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REVIEW

Pain Relief and Safety Outcomes with Cervical 10 kHz Spinal Cord Stimulation: Systematic Literature Review and Meta-analysis

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ABSTRACT

Background: Chronic pain in head, neck, shoulders and upper limbs is debilitating, and patients usually rely on pain medications or surgery to manage their symptoms. However, given the current opioid epidemic, non-pharmacological interventions that reduce pain, such as spinal cord stimulation (SCS), are needed. The purpose of this study was to review the evidence on paresthesia-free 10 kHz SCS therapy for neck and upper extremity pain.

Methods: Systematic literature search was performed for studies reporting outcomes for cervical 10 kHz SCS using date limits from May 2008 to November 2020. The study results were analyzed and described qualitatively. Additionally, when feasible, meta-analyses of the outcome data, with 95% confidence intervals (CIs), were conducted using both the fixed-effects (FE) and random-effects (RE) models.

Results: A total of 15 studies were eligible for inclusion. The proportion of patients who achieved ≥ 50% pain reduction was 83% (95% CI 77–89%) in both the FE and RE models. The proportion of patients who reduced/eliminated their opioid consumption was 39% (95% CI 31–46%) in the FE model and 39% (95% CI 31–48%) in the RE model. Pain or discomfort with the implant, lead migration, and infections were potential risks following cervical SCS. Explant rate was 0.1 (95% CI 0.0–0.2) events per 100 person-months, and no patients in the included studies experienced a neurological complication or paresthesia.

Conclusion: Findings suggest 10 kHz SCS is a promising, safe, minimally invasive alternative for managing chronic upper limb and neck pain.

Keywords: 10 kHz SCS; Cervical leads; Pain relief; Opioids; Disability

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Key Summary Points

Chronic pain in neck and upper extremities is debilitating; considering the lack of evidence for long-term efficacy of opioids, there is an urgent need for clinical evidence on non-pharmacological interventions like spinal cord stimulation (SCS).

Ten-kilohertz SCS, a paresthesia-free therapy, can be especially beneficial for patients who cannot tolerate uncomfortable paresthesia in the neck region. The current review aimed to systematically study the published clinical literature documenting the efficacy and/or safety of cervical 10 kHz SCS therapy.

Review identified 15 studies reporting efficacy and/or safety of cervical 10 kHz SCS therapy.

Meta-analysis of the data showed that 83% of the patients achieved response (≥ 50% reduction) and 39% reduced or eliminated their opioid use following 10 kHz SCS therapy. Implant site pain, lead migration, and infections were commonly reported adverse events.

Current findings suggest that 10 kHz SCS therapy could be a promising, safe, minimally invasive alternative for the treatment of pain in the neck and upper extremities.

DIGITAL FEATURES

This article is published with digital features, including a summary slide to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14448081.

INTRODUCTION

Chronic pain is a condition that can substantially impact a patient's ability to function and their overall quality of life [1, 2]. It is estimated that over 100 million adults in the United States (US) suffer from chronic pain, and its incidence is increasing due to the rise of obesity rates, an aging population, and improved survival following trauma [3, 4]. Historically, these patients have relied on pain-killing medications or surgery to manage their symptoms. However, given concerns surrounding opioid dependency, non-pharmacological interventions aimed at reducing pain are needed, highlighting the importance of therapies such as spinal cord stimulation (SCS) [5, 6].

Though the etiology of many pain disorders is unclear, pain occurring in the head, neck, shoulders, or upper limbs involves dermatomes in the cervical spinal cord [3, 4]. Stimulating the spinal cord through electrical impulses can create a neuromodulatory effect on the nervous system and can change the perception of pain in some patients [3, 4]. Although traditional SCS has been used in practice for decades for chronic back and leg pain, favorable clinical results are becoming increasingly apparent for cervical SCS systems [3, 6–11]. The Neuromodulation Appropriateness Consensus Committee (NACC) recommends cervical SCS for the treatment of upper extremity pain since it is a safe, minimally invasive, and reversible procedure [12].

The Senza® SCS system, which utilizes a proprietary high-frequency therapy at 10 kilohertz (10 kHz SCS), is a US Food and Drug Administration (FDA)-approved device, currently indicated as an aid in the management of chronic intractable pain of the trunk or limbs associated with failed back surgery syndrome, intractable low back pain, or leg pain [13, 14]. Traditional SCS devices provide pain relief by inducing paresthesia, an often-uncomfortable sensation of the skin, whereas 10 kHz SCS provides paresthesia-free pain relief [3, 11, 12, 15–18]. Evidence of efficacy and safety of 10 kHz SCS for back and leg pain has been reviewed in multiple studies [18–20], but

the outcomes in patients with upper extremity pain have not been reviewed. This study aimed to systematically review and analyze the clinical evidence on 10 kHz SCS therapy for neck and upper limb pain.

METHODS

This study conformed with the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21, 22].

