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Effect of Restorative Neurostimulation on Major Drivers of Chronic Low Back Pain Economic Impact

Christopher Shaffrey, MD*
Christopher Gilligan, MD, MBA [‡]

*Department of Neurological Surgery, Duke University Medical Center, Durham, North Carolina, USA; ‡Division of Pain Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Chestnut Hill, Massachusetts, USA

Correspondence:
Christopher Shaffrey, MD,
Departments of Orthopaedic and Neurological Surgery,
Box DUMC 3077,
Durham, NC 27710-4000, USA.
Email: christopher.shaffrey@duke.edu

Christopher Gilligan, MD, MBA,
Brigham and Women's Hospital,
Brigham and Women's Spine Center,
Department of Anaesthesia,
Harvard Medical School,
75 Francis St,
Boston, MA 02115, USA.
Email: cgilligan@bwh.harvard.edu

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BACKGROUND: High-impact chronic low back pain (CLBP) correlates with high healthcare resource utilization. Therapies that can alter impact status may provide beneficial long-term economic benefits. An implantable restorative neurostimulation system (ReActiv8, Mainstay Medical) designed to over-ride multifidus inhibition to facilitate motor control restoration, thereby resolving mechanical low back pain symptoms, has shown significant durable clinical effects in moderately and severely impacted patients.

OBJECTIVE: To examine changes in high-impact chronic low back pain in patients treated with restorative neurostimulation at 2 years.

METHODS: ReActiv8-B is a prospective, international, multicenter trial to evaluate the safety and efficacy of restorative neurostimulation in patients with intractable CLBP and no prior surgery. For this longitudinal subanalysis, patients were stratified into low-, moderate-, and high-impact CLBP categories using the US Department of Health and Human Services definition comprising pain intensity, duration, and impact on work, self-care, and daily activities.

RESULTS: Of 2-year completers (n = 146), 71% had high-impact CLBP at baseline and this proportion reduced to 10%, with 85% reporting no or low impact. This corresponds with measurements of HRQoL returning to near-population norms.

CONCLUSION: In addition to clinically meaningful improvements in pain and function with long-term durability, the overwhelming majority of patients transitioned from a high- to a no- or low-impact CLBP state. This is typically associated with significantly lower healthcare-utilization levels. The of recovery trajectory is consistent with a restorative mechanism of action and suggests that over the long term, the improvement in these health states will be maintained.

KEY WORDS: High-impact pain, Paraspinal muscles, Healthcare utilization, Low back pain, Restorative stimulation

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Chronic low back pain (CLBP) is the leading cause of years lived with disability worldwide and often a determinant for chronic opioid use.[1-3] In the United States, direct healthcare spending on low back and neck pain is estimated at $87.6 billion, with 60.5% of this spending in ambulatory care.[4] Patients with CLBP are frequent users of healthcare resources, reporting substantially higher average pain intensity, and describing higher pain-related interference with life and work-related activities.[5,6]

ABBREVIATIONS: CLBP, chronic low back pain; **EQ-5D-5L,** EuroQol 5 dimensions 5 level; **ISR,** insufficient symptom relief; **LBP,** low back pain; **LTF,** lost to follow-up; **ODI,** Oswestry Disability Index.

CLBP represents the second most common pain condition contributing to lost productive time at work,[7] either as diminished work capacity, paid absenteeism, or permanent exit from the workforce.[8] Indirect costs including disability benefits and days of work missed are estimated to be as high as $624.8 billion in the United States alone.[9]

Pain impact is an important construct that correlates with both functional and economic outcomes. High-impact pain has been defined by the US Department of Health and Human Services as pain that has been present on most days for 6 months or more that "is associated with substantial restriction of participation in work, social, and self-care activities."[10] Work function and employment is a major determinant of pain impact, and patients are more likely to seek interventional care when work performance is affected.[11] Thus, there is a strong relationship between pain, work performance, and direct and indirect economic consequences. When applied to specifically CLBP, high-impact pain is also tied to continued use of high-cost interventions, with estimates of overall direct healthcare costs of approximately $14 000 pa.[12]

RESTORATIVE NEUROSTIMULATION FOR CHRONIC LOW BACK PAIN

Therapies that deliver durable benefit in both pain and dysfunction reduce downstream direct healthcare costs and facilitate a reduction in indirect societal costs such as absenteeism and presenteeism. One such therapy when applied to the treatment of CLBP is restorative neurostimulation (ReActiv8, Mainstay Medical) of the medial branch of the dorsal ramus intended to restore motor control to the multifidus muscle, a key stabilizer of the lumbar spine.

