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Application of restorative neurostimulation for chronic mechanical low back pain in an older population with 2-year follow up

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ABSTRACT

Introduction Data on the Medicare-aged population show that older patients are major consumers of low back pain (LBP) interventions. An effective approach for patients with mechanical LBP that has been refractory to conservative management is restorative neurostimulation. The efficacy of restorative neurostimulation has been demonstrated in multiple prospective studies, with published follow-up over 4 years, showing a consistent durable effect.

Methods To further examine the effect of restorative neurostimulation in an older demographic, data from three clinical studies were aggregated: ReActiv8-B prospectively followed 204 patients, ReActiv8-C study prospectively followed 87 patients and ReActiv8-PMCF prospectively followed 42 patients.

Two hundred and sixty-one patients were identified with complete 2-year follow-up and divided into cohorts of equal size based of age quartiles.

At 2 years from device activation, patients in either cohort were classified by change in disability (Oswestry Disability Index (ODI)) or change in pain score(NRS/VAS) and assessed as proportion of patients per group at each time point. Additionally, health-related quality of life (HRQoL) (EQ5D-5L) was longitudinally compared with baseline. Differences in proportions were assessed using χ^2 and continuous variables by repeated measures analysis of variance.

Results The oldest quartile (n=65) had a median age of 60 (56–82) years compared with the entire population (n=261) who had a median age of 49 (22–82) years. The completer analysis on patients with 2 years of continuous data showed improvement of a 50% in pain was achieved by 62% and 65% and a 15-point ODI improvement in 48% and 60% in the oldest quartile and entire population, respectively. HRQoL (EuroQol 5-Dimension) improved from baselines of 0.568 and 0.544 to 0.763 and 0.769 in the oldest quartile and entire population respectively. All age quartiles improved statistically and clinically over baseline.

Conclusions This aggregate analysis of three independent studies provides insight into the performance of restorative neurostimulation in an older population. Patients derived significant and clinically meaningful benefit in disability, pain and HRQoL. When compared with a similarly indicated cohort of younger patients, there were no statistically or clinically significant differences.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Restorative neurostimulation for chronic mechanical low back pain has demonstrated long-term efficacy in multiple publications. Due to the nature of this disease, these publications report the efficacy in a population with a relatively low mean age.

WHAT THIS STUDY ADDS

⇒ By aggregating the data across three separate studies, we were able to identify an older population and examine the effect of restorative neurostimulation in an older age group. We showed in a well-selected older population, that the patients benefit substantially from this therapy, similarly to younger recipients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings should give confidence in the clinical outcomes that can be achieved irrespective of age. Treating physicians should consider this therapy in appropriate older patients.

INTRODUCTION

Etiology of low back pain

Worldwide, low back pain (LBP) is the most common pain condition and the leading cause of years lived with disability.[1] While acute LBP is common and improves spontaneously in most cases, chronic LBP (CLBP), typically defined as LBP persisting longer than 3 months, is associated with substantial economic costs due to both lost productivity and direct medical costs. In the USA, these costs are estimated to be as high as US$296 billion annually.[2–4]

The vast majority of patients with CLBP can be subdivided into neuropathic and nociceptive phenotypes, which have different etiologies as well as management strategies. Neuropathic CLBP frequently does not respond to non-opioid medications but is often managed with spinal surgery and neuromodulation including spinal cord stimulation and dorsal root ganglion stimulation,[5 6] In contrast, mechanical CLBP, which is predominantly nociceptive pain resulting from tissue injury/overload and

Box 1 Homogenized inclusion/exclusion criteria

- ⇒ Considered and adult at time of enrolment (21 USA/18 other).
- ⇒ Evidence of lumbar multifidus muscle dysfunction (radiologic and/or clinical tests).
- ⇒ Failed therapy including pain medications and physical therapy.
- ⇒ Not a candidate for spinal surgery.
- ⇒ Willing and able to provide informed consent.
- ⇒ Able to comply with study protocol.
- ⇒ Able to operate the ReActiv8 system.
- ⇒ Medically suitable for ReActiv8 implant surgery.

inflammation, has even fewer effective treatment options until recently.