Statement of Ethics Compliance

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Search Strategy

A literature search was developed to identify peer-reviewed clinical studies that evaluated 10 kHz SCS therapy for neck and upper extremity pain (see Supplementary Information: Search strategy). The following databases were searched using date limits from May 04, 2008 (2 years prior to the first marketing approval for Senza—CE mark) to November 07, 2020: Medline (MEDLINE (OVID)), PubMed, Embase, and the Cochrane Library. Additional search restrictions were also added to exclude non-English publications and review articles (i.e., narrative, literature, and systematic reviews).

Study Selection

Following the database searches, duplicate studies were identified and removed from the list of references. The remaining titles and abstracts were screened by two reviewers according to the eligibility criteria (see Supplementary Table S1). Studies were excluded if they were nonclinical, not peer-reviewed or reported with completeness (i.e., conference abstract or clinical trial registrations without detailed methods and results), involved patients with angina, peripheral nerve stimulation, peripheral vascular disease, peripheral artery disease, spinal cord injury, or spinal cord stimulation for movement induction, did not use high-frequency (10 kHz or higher) SCS, or SCS combined with other treatments to address the same indication (e.g., intrathecal drug pump).

The full-text articles of the studies deemed potentially eligible after title and abstract screening were then retrieved and screened by two reviewers for a final assessment of eligibility. Any disagreements regarding study eligibility were resolved via discussion or, when necessary, a third reviewer. References identified from other sources (i.e., industry or clinical experts, reference lists of included articles, coauthors, etc.) were also reviewed for inclusion.

Data Extraction

The primary outcome measures were the magnitude of change in pain from baseline to follow-up, the proportion of subjects achieving a 50% reduction in pain, and adverse events related to the device or procedure. Other outcome measures extracted included improvements in quality of life, disability, function, sleep, and changes in medication use. Study, treatment, and population characteristics and data related to the outcomes of interest were extracted from each included study by two reviewers (see Supplementary Table S2).

Data Analysis

The results of individual studies were analyzed qualitatively, including the similarity of subject populations, efficacy outcomes, and safety outcomes across studies. Continuous data are reported as mean or median values, and categorical data are reported as percentages.

When feasible, single-arm meta-analyses were conducted with consideration for the poolability of the individual study populations. Meta-analyses were conducted in R (R Foundation for Statistical Computing; Vienna, Austria)

using the meta package. For continuous outcomes, the data were analyzed as mean change from baseline scores. If the data in a given study were only reported as a median with a range or interquartile range, the data were converted to a mean and standard deviation using the methods proposed by Luo et al. [23]. For dichotomous outcomes, the data were analyzed as proportions. For safety outcomes, the analysis was based on events per 100 person-months to account for total exposure, since follow-up times varied between studies. This was completed by multiplying the number of months of follow-up by the sample size of each arm to obtain the total number of person-months of follow-up for each study [24]. The final results were then scaled using the statistical software package to present the number of events per 100 person-months, and a continuity correction factor of 0.05 was added to studies with zero events for a given outcome. For all outcomes, 95% confidence intervals (CIs) were calculated. Heterogeneity between studies was assessed using the I^2 statistic, where I^2 values greater than 50% represented significant heterogeneity. The results of both the fixed- and random-effects models were presented in forest plots.

Risk of Bias Assessment

The risk of bias (ROB) for each study was assessed by two reviewers using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [25]. This tool involves the assessment of seven domains through which bias may be introduced into a non-randomized clinical study: (1) bias due to confounding, (2) bias in selection of participants, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. Each domain was judged as having either a "low," "moderate," "serious," or "critical" ROB, and the final assessments for each domain were used to grade the overall ROB of the study. If a study is judged to be at low ROB, it is at low ROB for all seven domains and comparable to a well-performed randomized controlled trial (RCT). If the study is judged to be at moderate ROB, it is at low or moderate ROB for all seven domains and provides sound evidence for a non-randomized study, but cannot be considered comparable to a well-performed RCT. If the study is judged to be at serious ROB, it is at serious ROB in at least one domain, but not at critical ROB in any domain, and has some important problems. If the study is judged to be at critical ROB, it is at critical ROB in at least one domain and too problematic to provide any useful evidence and should not be included in any synthesis.

Quality of Evidence

The overall quality of evidence was rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [26, 27]. Evidence was rated based on criteria such as consistency, precision, indirectness, and study limitations, and quality of evidence for each outcome was graded as either "very low," "low," "moderate," or "high." If the included evidence for an outcome consists of randomized trials only, its corresponding GRADE level starts as high, whereas an evidence base of observational studies starts as low. Reasons for downgrading the GRADE include limitations in study quality (i.e., ROB), important inconsistency or heterogeneity between studies, uncertainty about directness, imprecise or sparse data, or a high probability of reporting or publication bias. The GRADE may be upgraded if there is strong or very strong evidence of association based on consistent and direct evidence with no plausible confounders and no major threats to validity, a large magnitude of effect, evidence of a dose–response relationship, or if it is determined that all plausible confounders would have reduced the effect.

RESULTS

Search Results

A total of 340 (327 from the electronic database search and 13 from other sources including

cross-references from the known studies) references were identified (see Supplementary Fig. S1). Of these, 144 were duplicate publications; therefore, 196 citations were reviewed during title and abstract screening. The full-text publications of 47 studies were then screened for eligibility, and 15 were included in this review [15–17, 28–39]. Reasons for exclusion of articles during abstract screening and full-text screening included not meeting criteria for patient population, study design articles, non-clinical studies, and conference presentations.