Conservative approaches such as motor control physical therapy have been used to attempt to restore motor control with varying effect; however, there remain a large cohort of patients who have pain and dysfunction that is refectory to conservative management.[13]

Restorative neurostimulation is intended for patients with CLBP with failed conservative management and have few viable therapeutic options remaining. The procedure and long-term clinical efficacy have been described elsewhere.[14,15] Here, we present an analysis of patients from this trial to establish whether the long-term clinical benefit also results in an improvement in the major drivers of economic impact of long-standing CLBP.

METHODS

Data for this secondary analysis were obtained from the 156 patients completing 2-year follow-up enrolled at 26 multidisciplinary centers in the United States, Australia, and Europe as part of the ReActiv8-B randomized, sham-controlled, double-blind pivotal trial to evaluate the safety and efficacy of the ReActiv8 implantable restorative neurostimulation system (Mainstay Medical) in patients with refractory mechanical CLBP and confirmed multifidus muscle dysfunction. The primary outcomes, intent-to-treat analysis and 2-year clinical follow-up, have been described elsewhere.[14,15] A cohort of 156 patients were enrolled at the 2-year follow-up; we report on a final cohort of 146 because 10 patients were missing relevant data at various time points. The purpose of this secondary analysis was to analyze the effect of restorative neurostimulation on known drivers of direct and indirect long-term healthcare costs.

The conduct of the trial complied with the Food and Drug Administration regulations, ISO 14155, International Conference on Harmonization, and the Declaration of Helsinki. Local institutional review board or ethics committee approval was obtained at each site, and all participants provided written informed consent. The study is registered on clinicaltrials.gov with identifier NCT02577354.

Study Population

This trial examined the effect of restorative neurostimulation on patients with disabling mechanical CLBP treated at centers in the United States, Europe, and Australia. Participants were age 22 to 75 years with pain on at least 50% of days in the prior year, which persisted despite >90 days of medical management, including medication and at least one past or new attempt of physical therapy, pain of ≥6.0 and ≤9.0 on the visual analog scale (VAS), and Oswestry Disability Index (ODI) of ≥21 and ≤60 points. Evidence of impaired motor control of the multifidus muscle and consequent lumbar segmental instability was required through a positive prone instability test.[16]

Exclusion criteria were prior fusion, other spine surgery below T8, pathology amenable to surgery, dominant neurological pain, Cobb angle >25°, comorbid pain conditions, rhizotomy below T8 in the previous year, anesthetic injection below T8 in the past 30 days, baseline daily opioid consumption >120 mg MME, and evidence of an active disruptive psychological or psychiatric disorder.

The demographics of the cohort are detailed in Table 1. For the purpose of this analysis, we examined the long-term treatment outcomes at the 1- and 2-year follow-ups. This was undertaken as part of the open-label prospective follow-up after patients crossed over from sham to active therapy. As such, there is no control group available for these long-term outcomes.

PATIENT-REPORTED OUTCOMES

Pain, disability, and health-related quality of life were assessed longitudinally using VAS,[17] ODI,[18] and the EuroQol 5 dimensions 5 levels (EQ-5D-5L).[19]

Employment Impact

To minimize interference from secondary gain, patients with active legal or compensation claims were excluded from the trial, resulting in a higher employment participation than otherwise expected. Therefore, to assess the interference of low back pain on work, at each follow-up visit, work status, ability to work, work