The initiation of acute LBP and its subsequent transition to chronic has been attributed in some cases to short-term acute nociceptive stimulus that disrupts back muscle function.[7] Specifically, the multifidus muscle is uniquely affected by this phenomenon with repeated insults eventually resulting in chronic inhibition of this important lumbar spine stabilizer. The resultant inhibition and inflammation lead to further changes to the structure and function of the back muscles including fat and connective tissue infiltration, atrophy, and muscle fiber type changes resulting in reduced strength/endurance. These changes persist through a self-sustaining cycle of injury, inhibition, inflammation, degeneration, disuse and injury. Ultimately, neuroplastic changes occur as an adaptive mechanism to attempt to disrupt this degenerative cascade by recruiting alternative, less well-suited structures for postural stability and motor function. This altered motor control subsequently underpins the recurrence of the acute episodes of LBP with resultant chronicity that ensues in these patients.[7]

The multifidus is uniquely vulnerable to neurological inhibition with resultant degenerative changes.[7] In a healthy spine large muscles such as the longissimus, transverse abdominus and erector spinae are responsible for gross movement through flexion and extension as opposed the multifidus that is functionally important for intersegmental stability.[8 9] However, in the presence of dysfunctional multifidi, the larger muscles attempt to compensate for the deficit in intersegmental stability by applying a compressive load, stiffening the entire lumbar spine.[10 11] These muscles are both structurally and anatomically poorly adapted for this task as they possess fewer slow twitch endurance type fibers required for long duration static contractions and are less medial than the multifidus.[12] This results in abnormal spinal motor control that has the potential to stimulate tissue nociceptors resulting in mechanical pain.[13]

The multifidus muscle has been the target of restorative motor control strategies using physical and exercise therapies for several decades.[14 15] As a front-line conservative approach, this is both clinically rational and variably effective, but due to multiple factors, a significant proportion of patients derive no benefit.[16] After non-responsive physical therapy, the remaining options are usually palliative, including medical management with opioids, steroid injections and ablation procedures. Restorative neuromodulation is both a viable and durable therapy that improves outcomes, reduces pain and improves activity in patients receiving such therapy.[17–24]

LBP in older individuals

LBP is often considered a disease particularly relevant to middle-aged people[25 26] due to the impact this condition has on work performance and productivity, but the prevalence in the older population has not been demonstrated to decrease despite the under-representation of this population in the literature.[27] Data from the US Medicare population show that eligible patients are still major consumers of LBP interventions.[28 29] For example, in 2016, CMS reported over 2.4 million facet joint-related procedures (injection or neurolysis) or 4326 procedures per 100,000 Medicare eligible patients.

Restorative neurostimulation for CLBP

An effective approach for patients with mechanical LBP due to multifidus dysfunction that has been refractory to conservative management is restorative neurostimulation (ReActiv8, Mainstay Medical, Dublin, Ireland). This Food and Drug Administration (FDA)-approved therapy involves direct stimulation of the medial branch of the dorsal ramus of the L2 spinal nerve via implanted leads and an implanted pulse generator. This modality of stimulation, performed twice daily for 30 min, elicits smooth tetanic contractions of the multifidus with a programmable