Characteristics of the Included Studies

The included studies were published between 2015 and 2020 (see Supplementary Table S3). Eight studies were retrospective observational studies [15, 17, 28, 29, 33, 35–37], four were prospective single-arm studies [16, 30, 31, 38], two were case reports [32, 34], and one study was a post-hoc sub-analysis that combined the data from two of the prospective observational studies [39]. Four studies were conducted in the United States (US) [16, 33, 34, 39], three in the United Kingdom [15, 28, 35], three in Australia [36–38], two in Italy [31, 32], one in Germany [17], one was conducted in both Australia and the US [29], and one study was conducted both the UK and US [30]. The sample sizes analyzed in these studies, excluding the case reports, ranged from seven to 1177 patients. The number of patients specifically with upper limb or neck pain and/or cervical SCS stimulation in those studies ranged from three to 134 (see Supplementary Table S3). Final follow-up periods ranged from 3 months to 11 years, whereas mean or median follow-ups ranged from 12.1 months to 2.3 years.

In terms of the target patient population, seven studies included upper limb and/or neck pain patients [16, 17, 29, 30, 36, 38, 39], four studies examined patients with neuropathic limb pain [15, 28, 34, 37], two evaluated patients with headache or migraine pain [31, 35], one study included patients with complex regional pain syndrome [33], and one case report studied a patient with a post-brachial plexus injury (see Supplementary Table S3) [32]. All studies used a 10 kHz SCS device, with five studies specifying lead placement in the C2–C3 region [31, 32, 34, 35, 37], three studies placed leads in the C2–C6 region [16, 29, 38], two studies each placed leads in the C2–C4 [30, 36] and C2–C7 regions [15, 33], and one study placed leads in the C2–C5 region [17]. Cervical lead position was not reported in the study by Amirdelfan et al. [39], and since Al-Kaisy et al.'s study [28] was a broad study on explant rates, it did not call out cervical leads in the analysis. As headache and migraine are off-label indications for 10 kHz SCS, the two studies which investigated cervical 10 kHz SCS in headache and migraine [31, 35] were considered in the analysis of the safety events.

Across clinical studies (excluding case reports), when reported, the mean or median age ranged from 45.8 to 61.4 years (see Supplementary Table S4). The percentage of patients that were female ranged from 42 to 74% across these studies, and the percentage of male patients ranged from 26 to 58%. The mean or median disease duration, when reported, ranged from 9.6 to 30.1 years across studies, and patients had a wide range of pain diagnoses. Lastly, three studies reported the percentage of patients who received traditional SCS prior to study enrollment, which ranged from 29 to 62%.

Efficacy Outcomes

Change in Pain with 10 kHz SCS

To quantify pain, studies tended to use either the numeric rating scale (NRS) or the visual analog scale (VAS) [16, 30, 37–39]. Four studies also measured pain using the Short-Form McGill Pain Questionnaire-2 (SFMPQ-2) [16, 30, 33, 38], and one with the Brief Pain Inventory (BPI) and Pain Catastrophizing Scale (PCS) [15]. Despite using these different measures of pain and at varying time points, studies consistently demonstrated reductions in pain scores with 10 kHz SCS (see Table 1 for a summary). For instance, reductions in pain have been observed as early as 1 month after treatment [15], with significant reductions in pain also evidenced at 3, 6, and 12 months post-

Table 1 Summary of pain outcomes for the whole group and according to individual upper limb or neck pain subgroups

Study	Final follow-up	Outcome	Outcomes	
			Baseline	Final follow-up
Al-Kaisy 2015 [15]	6 months	NRS* (n = 11)	8.2	3.3 (−59%)[a]
		≥ 30% NRS reduction^ (n = 11)	–	91%
		Subgroups		
		Upper limb (n = 8)		88%
		≥ 50% NRS reduction^ (n = 11)	–	73%
		Subgroups		
		Upper limb (n = 8)		75%
		BPI* (n = 10)	57.6	29.4
		PCS* (n = 11)	33	7
Amirdelfan 2020 [16]	12 months	VAS: neck pain* (n = 37)	7.6	1.5
		Subgroups		
		VAS: upper limb pain* (n = 20)	7.1	1.0
		≥ 50% VAS: neck pain reduction^ (n = 37)	–	89%
		Subgroups		
		≥ 50% VAS: upper limb pain reduction^ (n = 20)		95%
		SFMPQ-2 continuous pain* (n = 40)	5.8	2.0
		SFMPQ-2 intermittent pain* (n = 40)	4.5	1.0
		SFMPQ-2 neuropathic pain* (n = 40)	3.2	0.9
		SFMPQ-2 affective pain* (n = 40)	3.9	1.1
		SFMPQ-2 total* (n = 40)	4.4	1.3

