable information on which healthcare decisions may be based.[2] Reflecting the significance of this problem was the multibillion dollar funding of the Patient-Centered Outcomes Research Institute to respond to 'a widespread concern that, in many cases, patients and their healthcare providers, families, and caregivers do not have the information they need to make choices aligned with their desired health outcomes.'[3]

To provide patients suffering from postamputation phantom limb pain—as well as their caregivers and healthcare providers—with the information necessary to enable decisions on treatment options, we have reanalyzed data from a recently published clinical trial and presented the results in a patient-centered format.[4] We originally tested the hypothesis that, when added to a single-injection peripheral nerve block (PNB), a 6-day continuous PNB reduces phantom pain 4 weeks after treatment.[5] We found that after 4 weeks, average phantom limb pain intensity was a mean (SD) of 3.0 (2.9) in patients given local anesthetic vs 4.5 (2.6) in those given placebo ($p=0.003$).

Whereas our original analysis adequately tested the hypothesis and demonstrated the relationship between perineural infusion and decreased phantom pain ($p<0.05$), it left a myriad of questions unanswered for patients and providers contemplating use of this treatment.[6] For example, would a patient presenting with mild pain have a different probability of improvement compared with someone with severe pain at baseline? What is the likelihood that a patient with moderate phantom pain would experience a clinically meaningful decrease in pain? What change in pain score do patients suffering from postamputation phantom pain consider a small, medium, or large improvement?

The new information can also facilitate evaluation of previously published trials. For example, a randomized, controlled study published in 2002 found that in amputees with phantom limb pain the average pain score measured using a 0–10 Numeric Rating Scale improved 1.6 points more using gabapentin versus placebo.[7] Remaining unanswered is whether this was a clinically relevant difference.[8]

Finally, additional patient-centered data can enable future clinical researchers to improve study design and analysis.[9] For example, hypothesis testing is optimized when the smallest clinically meaningful improvement—or 'minimal clinically important difference'—is known prospectively,[10] yet this information was unavailable to us when planning our clinical trial involving phantom pain and so a value had to be inferred from surrogate patient populations (diabetic neuropathy, postherpetic neuralgia, chronic low back pain, fibromyalgia, osteoarthritis).[11] The use of amputee-specific values for the smallest important improvement to patients will help guide the design of future trials in this patient population.[12 13]

Consequently, we conducted a reanalysis of our previously published clinical trial and report patient-centered secondary outcomes in a format to optimize benefits to patients and providers.[5]

METHODS

The original trial followed Good Clinical Practice and was conducted within the ethical guidelines outlined in the Declaration of Helsinki. The trial was registered prior to patient enrollment (ClinicalTrials.gov, PI: Ilfeld, April 4, 2013; first participant enrolled December 1, 2013). An independent data safety monitoring board (online supplemental appendix) was responsible for the conduct and oversight of all aspects of the investigation. Written, informed consent was obtained from all participants. Deidentified data were used for the current secondary analysis.

Original trial

Protocol details and results of the original trial have been published previously.[5 14] In short, patients with an upper-limb or lower-limb amputation and established phantom pain received a single-injection ropivacaine infraclavicular or femoral/sciatic PNB(s) and perineural catheter insertion(s). They were subsequently randomized to receive a 6-day ambulatory perineural infusion of either ropivacaine or normal saline. A cross-over treatment mandated by the funding agency to occur at 4–16 weeks following the initial intervention allowed all subjects the opportunity to ensure they received perineural local anesthetic, but because it was optional also introduced selection bias from this time point forward. Consequently, we now include only data collected at the 4-week timepoint prior to the optional cross-over intervention.

The original primary outcome was the average intensity of phantom limb pain 4 weeks following initiation of the intervention as measured on a 0–10 Numeric Rating Scale within the Brief Pain Inventory, short form (BPI). End points included in the parallel gatekeeping procedure were termed 'secondary outcomes' in the original report to distinguish them from the remaining variables which were then termed 'tertiary' (described as 'other variables' in the on-line registry).