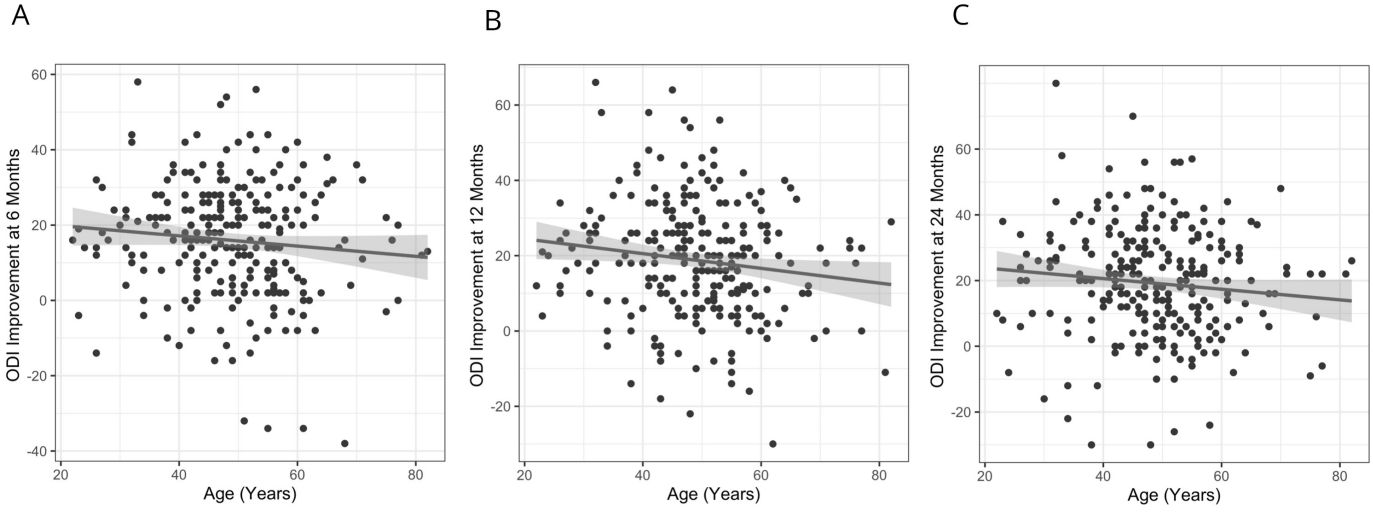

Figure 1 Regression analysis of age versus ODI change at (A) 6 months, (B) 12 months and (C) 24 months demonstrating no significant correlation (R^2_{6m}= 0.009, R^2_{12m}= 0.091, R^2_{24m}= 0.011) (n=261). ODI, Oswestry Disability Index.

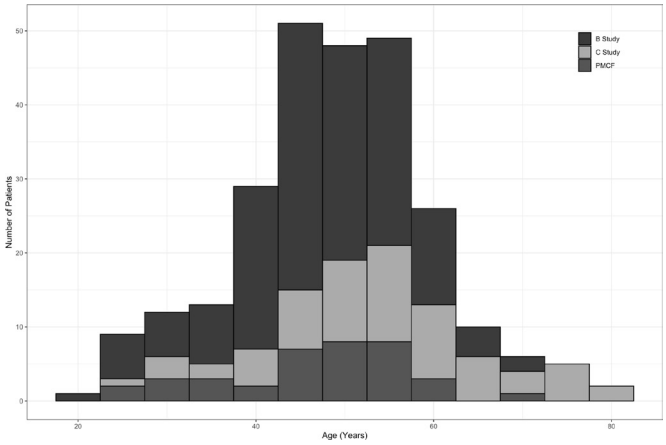

Figure 2 Distribution of patients by age over ReActiv8-B, ReActiv8-C and PMCF.

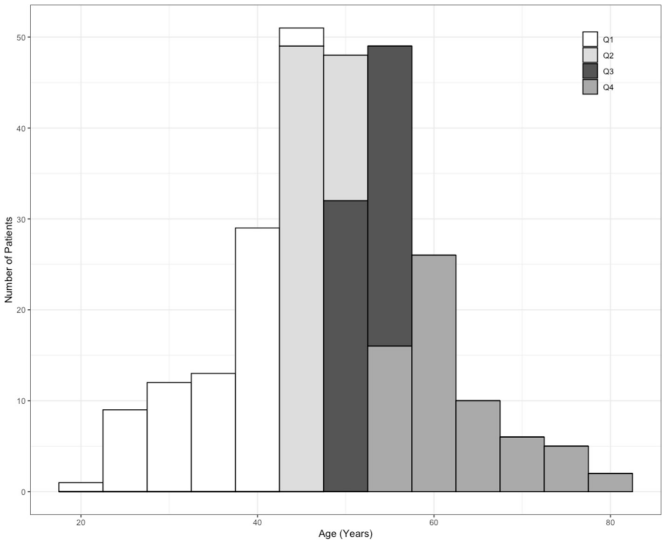

Figure 3 Distribution of age separated into quartiles.

intensity which is intended to improve LBP and disability, via a mechanism impacting motor control.