TABLE 1. Patient Baseline Demographics Stratified by Impact

	Median age, years (range)	Sex (% female)	Body mass index, mean ± SD	Median pain duration, years (range)	Previous rhizotomy (%)	Smoker (%)
All (*n* = 146)	47.0 (22.0-71.0)	51	27.9 ± 3.9	13.0 (0.6-44.1)	11	26
High (*n* = 103)	47.0 (22.0-71.0)	48	27.9 ± 3.8	12.9 (0.6-41.3)	12	25
Moderate (*n* = 39)	49.0 (23.0-63.0)	59	28.1 ± 4.1	13.1 (1.3-44.1)	8	26
Low (*n* = 4)	51.5 (45.0-58.0)	50%	28.9 ± 4.0	12.3 (5.2-30.0)	25	50

TABLE 2. Structured Interview Questions Specific to Employment Status
1. Has your work status changed?
If yes, how:
• Full-time employment
• Part-time or seasonal employment
• Part-time instead of full-time ***due to back pain***,
• Not working ***due to back pain***
• Not working for reasons other than back pain, (eg, retired, student, unemployed, etc.)
2. Assume that your ability to do your work at its best has a value of 10 points. How many points would you give your current ability to work?
• 10 • 9 • 8 • 7 • 6 • 5 • 4 • 3 • 2 • 1 • 0
3. How much of a problem is your chronic low back pain for your current job today?
• Low back pain ***does not*** prevent me from doing my job normally.
• Because of low back pain, I ***sometimes*** slow down work pace or change work methods.
• Because of low back pain, I ***always*** slow down work pace or change work methods.
• Because of low back pain, I am working part-time.
• Because of low back pain, I am ***not*** working at all.
4. Since the previous visit, how many days (>6 h) have you been off work because of low back pain?
• None
• 1-9 d
• 10-24 d
• 25-99 d
• 100+ d

problems, and work absence were assessed by a structured interview. The interview questions are included in Table 2.

The following operational definitions were applied:

Presenteeism was assessed as the "*ability to do your work at its best*" (Question 2) stratified for work status (Question 1).

Absenteeism was assessed as the number of days off work because of low back pain (Question 4).

Pain Impact Stratification

Patients were stratified for subanalysis into 3 categories to analyze the effect that pain impact had on clinical outcomes, and to be used as an estimation of drivers of healthcare utilization. Using the definition proposed by the US Department of Health and Human Services, we stratified patients to high-, medium-, and low-impact CLBP. A patient with high-impact CLBP was someone with at least 6 months of severe chronic pain and impacted in at least 2 of the 3 domains: work participation, self-care, and usual activities (Table 3). A moderate impact was defined as at least 6 months of severe chronic pain and restriction in 1 of 3 domains. Low impact was defined as someone who had at least 6 months of chronic pain but no impact in any domain, or pain no longer defined as severe (ie, VAS <4). The impact classification system is presented in Table 4.

TABLE 3. Domains Used to Stratify Patients Into High-, Medium-, and Low-Impact CLBP Categories
How much of a problem is your chronic low back pain for your current job today?
• **Not impacted** Low back pain ***does not*** prevent me from doing my job normally.
• **Impacted** Because of low back pain, I ***sometimes*** slow down work pace or change work methods.
• **Impacted** Because of low back pain, I ***always*** slow down work pace or change work methods.
• **Impacted** Because of low back pain, I am working part-time.
• **Impacted** Because of low back pain, I am ***not*** working at all.
Self-care
• **Not impacted** I have no problems washing or dressing myself
• **Not impacted** I have slight problems washing or dressing myself
• **Impacted** I have moderate problems washing or dressing myself
• **Impacted** I have severe problems washing or dressing myself
• **Impacted** I am unable to wash or dress myself
Usual activities (eg, work, study, housework, family or leisure activities)
• **Not impacted** I have no problems doing my usual activities
• **Not impacted** I have slight problems doing my usual activities
• **Impacted** I have moderate problems doing my usual activities
• **Impacted** I have severe problems doing my usual activities
• **Impacted** I am unable to do my usual activities

Self-care and usual activities were captured from EQ-5D-5L responses.

TABLE 4. Impact Classification

		Restriction in Activities of daily living		
	Pain duration/severity	Employment impact	Self-care impact	Usual activities' impact
High impact	✓	Impact in 2 or more domains		
Moderate impact	✓	Impact in 1 domain		
Low impact	✓	Impact in no domains		
Low impact	Pain severity <4	Impact in 1 domain		

Data Analysis

Patient-reported outcomes were compared with baseline using repeated-measures analysis of variance with Bonferroni correction for multiple comparisons conducted in R version 3.6.1 and RStudio version 1.2.5019.