Current analysis

However, since the current report describes the results of a secondary analysis without a gatekeeping procedure, there is no need to differentiate secondary and tertiary/other variables; and we describe all outcomes—other than the primary—as 'secondary end points' to use the conventional terminology of this journal. For the current secondary analysis, data are described using mean (SD) or median (IQR) for continuous variables and counts and percentages for categorical variables. When comparing randomized groups, we used the last observation carried forward to replace missing average and worst pain values at 4 weeks by their most recent measures (eg, postoperative day 1, 7, 14, or 21). The R programming language (The R Project for Statistical Computing) and SAS statistical software version 9.4M7 (Cary, North Carolina) were used for all analyses.

Analysis 1

Our original sample size estimate was based on the assumption that individual improvements from baseline of at least 1.7 along an 11-point Numeric Rating Scale (NRS) accurately identified participants who rated improvements as 'much improved' or more, compared with those who perceived no change or worsening following analgesic interventions based on previously published data.[11] Therefore, for the current analysis, we assessed the proportion in each treatment group that experienced (1) a clinically relevant difference based on data derived from non-amputee patient populations (improvement >1.5 points); (2) an improvement prespecified as not being clinically relevant (improvement 0.5–1.5 points); (3) no improvement (or worsening); or (4) no baseline pain. We used proportional odds logistic regression to compare active and placebo arms on this ordinal outcome for patients who had experienced any baseline pain.

Analysis 2

The previous study that served as the basis for estimating a clinically relevant improvement of at least 1.7 on the NRS also

demonstrated that an improvement from baseline of 28% or more similarly indicates a clinically relevant decrease in pain.[11] Since patients starting with different degrees of pain at baseline might expect different results following the continuous block, we report the n (%) of patients with any baseline pain who attained at least 28% improvement in NRS from baseline to week 4 stratified by baseline average NRS of mild pain (<5), moderate pain (5–7), and severe pain (>7) for each of phantom and residual pain. No statistical tests were conducted.

Analysis 3

To provide a global measure of worsening or improvement, the Patient Global Impression of Change (PGIC) was administered allowing patient evaluation of integrated treatment effects.[15] This measure is a 7-point ordinal scale requiring the patient to rate the current intensity of phantom limb pain compared with their pretreatment baseline: 1 for 'very much worse' to 7 for 'very much improved' (4 is 'no change').[15] We used this scale to determine what the participants of our study considered small, medium and large NRS improvements. Specifically, we report the mean (SD) change in average NRS pain score for each of five categories: worsening (PGIC 1–3), no improvement (PGIC=4), small improvement (PGIC=5), medium improvement (PGIC=6), and large improvement (PGIC=7).[15] We used a χ^2 test to examine the relationship between Treatment (placebo vs active) and any improvement defined by PGIC ≥ 5.

Analysis 4

The primary instrument of the original investigation was the BPI, short form, which assesses pain and its interference with physical and emotional functioning.[16] The form includes three domains: (1) pain, with four questions using an NRS to evaluate 4 pain levels: 'current', 'least', 'worst', and 'average'; (2) percentage of relief provided by pain treatments with one question; and (3) interference with physical and emotional functioning using a 0–10 scale (0=no interference; 10=complete interference). The seven interference questions involve general activity, mood, walking ability, normal work activities (both inside and outside of the home), relationships, sleep, and enjoyment of life.[16] The seven functioning questions can be combined to produce an interference subscale (0–70). The use of both single items (eg, mood) and the composite scores is supported by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for assessing pain in clinical trials.[15 17]

The IMMPACT consensus statement specifies that 'available data suggest that a change of 1 point on the Interference Scale… would be a reasonable benchmark for future studies designed to identify minimally clinically important changes.'[10] However, it also notes that 'because few studies have examined the importance of worsening on these measures, benchmarks are only provided for improvement in scores (emphasis added).'[10] To define amputee-specific clinically relevant improvements in the BPI, we used the PGIC data to determine the change in total BPI interference subscale (seven questions added together) that patients considered to be a worsening (PGIC=1–3), no improvement (PGIC=4), and small (PGIC=5), medium (PGIC=6) or large (PGIC=7) improvement.