The efficacy of restorative neurostimulation has been demonstrated in a prospective Investigational Device Exemption (IDE) trial with 3-year published follow-up[18 19] and several multicenter cohort studies with 2, 3[21–23] and 4 years[20] published data, showing a consistent durable effect.

In this paper, we review the available data collected during the ReActiv8 B (NCT02577354), C(NCT03255200) and Post-Market Clinical Follow-up (PMCF) (NCT01985230) clinical studies, to establish outcomes in a cohort of older patients. This patient population remains challenging as they tend to suffer from multiple comorbidities, and a lack of physical activity due to their CLBP can exacerbate other health problems. Therapies that are minimally invasive, restorative, durable and if needed reversible can significantly improve the quality of life in this group.

METHODS

Clinical studies

The data from three clinical studies were aggregated. The ReActiv8 B study[17–19] prospectively followed 204 patients in the USA, the UK Europe and Australia, the ReActiv8-C study followed 87 patients in Germany and the ReActiv8-PMCF prospectively followed 42 patients in the UK.

Each study had slightly differing inclusion and exclusion criteria; the minimum requirements for inclusion are detailed in box 1 and effectively meet the current labeling and regulatory requirements in the country that the study was performed.

Data collection and statistical analysis

Across the three studies, we identified a cohort of 261 patients (all completers) with complete assessments performed during clinic visits preoperatively, and at 6, 12 and 24 months after device activation. Assessments of LBP Numerical Rating Scale (NRS) /Visual Analoge Scale (VAS), disability (Oswestry Disability Index (ODI)), quality of life (EuroQol 5-Dimension 5-Level, EQ-5D-5L) were collected directly from the patients. The surgical procedure and stimulation protocol have been described in the primary publications.[17]

A correlation between patient-reported outcome and age was conducted and showed no significant relationship between age and outcome for the full cohort (figure 1). As such, we identified four equal-sized post hoc cohorts based on age range (n=65) for subsequent comparative analysis.

The primary hypothesis was that there was no difference in ODI or EQ5D between cohorts.

Parametric continuous variables such as patient-reported outcomes were compared with baseline values using repeated measures analysis of variance (ANOVA), with post hoc pairwise testing performed using Bonferroni adjustments. Non-parametric variables were compared using Kruskal-Wallis tests and comparisons of proportion using χ^2 tests. We used an α level of 0.05 for all statistical tests. All statistical analyses were conducted using R V.3.6.1 (https://www.R-project.org).

Therapy response for disability was established as a greater than 15 point improvement in ODI and considered to be a clinically substantial improvement. Differences in proportion of responders were assessed using χ^2. EQ-5D index scores for 2-year completers adjusted for the country were reported as mean compared between cohort and to baseline using repeated measures ANOVA.

Back pain was recorded differently between trials, ReActiv8-B: VAS and ReActiv8-C and PMCF: NRS, which complicated direct comparison of pain measurements between trials. In order to provide consistency among cohorts, we considered: ≥30% reduction in VAS or NRS as moderate improvement, and ≥50% reduction in VAS or NRS as a substantial improvement. Remitters were those with VAS≤2.5 or an NRS≤3, respectively, that reflects the difference between the continuous and ordinal scales, respectively. Responder rates throughout this analysis are presented as the proportion of patients meeting these respective thresholds at each assessment time point.

The ReActiv8-B study is registered on ClinicalTrials.gov with identifier NCT02577354 (first registered October 2015, study

Table 1 Cohort composition by study

Group	B study	C study	PMCF
Q1 (n=65)	45	11	10
Q2 (n=65)	45	9	11
Q3 (n=65)	37	20	8
Q4 (n=65)	28	29	8
Total	155	69	37

start August 2016), ReActiv8 C study on ClinicalTrials.gov with identifier NCT03255200 (first registered August 2017, study start October 2017) and ReActiv8-A- PMCF on ClinicalTrials.gov with identifier NCT01985230 (first registered November 2013, study start February 2013).