RESULTS

Unstratified Demographics and Outcomes

The baseline demographics of the study cohort (n = 146) are shown in Table 4. Patients in this subanalysis were relatively young, with a median age of 47 years, but had an extensive history of low back pain with a median of over 88% reporting symptomatic pain on greater than 90% of days in the previous year. The clinical outcomes of the ReActiv8-B trial have been discussed in detail elsewhere,[14,15] and the disposition of patients from this trial is summarized in Table 5. This analysis of 2-year clinical outcomes measured the impact of missingness of data using a highly conservative approach to imputation, mixed-methods repeated-measures comparison.[15] This analysis showed only minor differences between the imputed values for VAS, ODI, and EQ-5D and those for the completers, justifying the use of a completer cohort for this subanalysis. Between baseline and 2 years, 18 (8.8%) exited the study due to insufficient pain relief, 7 (3.4%) were lost to follow-up, 5 (2.5%) were explanted due to infection, 6 (2.9%) required an explant due to MRI conditionality, 1 (0.5%) felt their symptoms had resolved to the point that the device was no longer required, and 1 (0.5%) moved country and could no longer participate in follow-up appointments. In addition, 10 patients had incomplete data meaning rendering them unable to be included in this subanalysis.

Baseline demographics were equivalent between completers at year 2 and the subanalysis cohort, and mean low back pain VAS had improved from 7.2 ± 0.1 at baseline to 2.7 ± 0.2 at year 1 ($P < .001$) and 2.3 ± 0.2 at year 2 ($P < .001$), which is also comparable with the previously reported ITT and imputed outcomes.

Impact-Stratified Demographics and Outcomes

Patients were stratified into the high-, moderate-, or low-impact CLBP categories according to the definition in Table 3. Of these, 103 (70.5%) patients met the definition of high-, 39 (26.7%) moderate-, and 4 (2.7%) low-impact CLBP at baseline. Impact-stratified demographics (Table 1) and patient-reported outcomes (Table 6) show patients were consistent across groups for demographics, mean VAS, and ODI; however, the high-impact group reported a significantly worse EQ-5D at baseline.

At 2 years, 124 (84.9%) patients were classified as low impact. Of the 103 high-impact patients, 85 (82.5%) reported low impact, 5 (4.8%) moderate impact, and only 13 (12.6%) remained unchanged. Figure 1 shows the impact class transitions from baseline to 2 years.

TABLE 5. Patient Disposition Over the 120-Day Crossover, 1 and 2 Years, and Current Subanalysis

	Baseline- crossover[14]	Crossover - 12 mo[14]	12-24 mo[15]	Subanalysis cohort	Total
ISR	0	8	10	—	18 (8.8%)
LTF	0	3	4	—	7 (3.4%)
Infection	0	5	0	—	5 (2.5%)
MRI	0	4	2	—	6 (2.9%)
Resolution	0	0	1	—	1 (0.5%)
Other	0	0	1	—	1 (0.5%)
Missed visit	3	8	10	—	
Total exited	0	20	38	—	38 (18.6%)
Incomplete data				10	
Available for analysis	**201**	**176**	**156**	**146**	

ISR, insufficient symptom relief; LTF, lost to follow-up.
MRI—explant required due to MRI compatibility; other—patient moved outside the physician's coverage area.