Table 1 continued

Study	Final follow-up	Outcome	Outcomes	
			Baseline	Final follow-up
Amirdelfan 2020 [39]	12 months	VAS: neck pain*		
		All subjects	8.1	2.2[a]
		Subgroups		
		Decreased/eliminated opioids (n = 21)	8.0	1.3[a]
		Increased/maintained opioids (n = 20)	8.1	3.1[a]
		High-risk, > 90 morphine equivalents (n = 10)	8.9	2.5[a]
		≥ 50% VAS: neck pain reduction^	–	
		All subjects		87%
		Subgroups		
		Decreased/eliminated opioids (n = 21)		95%
		Increased/maintained opioids (n = 20)		67%
		VAS: upper limb pain*		
		All subjects	7.6	1.4[a]
		Subgroups		
		Decreased/eliminated opioids (n = 21)	7.2	1.0[a]
		Increased/maintained opioids (n = 20)	8.0	2.0[a]
		High-risk, > 90 morphine equivalents (n = 10)	7.3	1.2[a]
		≥ 50% VAS: upper limb reduction^	–	
		All subjects		87%
		Subgroups		
		Decreased/eliminated opioids (n = 21)		89%
		Increased/maintained opioids (n = 20)		85%

Table 1 continued

Study	Final follow-up	Outcome	Outcomes	
			Baseline	Final follow-up
Burgher 2020 [30]	12 months	VAS: upper limb pain* (n = 32)	8.0	1.2[a]
		Subgroups		
		VAS: neck pain* (n = 24)	8.8	1.2[a]
		≥ 50% VAS: upper limb pain reduction^ (n = 32)	–	78%
		Subgroups		
		≥ 50% VAS: neck pain reduction^ (n = 24)		75%
		SFMPQ-2 continuous pain* (n = 32)	5.8	2.2
		SFMPQ-2 intermittent pain* (n = 32)	6.3	1.2
		SFMPQ-2 neuropathic pain* (n = 32)	4.0	1.2
		SFMPQ-2 affective pain* (n = 32)	4.6	0.5
		SFMPQ-2 total* (n = 32)	5.1	1.3
El Majdoub 2019 [17]	12 months	VAS: neck pain* (n = 20)	8.5	2.2
		VAS: upper limb pain* (n = 20)	7.3	1.7
Floridia 2018 [32]	6 months	NRS (n = 1)	8.0	0
Gill 2019 [33]	Mean = 12.1 months	NRS* (n = 12)	NR	(− 47%)[a]
		≥ 30% NRS reduction^ (n = 12)	–	83%
		Subgroups		
		Upper limb (n = 2)		100%
		≥ 50% NRS reduction^ (n = 12)	–	67%
		Subgroups		
		Upper limb (n = 2)		50%
		SFMPQ-2 continuous pain* (n = 12)	NR	(− 45%)[a]
		SFMPQ-2 intermittent pain* (n = 12)	NR	(− 53%)[a]
		SFMPQ-2 neuropathic pain* (n = 12)	NR	(− 48%)[a]
		SFMPQ-2 affective pain* (n = 12)	NR	(− 54%)[a]
Harandi 2018 [34]	3 months	NRS (n = 1)	8.0	2.0
Russo 2016 [36]	6 months	NRS* (n = 156)	7.5	3.7[a]
		Subgroups		
		Neck ± arm or shoulder (n = 10)	7.6	4.2[a]
		Head ± neck (n = 9)	8.0	3.5[a]

Table 1 continued

Study	Final follow-up	Outcome	Outcomes	
			Baseline	Final follow-up
Salmon 2019 [37]	Mean = 2.3 years	NRS* (n = 35)	7.1	3.7[a]
Sayed 2020 [29]	Median = 19.4 months	NRS* (n = 47)	7.9	2.9[a]
		≥ 50% pain relief^ (n = 47)	NR	76%
Verrills 2020[38]	12 months	VAS: neck pain* (n = 27)	8.2	2.2 (− 74%)
		VAS: upper limb pain* (n = 18)	7.3	2.8 (− 62%)
		≥ 50% VAS: neck pain reduction^ (n = 27)	–	85%
		≥ 50% VAS: upper limb pain reduction^ (n = 17)	–	77%
		SFMPQ-2 total* (n = 27)	4.2	1.9 (− 2.4)
		SFMPQ-2 continuous pain* (n = 27)	4.9	2.2 (− 2.8)
		SFMPQ-2 intermittent pain* (n = 27)	4.4	1.8 (− 2.7)
		SFMPQ-2 neuropathic pain* (n = 27)	3.3	1.8 (− 1.4)
		SFMPQ-2 affective pain* (n = 27)	4.3	1.5 (− 2.9)

Headache/migraine patients were not included in pain outcomes as headache and migraine are off-label indications for SCS. Al-Kaisy et al. [28] study did not report pain relief outcomes

BPI Brief Pain Inventory, *n* number of patients analyzed, *NR* not reported, *NRS* Numeric Rating Scale, *PCS* Pain Catastrophizing Scale, *SCS* spinal cord stimulation, *SFMPQ-2* Short-Form McGill Pain Questionnaire-2, *VAS* Visual Analogue Scale

*Mean or median value (change or % change from baseline)