RESULTS

A total of 144 participants (figure 1) were enrolled in the original clinical trial and randomized to a 6-day infusion of either active treatment with a ropivacaine (n=71) or a normal saline placebo (n=73).[5]

Analysis 1

Among patients with any phantom pain at baseline who were given a 6-day ropivacaine infusion, 57% experienced at least a 2-point improvement on the 11-point numeric rating scale in their average and worst phantom pain 4 weeks postbaseline as compared with 26% for average (relative risk (95% CI) of 1.6 (1.2, 2.1), p<0.001) and 25% for worst pain (relative risk (95% CI) of 1.8 (1.3, 2.7), p<0.001) in patients given a placebo infusion (figure 2). Overall, active patients were an estimated

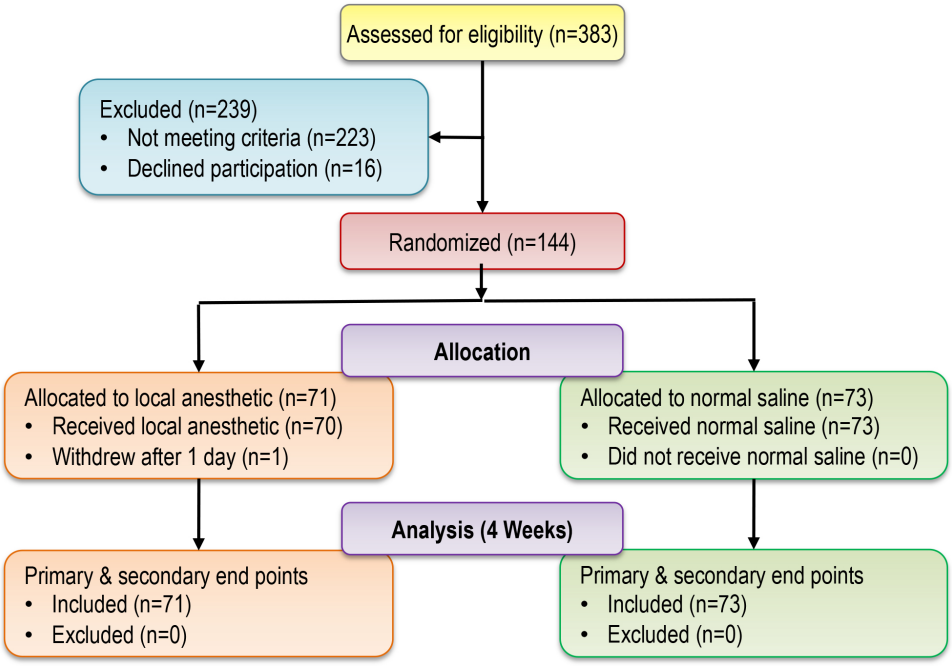

Figure 1 Consolidated standards of reporting trials diagram.