TABLE 6. Outcomes in Each Impact Class, Mean ± (SD)

	B-study 2 y imputation[15] (n = 204)	All (n = 146)	High (n = 103)	Moderate (n = 39)	Low (n = 4)
VAS					
Baseline	7.3 ± 0.05	7.2 ± 0.1	7.4 ± 0.1	6.9 ± 0.1	6.8 ± 0.4
Year 1	3.4 ± 0.2	2.7 ± 0.2	2.9 ± 0.3	2.3 ± 0.3	2.3 ± 1.9
Year 2	3.1 ± 0.2	2.3 ± 0.2	2.4 ± 0.2	2.0 ± 0.3	2.5 ± 2.0
ODI					
Baseline	39.1 ± 0.7	38.8 ± 0.8	41.3 ± 1.0	33.0 ± 1.1	29.5 ± 1.9
Year 1	20.7 ± 1.0	17.1 ± 1.1	18.5 ± 1.4	13.6 ± 1.8	14.5 ± 8.7
Year 2	20.2 ± 1.0	16.5 ± 1.1	17.5 ± 1.5	13.4 ± 1.9	21.0 ± 12.4
EQ-5D					
Baseline	0.585 ± 0.012	0.586 ± 0.015	0.535 ± 0.017	0.706 ± 0.018	0.716 ± 0.064
Year 1	0.762 ± 0.011	0.802 ± 0.011	0.786 ± 0.014	0.838 ± 0.017	0.861 ± 0.086
Year 2	0.768 ± 0.011	0.808 ± 0.013	0.799 ± 0.017	0.842 ± 0.018	0.728 ± 0.097

EQ-5D, EuroQol 5 dimensions; ODI, Oswestry Disability Index; VAS, visual analog scale.

Work Impact

Presenteeism and Absenteeism

Presenteeism or a reduced ability to perform occupational tasks because of back pain was captured as *impact on work status* (Table 3 Question 3) and is shown in Figure 2. At baseline, 9/146 (6.2%) patients reported no work problems due to low back pain, improving to 67/146 (45.9%) and 73/146(50.1%) patients after 1 and 2 years, respectively. The proportion of patients reporting "always slow down work pace or change work methods" due to their low back pain was 62/146 (42.5%) at baseline and was reduced to 19/146 (13.0%) after 2 years. A second measure of impact on work performance was a self-assessment "*ability to do your work at its best*" collected on a 10-point numerical rating scale. Figure 3 shows the distribution of scores in this cohort and shows an improvement in mean work ability score from 6.0 ± 0.2 at baseline to 7.8 ± 0.2, 8.1 ± 0.2, and 8.3 ± 0.2 at 6 months, 1 year, and 2 years, respectively. The proportion of patients rating their work ability as a 9 or 10 was 87/146 (60%) at 2 years compared with 21/146 (14%) at baseline. Treatment with restorative neurostimulation also resulted in reduced absenteeism (Figure 4), showing that 88% did not require any time off work due to low back pain by 2 years of therapy.

DISCUSSION

Most of the societal and economic burden of low back pain is generated by those most affected in terms of disabling impact. The goal of this analysis was to stratify the current cohort of patients with low back pain based on their level of pain impact and to longitudinally