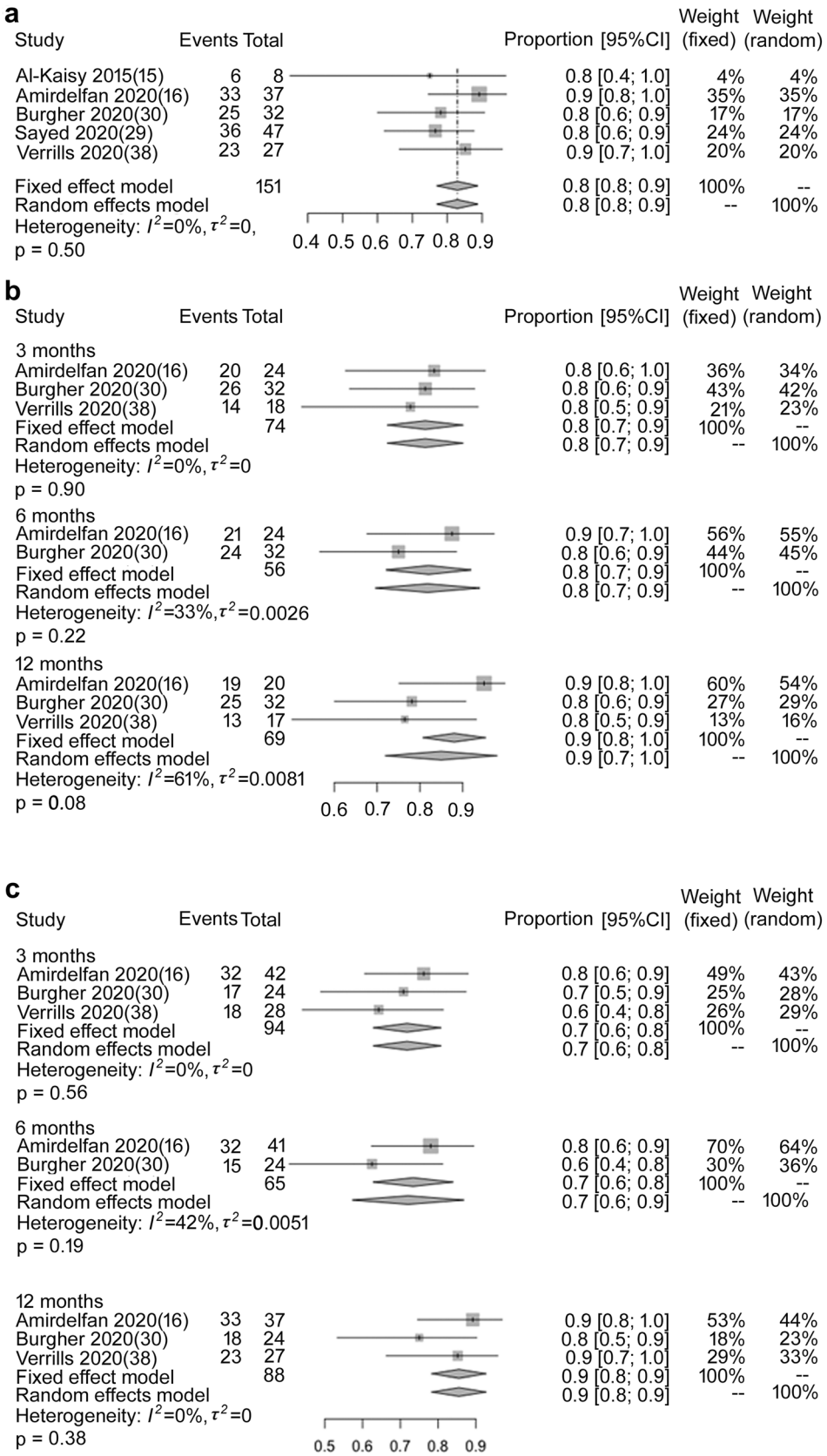
^Proportion of patients

[a] Statistically significant ($p < 0.05$) versus baseline value

intervention [16, 17, 30, 36, 38, 39]. In addition, improvements in pain have been reported in the more moderate term, including at mean/median follow-ups of 12.1 months, 2.3 years, and 19.4 months [29, 33, 37]. Interestingly, significant improvements in pain occurred after 12 months of treatment across different opioid consumption subgroups (those who decreased/eliminated opioids versus those who increased/maintained their opioid intake), including patients taking a high-risk dose (> 90 morphine equivalents) at baseline [39]. Reductions in pain between baseline and follow-up have also been observed in a case report of brachial plexus injury [32] and in a case report of neuropathic pain [34].