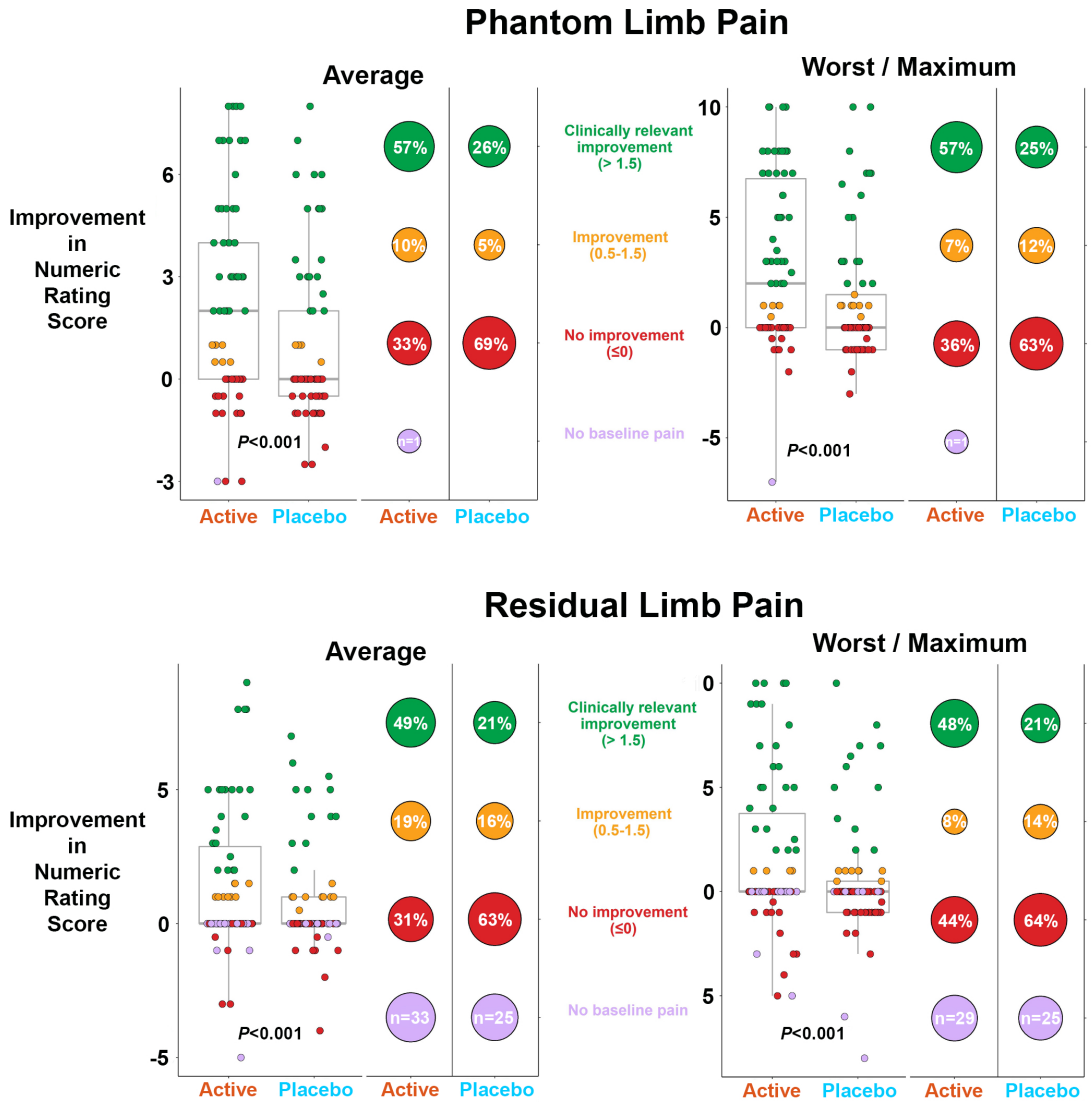

Figure 2 Improvement in average and worst phantom and residual limb pain scores 4 weeks following baseline. Only patients with the specific type of pain at baseline are included (eg, 41 patients without residual limb pain at baseline are excluded because they could not experience an improvement). Data expressed as median (dark horizontal bars) with IQR (IQR, Q1 to Q3) (box), minimum between maximum value and Q3+1.5×IQR and maximum between minimum value and Q1−1.5×IQR (whiskers). Scatter points represent the data points. Numbers on the bubbles represent the percent of each category within treatment group with the exception of patients without pain at baseline (purple) which denote the actual number of subjects. Size of the bubbles are proportional to percentage/number. Both plots are color-coded by the level of improvement: No improvement (red), improvement (orange), and clinically relevant improvement (green).

4 (95% CI 2, 8) times more likely to have a better change in average phantom limb pain from baseline (ie, among no change or worse, 0.5–1.5 'improvement' and >1.5 'clinically relevant improvement'). Among patients with any baseline residual limb pain, 49% and 48% of patients who received active treatment experienced a clinically relevant improvement in their average and worst pain, respectively, compared with 21% (p<0.001) and 21% (p<0.001) for participants who had received placebo (figure 2). Overall, active patients were an estimated 2 (95% CI 1.4, 4) times more likely to have a better change in average residual limb pain from baseline compared with placebo.