RESULTS

Patient cohort and demographics

Cumulatively, the three studies enrolled 333 patients. The patient disposition and reasons for study exit have been documents elsewhere for the ReActiv8-B[30] and PMCF[22] studies and ReActiv8C.[21] Briefly 27/333 (8.1%) were explanted for inadequate symptom relief, 14/333 (4.2%) missed their 2-year visit, 14/333 (4.2%) were lost to follow-up, 7/333 (2.1%) required MRI, 5/333 (1.5%) had an early infection, 1/333 (0.3%) had resolution of their symptoms, and 3/333 (1.1%) were withdrawn for other reasons unrelated to the performance of the device. This yielded the completer cohort of 261 patients included in this analysis (figure 2 and table 1). The overall study cohort illustrated in (figure 3) presented with a mean age (±SE) of 49.1±0.7, the upper cohort with 62.4±0.8 and lower cohort 35.3±0.7. Table 2 shows the aggregated baseline demographics showing no statistical difference between cohorts, besides age.

Disability, pain, and health-related quality of life

Statistically significant improvements in disability (ODI) and quality of life (EQ-5D-5L) were seen at all assessment time points compared with baseline (figure 4). There were no statistically significant differences between any cohort in mean ODI or Mean EQ-5D index at particular times. A responder rate analysis (table 3) showed that response rates for a reduction in pain (VAS/NRS) and ODI were similar between groups and not statistically significantly different by the 2-year time point.

Table 2 Baseline demographics

	Q1 (n=66)	Q2 (n=65)	Q3 (n=65)	Q4 (n=65)	Total (n=261)	P value
Age mean	35.3	46.2	52.6	62.4	49.1	<0.001*
(SE)	(0.7)	(0.2)	(0.3)	(0.8)	(0.7)	
Age median	37	47	53	60	49	
(Range)	(22–43)	43–49	49–56	56–82	22–82	
BMI mean	28.2	29.3	28.5	27.9	28.4	0.34*
(SE)	(0.6)	(0.6)	(0.5)	(0.6)	(0.6)	
Sex % female	47.0	46.2	47.7	61.5	50.6	0.24†
Baseline ODI mean	39.4	42.6	41.5	38.9	40.6	0.29*
(SE)	(1.6)	(1.4)	(1.6)	(1.6)	(0.8)	
Baseline EQ-5D mean	0.552	0.523	0.532	0.568	0.544	0.64*
(SE)	0.023	0.028	0.027	0.027	0.013	

*Significance tested using one way ANOVA.
†Significance tested using χ^2.
ANOVA, analysis of variance; BMI, body mass index; EQ-5D, EuroQol 5-Dimension; ODI, Oswestry Disability Index.