Pain Relief with 10 kHz SCS

Pain intensity is usually measured on a VAS (range, 0–10 cm), NRS (range, 0–10), or verbal numeric rating scale (VNRS; range, 0–10). Pain relief or pain reduction is estimated from the difference between pain intensity score at baseline and follow-up. Pain relief is also measured as patient-reported percentage relief (range, 0–100%). Response to therapy is defined as ≥ 50% pain relief, whereas ≥ 30% pain relief is considered as clinically meaningful change [40]. The response rate to 10 kHz SCS therapy ranged from 67 to 89% across six studies with 12 months or more follow-up [15, 16, 29, 30, 33, 38].


a
Study Events Total Proportion [95%CI] Weight (fixed) Weight (random)
Al-Kaisy 2015(15) 6 8 0.8 [0.4; 1.0] 4% 4%
Amirdelfan 2020(16) 33 37 0.9 [0.8; 1.0] 35% 35%
Burgher 2020(30) 25 32 0.8 [0.6; 0.9] 17% 17%
Sayed 2020(29) 36 47 0.8 [0.6; 0.9] 24% 24%
Verrills 2020(38) 23 27 0.9 [0.7; 1.0] 20% 20%
Fixed effect model 151 0.8 [0.8; 0.9] 100% --
Random effects model 0.8 [0.8; 0.9] -- 100%
Heterogeneity: I^2=0%, τ^2=0, p = 0.50
0.4 0.5 0.6 0.7 0.8 0.9
b
Study Events Total Proportion [95%CI] Weight (fixed) Weight (random)
3 months
Amirdelfan 2020(16) 20 24 0.8 [0.6; 1.0] 36% 34%
Burgher 2020(30) 26 32 0.8 [0.6; 0.9] 43% 42%
Verrills 2020(38) 14 18 0.8 [0.5; 0.9] 21% 23%
Fixed effect model 74 0.8 [0.7; 0.9] 100% --
Random effects model 0.8 [0.7; 0.9] -- 100%
Heterogeneity: I^2=0%, τ^2=0 p = 0.90
6 months
Amirdelfan 2020(16) 21 24 0.9 [0.7; 1.0] 56% 55%
Burgher 2020(30) 24 32 0.8 [0.6; 0.9] 44% 45%
Fixed effect model 56 0.8 [0.7; 0.9] 100% --
Random effects model 0.8 [0.7; 0.9] -- 100%
Heterogeneity: I^2=33%, τ^2=0.0026 p = 0.22
12 months
Amirdelfan 2020(16) 19 20 0.9 [0.8; 1.0] 60% 54%
Burgher 2020(30) 25 32 0.8 [0.6; 0.9] 27% 29%
Verrills 2020(38) 13 17 0.8 [0.5; 0.9] 13% 16%
Fixed effect model 69 0.9 [0.8; 1.0] 100% --
Random effects model 0.9 [0.7; 1.0] -- 100%
Heterogeneity: I^2=61%, τ^2=0.0081 p = 0.08
0.6 0.7 0.8 0.9
c
Study Events Total Proportion [95%CI] Weight (fixed) Weight (random)
3 months
Amirdelfan 2020(16) 32 42 0.8 [0.6; 0.9] 49% 43%
Burgher 2020(30) 17 24 0.7 [0.5; 0.9] 25% 28%
Verrills 2020(38) 18 28 0.6 [0.4; 0.8] 26% 29%
Fixed effect model 94 0.7 [0.6; 0.8] 100% --
Random effects model 0.7 [0.6; 0.8] -- 100%
Heterogeneity: I^2=0%, τ^2=0 p = 0.56
6 months
Amirdelfan 2020(16) 32 41 0.8 [0.6; 0.9] 70% 64%
Burgher 2020(30) 15 24 0.6 [0.4; 0.8] 30% 36%
Fixed effect model 65 0.7 [0.6; 0.8] 100% --
Random effects model 0.7 [0.6; 0.9] -- 100%
Heterogeneity: I^2=42%, τ^2=0.0051 p = 0.19
12 months
Amirdelfan 2020(16) 33 37 0.9 [0.8; 1.0] 53% 44%
Burgher 2020(30) 18 24 0.8 [0.5; 0.9] 18% 23%
Verrills 2020(38) 23 27 0.9 [0.7; 1.0] 29% 33%
Fixed effect model 88 0.9 [0.8; 0.9] 100% --
Random effects model 0.9 [0.8; 0.9] -- 100%
Heterogeneity: I^2=0%, τ^2=0 p = 0.38
0.5 0.6 0.7 0.8 0.9

◀**Fig. 1** Meta-analysis of responder rate (≥ 50% reduction in pain). Forest plot of the proportion of patients with response to upper limb or neck pain at final follow-up (**a**), upper limb pain at 3, 6, and 12 months (**b**), and neck pain at 3, 6, and 12 months (**c**). Reference numbers for each study are included in parentheses

Meta-analysis of the percentage of patients with upper limb or neck pain who achieved ≥ 50% pain relief in the final follow-up visits included five studies and 151 patients. The final follow-up was 12 months in three studies [16, 30, 38], 6 months in one [15], and a median of 19.4 months in another [29]. In both the fixed- and random-effects models, the overall pooled estimate was 83% (95% CI 77–89%) and I^2 for heterogeneity was 0% (see Fig. 1a).

For those who achieved ≥ 50% upper limb pain relief at 3 months (three studies; 74 patients), the overall pooled estimate was 81% (95% CI 72–90%), and I^2 was 0% in both the fixed- and random-effects models. At 6 months (two studies; 56 patients), the overall pooled estimate was 82% (95% CI 72–92%) in the fixed-effects model and 82% (95% CI 70–94%) in the random-effects model, with an I^2 of 33%. At 12 months (three studies; 69 patients), the overall pooled estimate was 88% (95% CI 81–95%) in the fixed-effects model and 85% (95% CI 72–98%) in the random-effects model, with an I^2 of 61% (see Fig. 1b).