Analysis 2

The percentage of patients experiencing a clinically relevant improvement in phantom and residual limb pain varied by their baseline pain intensity (tables 1 and 2). Patients beginning with severe pain (NRS >7) did not improve with active treatment versus placebo to the same degree as did participants with mild or moderate pain at baseline (tables 1 and 2).

Analysis 3

Based on the PGIC at 4 weeks, the percentage of participants rating their pain as improved was 53% for the active vs 30% for the placebo groups (95% CI 1.7 (1.1 to 2.7), p=0.008). This indicates an individual was 74% more likely to experience self-described improvement in the active compared with the placebo group. The mean (SD) average phantom pain NRS improvements considered small, medium, and large by patients were 0.9 (1.9), 3 (1.8), and 5 (2.0), respectively (table 3). The corresponding median (IQR) were 2 (0–2), 3 (2–5), and 5 (3–7) (figure 3, table 3).

Analysis 4

Based on the PGIC at 4 weeks, the mean (SD) BPI (interference subscale) improvement considered small, medium, and large by

Table 1 Average phantom pain: at least 28% improvement at 4 weeks from baseline stratified by baseline pain level in patients with phantom pain at baseline

Baseline average phantom pain (NRS)	Active (n=69)*		Placebo (n=73)	
	Improvement ≥28%		Improvement ≥28%	
	Yes (n=37)	No (n=32)	Yes (n=20)	No (n=53)
Mild pain (<5)	48% (12)	52% (13)	22% (5)	78% (18)
Moderate pain (5–7)*	59% (19)	41% (13)	28% (12)	72% (31)
Severe pain (>7)	50% (6)	50% (6)	43% (3)	57% (4)
Percent†	54	46	27	73

Data reported as row percentage within treatment (n).
n=7 missing outcome at 1 month, replaced using the last observation carried forward method for active (n=3) and placebo (n=4) groups.
*n=2 excluded due to a missing postintervention pain measurement (n=1) and a lack of phantom limb pain at baseline (n=1).
†Percent: total column percentage within treatment.
NRS, Numeric Rating Scale.

patients was 11 (12), 22 (16), and 34 (23), respectively (table 3). The corresponding median (IQR) were 8 (1–18), 22 (14–31), and 39 (26–47) (table 3).

DISCUSSION

This reanalysis of data from a previously published clinical trial provides patients and healthcare providers with 'information they can use to make decisions that reflect their desired health outcomes.'[18] Our original publication describing the trial results reported that 'after 4 weeks, average phantom limb pain intensity was a mean (SD) of 3.0 (2.9) in patients given local anesthetic vs 4.5 (2.6) in those given placebo… (p=0.003).' However, this 1.5-point difference between group means cannot be extrapolated to individuals: it does not provide actionable information to individual patients regarding the probability of any single person experiencing a clinically relevant analgesic improvement.[8–10 15] The purpose of the original statement regarding the primary outcome measure was to report the results of hypothesis testing—to determine if there is an association between a continuous PNB and improvement in phantom limb pain. While obviously important, the original report reflected the physician-scientist focus of the investigators.

Table 2 Average residual limb pain: at least 28% improvement at 4 weeks from baseline stratified by baseline pain level in patients with residual pain at baseline

Baseline average residual limb pain (NRS)	Active (n=47)*		Placebo (n=55)†	
	Improvement ≥28%		Improvement ≥28%	
	Yes (n=28)	No (n=19)	Yes (n=14)	No (n=41)
Mild pain (<5)	64% (14)	36% (8)	26% (6)	74% (17)
Moderate pain (5–7)	63% (10)	37% (6)	24% (7)	76% (22)
Severe pain (>7)	44% (4)	56% (5)	33% (1)	67% (2)
Percent‡	60	40	25	75

Data reported as row percentage within treatment (*n*).
n=7 missing outcome at 1 month, replaced using the last observation carried forward method for active (n=3) and placebo (n=4) groups.
*n=24 excluded due to a missing postintervention pain measurement (n=1) and a lack of phantom limb pain at baseline (n=23).
†n=18 excluded due to a lack of residual limb pain at baseline.
‡Percent: total column percentage within treatment.
NRS, Numeric Rating Scale.