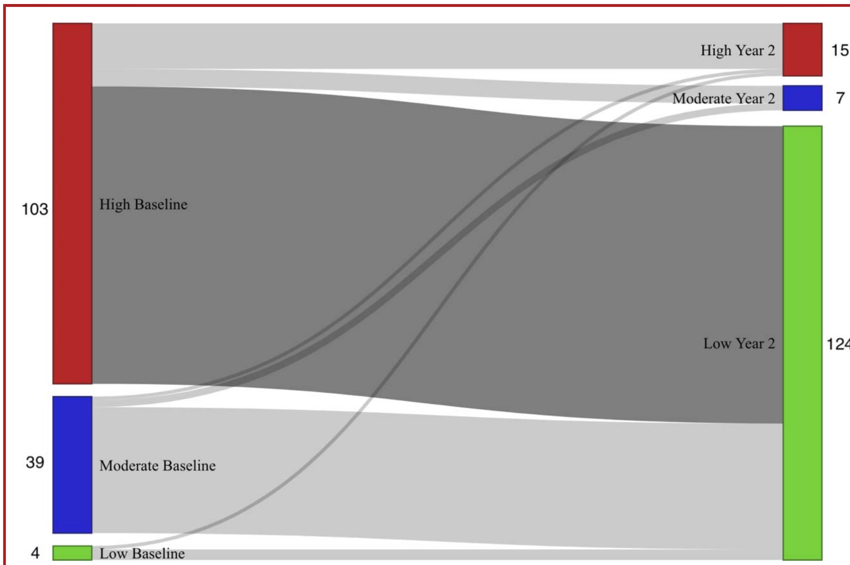

FIGURE 1. *Transition from impact classes in 2-year completers (n = 146).*

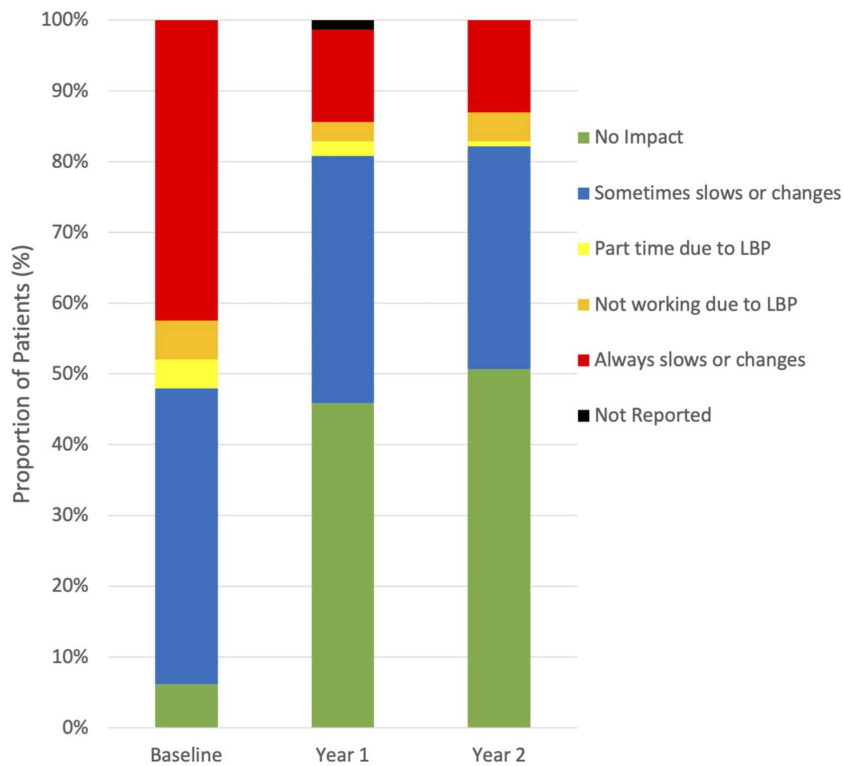

FIGURE 2. *Patient-reported impact of chronic low back pain on work status (responses to structured interview question 3) at baseline and study follow-up visits for 2-year completers (n = 146). LBP, low back pain.*

assess their transition to lower impact states when treated with restorative neurostimulation as this transition has a strong correlation with a reduction healthcare resource utilization.[12,20]

The longitudinal follow-up of the ReActiv8-B clinical trial has continued to demonstrate durable and clinically meaningful results in the past 2 years.[15] When stratified for impact, 72% and 60% of the high-impact cohort experienced a 50% VAS or 20 ODI point reduction, respectively, and 78% had a 50% VAS and/or 20-point ODI reduction.

Pain and disability (ie, activity limitations) are interdependent symptoms of the underlying etiology and codeterminants of a patient's well-being or health state.[21] The ability to recover from a high-impact pain state is dependent on the reduction in reported pain, the improvement in disability, and the self-efficacy that drives the relationship between the two.[22,23]

Direct Costs

There is a disproportionate distribution of healthcare resource utilization between mild and highly impacted patients, such as those included in this study. In a recent analysis of healthcare costs of nonsurgical treatment of refractory CLBP, the median total cost per patient per year was $6590; however, the most highly impacted 25% of patients incurred over $13 000.[20] Similarly, a second cost analysis found that 45% of patients with intractable chronic spinal pain were considered to be highly impacted and incurred an average overall cost of $14 661 per patient per year.[12] In a recent longitudinal analysis of over 6000 patients with CLBP, pain severity and disability were found to be significantly associated with societal and healthcare costs, highlighting the considerable cost-savings that may be gained by treatments that provide clinically relevant improvements in pain and disability.[24] The Medicare National Average allowed amounts for implantation of this device in a hospital outpatient department, falls under Ambulatory Payment Classification 5464, Level 4 Neurostimulator and Related Procedures. As of 2022 this attracts a facility payment of $20 913, suggesting cost effectiveness is achieved rapidly.