For patients who achieved ≥ 50% neck pain relief at 3 months (three studies; 94 patients), the overall pooled estimate was 72% (95% CI 63–81%), and I^2 was 0% in both the fixed- and random-effects models. At 6 months (two studies; 65 patients), the overall pooled estimate was 73% (95% CI 63–84%) in the fixed-effects model and 72% (95% CI 57–87%) in the random-effects model with an I^2 of 42%. At 12 months (three studies; 88 patients), in both the fixed- and random-effects models, the overall pooled estimate was 86% (95% CI 78–93%) and I^2 was 0% (see Fig. 1c).

Function and Quality of Life (QoL) with 10 kHz SCS

Improvements from baseline were seen across various functional scores, including the Pain Disability Index (PDI) [16, 30, 38], global assessment of functioning (GAF) [16, 17, 30, 38], QuickDASH [30], Oswestry Disability Index (ODI) [17, 36], Roland Morris Disability Questionnaire (RMDQ) [37], and Pain Self-efficacy Questionnaire (PSEQ, see Table 2 for a summary) [37]. Indeed, Sayed et al. reported 72% of implanted patients had improvements in function at the last follow-up (median, 19.4 months) [29]. For QoL, scores improved from baseline on various measures, including the EuroQoL-5D (EQ-5D) [15] and Short Form-12 (SF-12) [16, 30, 38]. Sleep was also found to improve with 10 kHz SCS when measured via the Pittsburgh Sleep Quality Index (PSQI) [16, 38], and the 3-Point Pain and Sleep Questionnaire (PSQ-3) [16, 30] (see Table 2). In addition, 53% of implanted patients noted their sleep improved at the last follow-up (median, 19.4 months) [29]. In the multicenter, retrospective study by Russo et al., median sitting tolerance, median standing tolerance, and median walking tolerance of patients implanted with 10 kHz SCS devices was improved by 40 min, 15 min, and 15 min, respectively, at 6 months post-implant [36].

Global Impression of Change and Patient Satisfaction with 10 kHz SCS

Global impression of change (GIC) is a clinician- or patient-reported measure that reflects their belief about the treatment efficacy. GIC is usually rated by clinicians (CGIC) and patients (PGIC) as "no change," "almost same," "somewhat better," "a little better," "better," "moderately better," and "a great deal better." For the CGIC, 78–98% of patients were "better," "moderately better," or "a great deal better" at the final follow-up [16, 30, 38]. For patient global impression of change (PGIC), this ranged from 75 to 95% [16, 30, 37, 38]. Meta-analysis on the PGIC data from these four studies included 130 patients with final follow-up visits at 12 months in three studies [16, 30, 38] and a mean of 2.3 years in another study [37]. The overall pooled estimate was 89% (95% CI 83–94%) in the fixed-effects model and 84% (95% CI 72–95%) in the random-effects model, with an I^2 of 70% (see Fig. 2a).

Patient satisfaction is recorded in the studies by the patients as "dissatisfied," "very

Table 2 Summary of studies reporting functional, quality of life, and patient satisfaction outcomes

Study	Function	QoL	Satisfaction
Al-Kaisy 2015 [15]	NR	Mean EQ-5D scores improved by 101% from baseline to 6 months	At 6 months, 46% were "excellent," 46% were "good," and 9% were "not satisfied"; in the upper limb subgroup, these proportions were 50%, 38%, and 13%, respectively 91% would recommend the treatment to other patients
Amirdelfan et al. 2020 [16]	Mean PDI scores improved from 42.4 at baseline to 16.9 at 12 months Mean GAF scores improved from 66.4 at baseline to 85.8 at 12 months PGIC at 12 months: 95% were "better, moderately better, or a great deal better," 5% were "somewhat or a little better," and 0% were "no change or almost the same" CGIC at 12 months: 98% were "better, moderately better, or a great deal better," 0% were "somewhat or a little better," and 3% were "no change or almost the same"	Mean SF-12: PCS scores improved from 30.7 at baseline to 41.3 at 12 months Mean SF-12: MCS scores improved from 45.0 at baseline to 49.5 at 12 months Mean PSQI scores improved from 12.5 at baseline to 8.3 at 12 months Mean PSQ-3 scores improved across all three subscales from 6.3, 6.8, and 6.8 at baseline to 2.2, 1.9, and 2.0 at 12 months	At 12 months, 95% were "satisfied or very satisfied," 3% were "undecided," and 3% were "dissatisfied or very dissatisfied"
Burgher 2020 [30]	Median PDI scores improved from 48.5 at baseline to 18 at 12 months Median QuickDASH scores improved from 68.2 at baseline to 31.8 at 12 months Median GAF scores improved from 55 at baseline to 74.5 at 12 months PGIC at 12 months: 75% were "better, moderately better, or a great deal better," 13% were "somewhat or a little better," and 13% were "no change or almost the same" CGIC at 12 months: 78% were "better, moderately better, or a great deal better," 13% were "somewhat or a little better," and 9% were "no change or almost the same"	Median SF-12: PCS scores improved from 27.3 at baseline to 39.6 at 12 months Median SF-12: MCS scores improved from 43.2 at baseline to 50 at 12 months Median PSQ-3 scores improved from 25.1 at baseline to 5.5 at 12 months	At 12 months, 84% were "satisfied or very satisfied," 9% were "undecided," and 6% were "dissatisfied or very dissatisfied"