Far more meaningful and helpful to patients and healthcare providers is the outcome described in the current analysis: among patients who were given a 6-day ropivacaine infusion, 57% experienced at least a 2-point improvement on the 11-point numeric rating scale in their average and worst phantom pain 4 weeks postbaseline as compared with 26% (p<0.001) and 25% (p<0.001) for patients given a placebo infusion, respectively. Similarly, patients can now predict the probability of a clinically relevant analgesic improvement based on their baseline pain level, with those beginning with severe pain experiencing a lower probability of experiencing a clinically meaningful improvement in both phantom and residual limb pain (tables 1 and 2). Providing patient-centered outcomes enables informed treatment decisions based on individuals' personal priorities as well as a risk–benefit evaluation when these benefits are paired with known intervention complications.[19]

These results also demonstrate the important—yet frequently overlooked—fact that minimal clinically important differences in pain scores among individual patients cannot be extrapolated to differences between the means of two treatment groups[8–10 15]: in our study the difference between the two treatment group means was only 1.5 on the 0–10 point NRS, smaller than the 1.7–2.0 rated as clinically relevant to individual patients. However, the intervention resulted in more than doubling the number of participants who rated their change in pain as clinically relevant.

This reanalysis also provides new information that can help interpret currently published data and design future clinical trials. While past studies involving the treatment of phantom limb pain may describe a change in pain scores associated with a specific intervention, whether an improvement was clinically relevant to the amputees has generally been speculative. Based on our study, patients described an improvement in phantom pain as small, medium, and large with a mean NRS change of 2 (0, 2), 3 (2, 5), and 5 (3, 7), respectively (table 3). This information will allow far more precision for prospective sample size estimation for future clinical trials. Of similar benefit is the information provided in the current report regarding improvements in the BPI's interference subscale (0–70 range) that patients associated with small, medium, and large changes in pain scores (median (IQR)): 8 (1–8), 22 (14–31), and 39 (26–47), respectively (table 3). These values are far higher than the 'benchmark' minimum clinically relevant improvement of 1 point originally sited in the IMMPACT recommendations.[15 17]

Limitations

A major limitation of the current analysis is that we present exclusively secondary outcomes that were not included in the original protocol and statistical plan. Therefore, this is a retrospective analysis of prospectively collected data. Additionally, our results are exclusively derived from patients with postamputation phantom and/or residual limb pain, and therefore, may not apply to other more common pain etiologies (although the specificity of our results to this population is also a strength of the study). A further limitation is that while the PGIC question distinguished between phantom and residual limb pain—specifying phantom limb pain—some patients apparently responded for pain in general. The result is apparent in figure 3: there was one participant who described their pain as worsening on the PGIC, yet the actual phantom limb pain score improved 3.5 points between baseline and 4 weeks. Conversely, there was a patient who described their change in pain as a large improvement, yet the actual phantom pain score worsened 1 point between baseline and 4 weeks. In nearly all participants, the

Table 3 Improvement in average phantom pain (above) and Brief Pain Inventory interference subscale (below) at 4 weeks defined as small, medium, and large by participants based on the Patients' Global Impression of Change (PGIC)

PGIC descriptor PGIC score	Worsening 1–3 (n=7)	None 4 (n=72)	Small 5 (n=9)	Medium 6 (n=10)	Large 7 (n=37)
Phantom limb pain score improvement (Numeric Rating Scale)					
Mean (SD)	−0.6 (2.1)	−0.1 (1.0)	0.9 (1.9)	3.0 (1.8)	5.0 (2.0)
Mean (95% CI)	−0.6 (−1.3, 3)	−0.1 (−0.3, 0.2)	0.9 (−0.5, 2)	3 (2, 5)	5 (4, 6)
Median (IQR)	−1 (−0.3, −1.8)	0 (−0.5, 0)	2 (0, 2)	3 (2, 5)	5 (3, 7)
Brief Pain Inventory Improvement (Interference Subscale)					
Mean (SD)	2 (9)	1.6 (8)	11 (12)	22 (16)	34 (23)
Mean (95% CI)	2 (−6, 11)	1.6 (−0.3, 4)	11 (1.8, 20)	22 (10, 34)	34 (26, 41)
Median (IQR)	−2 (−4, 8)	0 (−1, 1)	8 (1, 18)	22 (14, 31)	39 (26, 47)