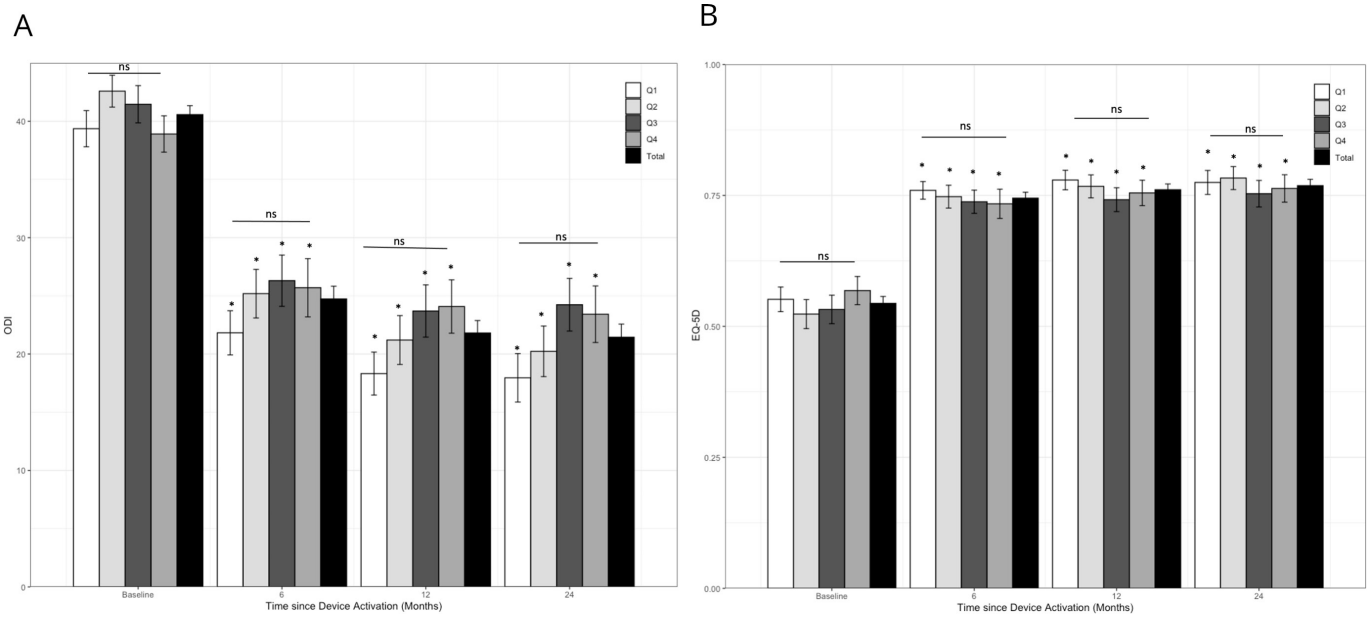

Figure 4 Two-year completer analysis of the cohorts (A) ODI and (B) EQ-5D-5L showing statistically significant improvements over baseline at all time points for each quartile (*p<0.01 between age quartiles and baseline for that quartile). There were no statistically significant differences between any of the quartiles at each time point (ns). EQ-5D-5L, EuroQol 5-Dimension 5-Level; ODI, Oswestry Disability Index.

HRQoL (EuroQol 5-Dimension) improved from baselines of 0.568 and 0.544 to 0.763 and 0.769 in the oldest quartile and entire population respectively. We performed an analysis of EQ-5D across the reported domains to examine if older patients derived benefit differently to the younger group. Notably, table 4 shows that 26% of the older cohort reported severe impact to mobility compared with 12% of the lower cohort and by 2 years this had reduced to 8% and 3%, respectively. The other four domains of the EQ5D were not different between cohorts.

DISCUSSION

This paper presents an aggregate assessment of data from three ongoing clinical studies, to identify differences across age groups. Restorative neurostimulation is indicated for patients with refractory mechanical CLBP secondary to multifidus muscle dysfunction and no surgically indicated pathology seen on MRI. Consistent with the prevailing perception that LBP is a disease that mostly affects adult of working age with the reported prevalence decreasing around the 6th decade, the mean age of all patients included in all three studies was 49 years. However, back pain is still among the four most commonly reported symptoms in the elderly[31 32] and a recent systematic review has challenged this thinking and suggested that prevalence of severe back pain increases with age while benign and mixed back pain becomes less common.[33] As such we were able to identify a older cohort of 65 patients treated in these studies with a mean age of 62 years.

We hypothesized that patients in this age group would receive similar benefit to the overall group. As follow-up is ongoing in some of these studies, we performed an analysis of currently available data across all time points and a completer analysis of those patients with a minimum of 2 years follow-up.

At 2-year follow-up, a substantial (≥15 points) relief of spine-related disability was achieved in 48% of the older patient cohort compared with 60% from all completers and there was no significant difference in responder rates ($p=0.1\,\chi^2$). Pain reduction (50% pain reduction) was 62% vs 65% for the oldest and complete data set, respectively, and pain remitter rates (55% vs 59%) were also similar between cohorts suggesting the viability and durability of restorative neurostimulation in a well-selected older population.

Table 3 Responder rate—back pain (VAS/NRS) and ODI across cohorts

		30% Δ Pain	50% Δ Pain	Remitter*	15 Point Δ ODI
Q1	6 months	67%	48%	36%	64%
	12 months	80%	68%	56%	67%
	24 months	86%	71%	65%	68%
Q2	6 months	72%	54%	43%	58%
	12 months	48%	48%	48%	68%
	24 months	83%	74%	69%	74%
Q3	6 months	63%	54%	42%	46%
	12 months	68%	58%	55%	60%
	24 months	65%	52%	48%	49%
Q4	6 months	63%	49%	45%	46%
	12 months	65%	57%	48%	51%
	24 months	75%	62%	55%	48%
All completers	6 months	66%	51%	41%	54%
	12 months	69%	60%	52%	61%
	24 months	77%	65%	59%	60%

*Remitter defined as NRS≤2.5 on VAS or ≤3 on NRS.
ODI, Oswestry Disability Index.