The impact classification presented here is not a direct measure of healthcare resource utilization, rather a proxy to identify the likelihood that an individual will incur significant costs. Patients with high-impact pain have demonstrated much higher utilization compared with patients with low-impact pain, and these classifications correlate with other literature[25-28] that associate care-seeking behavior with limitations in activities of daily living, pain severity, and pain frequency. The reliable resolution of pain, the transition from high disability to low disability, and conversion from high- to a low-impact pain state can be expected to drive significantly lower utilization of healthcare resources. In this study 95/111 (85.6%) patients initially presenting with high-impact

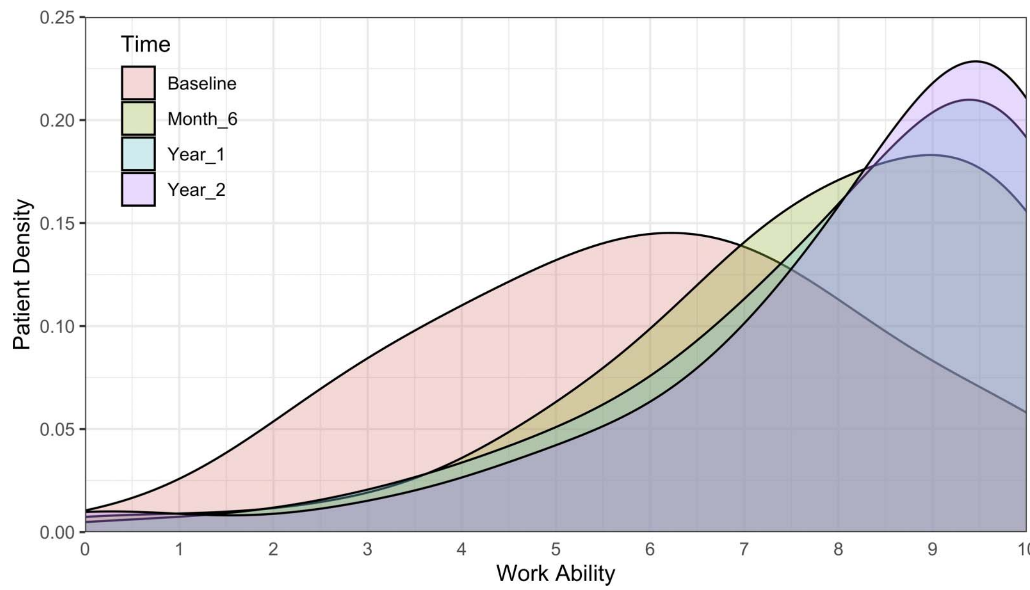

FIGURE 3. *Patient-reported impact of chronic low back pain on their ability to perform work activities (responses to structured interview question 2) at baseline and study follow-up visits (n = 146). LBP, low back pain.*

pain, and 36/38 (94.7%) patients initially presenting with moderate-impact pain reported low-impact pain after 2 years of treatment with restorative neurostimulation.