n=6 missing outcome at 1 month, replaced using the last observation carried forward method for active (n=3) and placebo (n=3) groups.
Nine patients did not have a PGIC response and were excluded (n=135).

changes in phantom and residual limb pain were in the same direction (either improving or not). However, in a few cases, phantom pain improved while residual limb pain worsened, and the participant responded their 'pain' had 'worsened' referring to the latter (or vice versa).

In summary, a continuous PNB more than doubles the chance of a clinically relevant improvement among patients with postamputation phantom and/or residual limb pain. Patients with postamputation pain rate analgesic improvements as clinically relevant similarly to other chronic pain etiologies, although their smallest relevant improvement in the BPI was significantly larger than previously published values. Defining clinically relevant analgesic changes requires the study of populations with various pain etiologies and differing treatment interventions. Patient-centered outcomes help inform individual and healthcare provider decisions, assist interpreting results from previously published studies, and improve the design of future clinical trials.

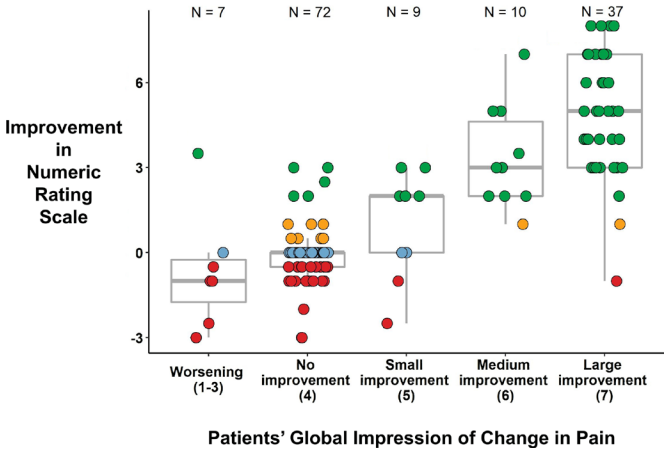

Figure 3 Improvement in average phantom pain as measured on a Numeric Rating Scale defined by Patients' Global Impression of Change 4 weeks following baseline. Data expressed as median (dark horizontal bars) with (IQR, Q1–Q3) (box), minimum between maximum value and Q3+1.5×IQR and maximum between minimum value and Q1−1.5×IQR (whiskers). Scatter points represent the data points color-coded by the level of improvement: worsening (red), no change (blue), improvement (orange), and clinically relevant improvement (green).

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Acknowledgements The authors appreciate the invaluable assistance of the members of the uncompensated Data Safety Monitoring Board, without whom this study would not have been possible: Beverly A Morris, RN, ANP-BC, MBA (University of California, San Diego, CA); Peter Szmuk, MD (University of Texas Southwestern and Children's Health Medical Center, Dallas, TX; and Outcomes Research Consortium, Cleveland, OH); and Gerald Beck, PhD (Cleveland Clinic, Cleveland, OH).

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Contributors All authors helped plan, execute, analyze, and/or write/revise the manuscript. Brian Ilfeld, MD, accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The US Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office. This work was supported by the Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense, through the Congressionally Directed Medical Research Program under Award No. W81XWH-13-2-0009 (DM120032). The project was also partially supported by the National Institutes of Health, Grant UL1TR001442.

Disclaimer Opinions, interpretations, conclusions and recommendations are those of the authors and are not necessarily endorsed by the funding entities.