Table 4 Response by EQ-5D dimension in 2-year completers across cohorts

	Severe problems baseline				Severe problems 2 years			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Mobility	12%	14%	18%	26%	3%	2%	6%	8%
Self-care	5%	3%	5%	2%	2%	2%	0%	2%
Activities	21%	35%	38%	22%	6%	6%	11%	8%
Pain	48%	46%	51%	42%	9%	5%	9%	9%
Anxiety	5%	3%	8%	3%	6%	0%	3%	3%

EQ-5D, EuroQol 5-Dimension.

Health-related quality of life (EQ-5D-5L index values) showed no statistically significant difference between all cohorts. However, when the response in each domain was assessed and ranked between cohorts (table 4), we observed some interesting differences. In particular, the strongest benefit in the older cohort was seen as improvements in pain activities and mobility while the dominant improvement for the younger cohort manifested in improvements in pain and usual activities. We hypothesize that this may be due to changes in preferences between different functional behaviors in the different age categories. Consistent with this hypothesis, we observed that the least benefit was derived by both groups in anxiety and self-care.

CONCLUSION

This is the first aggregate analysis combining outcome data from three independent studies with 2-year follow-up that provides insight into the performance of restorative neurostimulation in an older population who are suffering from CLBP due to multifidus dysfunction. In all cases, patients derived significant and clinically meaningful benefit in disability, health-related quality of life and pain irrespective of age. When compared, cohorts of patients with similar inclusion/exclusion criteria, only separated by age, show no statistically or clinically significant between-group differences. These findings suggest that when restorative neurostimulation is applied to older patients with a history of persistent mechanical LBP and signs of multifidus dysfunction the likelihood of meaningful improvement is consistent with established published outcomes. Further studies should focus on the use of restorative neurostimulation in older patients suffering from mechanical CLBP as a therapy to address this underlying condition as it appears to demonstrate statistically significant reduction in pain and increase in activity in this population with lasting durability.

Limitations of this study include the small cohort of patients identified in the upper age group and the retrospective identification of the cohorts. Pain was collected differently between studies enabling a responder rate analysis only and no direct assessment of mean change from baseline. The inclusion and exclusion criteria for the various studies used in this analysis did vary slightly, however, the identification of these patients was achieved by applying the minimum requirements for inclusion for all patients.

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Contributors All authors ran their relevant studies ST (PMCF), CJG(B Study) MA(C Study), collected data and reviewed the final version of the manuscript. CJG and AA designed the analysis and constructed the manuscript, AA is responsible for the publication and the decision to publish.

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Competing interests AA reports consulting fees and honoraria from Nevro Corp and Mainstay Medical MA reports consulting fees and honoraria from Mainstay Medical. ST reports Consulting fees and honoraria from Boston Scientific, Mainstay Medical and Saluda Medical and advisory board membership from Galvani Bioelectronics, Saluda Medical. CJG reports consulting fees and honoraria from Mainstay Medical, Saluda, Persica and Iliad Lifesciences and Stock options from Mainstay Medical, provides expert testimony, Data Safety Monitoring Board for Brixton and Agnovos, Director at Large of The International Neuromodulation Society, Finance Committee of the North American Neuromodulation Society and Board Member of the Boston Pain Society and is Editor-in-Chief of Pain Practice.

Patient consent for publication Not applicable.

Ethics approval All studies were approved by the relevant ethical review process, ReActiv8-B; Western Institutional Review Board PROTOCOL NUM: 950057 and local institutional review board or ethics committee approval was obtained at each site, ReActiv8 PMCF; NHS Health Research Authority North East—York Research Ethics Committee IRA's project ID number 149412 ReActiv8-C; Schleswig Holstein Ethics Committee endorsing the decision of the North Rhine Medical Association Ethics Committee

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Request should be made to the sponsor of the trials.

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