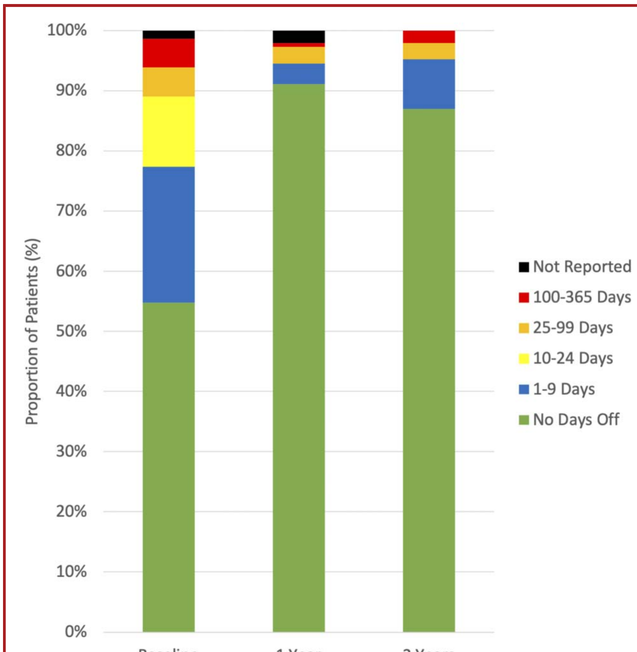

FIGURE 4. *Patient reported days off work (in the previous year) due to chronic low back pain (responses to structured interview question 4) at baseline and at 24 months after device activation (n = 146). LBP, low back pain.*

Indirect Costs

Absenteeism and presenteeism represent a significant productivity deficit for most employers and are a major driver of the indirect economic consequences of CLBP. The results of an American Productivity Audit[29] conducted in 2003 demonstrated that health-related lost productive time was costing employers approximately $225.8 billion per year. The bulk of this (71%) was a result of reduced performance at work, not work absence. Pain-related lost productive time accounted for 27% of the total cost.[7] Specifically, back pain–related productivity costs related to presenteeism were double the costs related to absenteeism.

The data collected on absenteeism and presenteeism in this trial demonstrate that restorative neurostimulation impacts the number of workdays missed and patients' self-rated ability to perform their work functions. The proportion of patients not missing work because of their low back pain increased from 50% at baseline to 88% after year 2 (Figure 4).

There was also a significant improvement in self-reported mean work ability. Full-time and part-time employees reported an increase in their work ability score. Mean change in scores from baseline to 1 and 2 years after activation showed statistically significant improvements in this patient group, as well as for patients who reported reduced work performance because of back pain, and patients not working because of back pain.

Limitations

This analysis demonstrates the impact to drivers of direct and indirect economic costs associated with restorative neurostimulation for CLBP. A limitation of this approach is that it only indirectly assessed the economic impact. In addition, presenteeism was assessed by patient self-report and may have inherent bias; occupation type was also not accounted for. There is also potential for selection bias in the identification of the high-impact cohort, but this definition is consistent with current descriptions of this pain phenotype. The absence of a long-term control group makes it difficult to definitively account for spontaneous recovery, although this is less likely to occur in patients presenting with extensive histories of CLBP that has already manifested as functional and occupational impairments. The strength of this analysis lies in the robust clinical data from the original study.

CONCLUSION

The patient population was overwhelmingly identified as highly impacted (70.5% high- and 26.7% moderate-impact), and the application of the therapy consistently reduced the impact on these patients to a low state at 2-year follow-up (84.9% low-impact). The correlation between pain impact and direct healthcare resource utilization is strong, and the magnitude of this effect suggests significant direct and indirect savings from the application of this therapy to these patients. In addition to direct drivers of economic impact, we show that indirect drivers such as presenteeism and absenteeism are significantly improved.

Thus, the ReActiv8-B study at the 2-year mark demonstrated durability of effect related to pain and disability, but also pain impact, presenteeism, and absenteeism were improved and durable over that same 2-year period. As direct and indirect costs disproportionally increase with impact level, this stratification is expected to correlate with an increase in overall cost-effectiveness. This is a patient population with very limited therapeutic options other than ongoing palliative management. The introduction of a safe, durable restorative therapy that reliably alters the impact trajectory of these patients will deliver downstream clinical, direct and indirect economic benefit.

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Disclosures

Dr Shaffrey reports no personal conflicts related to this study and reports unrelated royalties: Medtronic, Nuvasive, and Zimmer Biomet; stock ownership: Nuvasive; consulting: Biomet Spine, Medtronic, Nuvasive, and Stryker; speaking and/or teaching arrangements: Medtronic and Nuvasive; board of directors: Spine Deformity; scientific advisory board/other office: AANS, Cervical Spine Research Society, and Spine; research support (investigator salary, staff/materials): DePuy, Globus Medical, Medtronic, and Neurosurgery RRC. Dr Gilligan reports personal fees from Mainstay Medical, Saluda, Persica, and Iliad Lifesciences, stock options in Mainstay Medical, and expert witness testimony fees.

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