Competing interests BMI and BK: The University of California has received funding and/or equipment for other research projects from Epimed International (Dallas, TX), Infutronics (Natick, MA), Avanos (Irvine, CA), and SPR Therapeutics (Cleveland, OH). DIS: Chair Data and Safety Monitoring Board, Neuros Medical QUEST trial. Consultant for Pacira Pharmaceuticals (Parsippany, NJ), and this company funds trials in the Department of Outcomes Research. SPC: receives research funding (paid to the institution) from Avanos (Irvine, CA), and research funding (paid to the institution) from Scilex (San Diego, CA). He serves as a consultant for SPR Therapeutics (Cleveland, OH). AT: Pacira Pharmaceuticals (Parsippany, NJ) funds trials in the Department of Outcomes Research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by UC San Diego Institutional Review BoardID: 130341. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Deidentified patient-level data will be shared for collaborative analyses on request to BMI (email: bilfeld@ucsd.edu) shortly after publication. The data dictionary and statistical tables and code will be provided as appropriate; a data-sharing contract will be required. The protocol is available by request.

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REFERENCES

1 Frank L, Basch E, Selby JV. Patient-centered outcomes research I: the PCORI perspective on patient-centered outcomes research. *JAMA* 2014;312:1513–4.
2 Zwarenstein M, Oxman A. Pragmatic trials in health care S: why are so few randomized trials useful, and what can we do about it. *J Clin Epidemiol* 2006;59:1125–6.
3 Washington AE, Lipstein SH. The patient-centered outcomes research Institute -- promoting better information, decisions, and health. *N Engl J Med* 2011;365:e31.
4 Brubaker L, Shull B. Eggs for patient-centered outcomes. *Int Urogynecol J Pelvic Floor Dysfunct* 2005;16:171–3.
5 Ilfeld BM, Khatibi B, Maheshwari K, *et al*. Ambulatory continuous peripheral nerve blocks to treat postamputation phantom limb pain: a multicenter, randomized, quadruple-masked, placebo-controlled clinical trial. *Pain* 2021;162:938–55.
6 Mariano ER, Dickerson DM, Szokol JW, *et al*. A multisociety organizational consensus process to define guiding principles for acute perioperative pain management. *Reg Anesth Pain Med* 2022;47:118–27.
7 Bone M, Critchley P, Buggy DJ. Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. *Reg Anesth Pain Med* 2002;27:481–6.
8 Dworkin RH, Turk DC, McDermott MP, *et al*. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2009;146:238–44.
9 Ilfeld BM. Why science is less scientific than we think (and what to do about it): the 2022 Gaston labat Award Lecture. *Reg Anesth Pain Med* 2022;47:395–400.
10 Dworkin RH, Turk DC, Wyrwich KW, *et al*. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105–21.
11 Farrar JT, Young JP Jr, LaMoreaux L, *et al*. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–58.
12 Dworkin RH, McDermott MP, Raja SN. Preventing chronic postsurgical pain: how much of a difference makes a difference? *Anesthesiology* 2010;112:516–8.
13 Myles PS, Myles DB. Conflating effect size and minimal clinically important difference. *Comment on Br J Anaesth* 2021;126:1029–37.
14 Ilfeld BM, Khatibi B, Maheshwari K, *et al*. Immediate effects of a continuous peripheral nerve block on postamputation phantom and residual limb pain: secondary outcomes from a multicenter randomized controlled clinical trial. *Anesth Analg* 2021;133:1019–27.
15 Dworkin RH, Turk DC, Peirce-Sandner S, *et al*. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain* 2010;149:177–93.
16 Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singap* 1994;23:129–38.
17 Turk DC, Dworkin RH, Burke LB, *et al*. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. *Pain* 2006;125:208–15.
18 Hinson HE, Hamilton RH, Matchar DB. Making public and patient involvement in clinical trials more than aspirational. *Neurol Clin Pract* 2020;10:188–9.
19 Ilfeld BM. Continuous peripheral nerve blocks: an update of the published evidence and comparison with novel, alternative analgesic modalities. *Anesth Analg* 2017;124:308–35.