Table 2 continued

Study	Function	QoL	Satisfaction
El Majdoub 2019 [17]	Mean ODI scores improved from 31 at baseline to 19.8 at 12 months Median GAF interval improved from 41–50% at baseline to 61–70% at 12 months	NR	At 12 months, 75% were "very satisfied," 10% were "satisfied," and 15% were "undecided"
Floridia 2018 [32]	NR	Quality of life improved to "normal" life based on the Minnesota Multiphase Personality Inventory	NR
Russo 2016 [36]	Mean ODI scores improved from 41.4 at baseline to 32.8 at 6 months ($p < 0.001$)	NR	NR
Salmon 2019 [37]	Mean RMDQ scores improved from 12.3 at baseline to 7.8 at 2.3 years ($p < 0.05$) Mean PSEQ scores improved from 21 at baseline to 34 at 2.3 years PGIC at 2.3 years: 80% were "better, moderately better, or a great deal better," 21% were "somewhat better or a little better," and none of the patients were "almost the same or no change"	NR	At 2.3 years, 93% were "satisfied or very satisfied," and 7% were "not sure" or "unsatisfied"
Sayed 2020 [29]	Functional status at 19.4 months: 72% had improved function, 19% had unimproved function, and 9% provided no details	Sleep status at 19.4 months: 53% had improved sleep, 32% had unimproved sleep, and 15% provided no details	NR

Table 2 continued

Study	Function	QoL	Satisfaction
Verrills 2020 [38]	Mean PDI scores improved from 42.6 at baseline to 21.2 at 12 months Mean BDI scores improved by 7.8 points from baseline to 12 months Mean GAF scores improved by 23.8 points from baseline to 12 months PGIC at 12 months: 83% were "better, moderately better, or a great deal better," 17% were "somewhat better or a little better," and none of the subjects were "almost the same or no change" CGIC at 12 months: 90% were "better, moderately better, or a great deal better," 0% were "somewhat better or a little better," and 10% were "almost the same or no change"	Mean SF-12: PCS scores improved by 10.8 points from baseline to 12 months Mean SF-12: MCS scores improved by 5.8 points from baseline to 12 months Mean PSQI scores improved by 2.6 points from baseline to 12 months	At 12 months, 76% were "satisfied or very satisfied," 17% were "undecided," and 7% were "dissatisfied or very dissatisfied"

BDI Beck Depression Index, *CGIC* clinician global impression of change, *EQ-5D* EuroQoL-5D, *GAF* global assessment of functioning, *HIT-6* headache impact test, *MIDAS* Migraine Disability Assessment Scale, *NR* not reported, *ODI* Oswestry Disability Index, *PDI* Pain Disability Index, *PGIC* patient global impression of change, *PSEQ* Pain Self-efficacy Questionnaire, *PSQ-3* 3-Point Pain and Sleep Questionnaire, *PSQI* Pittsburgh Sleep Quality Index, *QoL* quality of life, *RMDQ* Roland Morris Disability Questionnaire, *SF-12: MCS* Short Form-12 mental component summary, *SF-12: PCS* Short Form-12 physical component summary

dissatisfied," "not sure," "satisfied," and "very satisfied." The percentage of patients who stated they were "satisfied" or "very satisfied" with 10 kHz SCS at the final follow-up ranged from 76 to 95% (see Table 2) [15–17, 30, 37, 38]. Additionally, 88% of upper limb patients were "excellent" or "good" with 91% of the total sample stating they would recommend the treatment to other patients [15]. Meta-analysis on these data included five studies and 150 patients. The final follow-up was 12 months in four studies [16, 17, 30, 38] and a mean of 2.3 years in one study [37]. The overall pooled estimate was 91% (95% CI 86–95%) in the fixed-effects model and 89% (95% CI 83–95%) in the random-effects model, with an I^2 of 41% (see Fig. 2b).

Medication Consumption with 10 kHz SCS

On average, medication consumption (i.e., opioids or other analgesics) declined following 10 kHz SCS (see Table 3). The proportion of patients who reduced or eliminated the use of their pain medication ranged from 29 to 58% [16, 17, 29–31, 34, 37–39]. Meta-analysis on the patients who reduced or eliminated consumption of pain medication at the final follow-up visit included five studies and 156 patients. The final follow-up was 12 months in three studies [16, 30, 38], a median of 19.4 months in one study [29], and a mean of 2.3 years in another [37]. In terms of the specific medications captured, four studies measured the reduction or cessation of opioids [16, 30, 37, 38], and one study did not provide granular information on medications [29]. The overall pooled estimate was 39% (95% CI 31–46%) in the fixed-effects

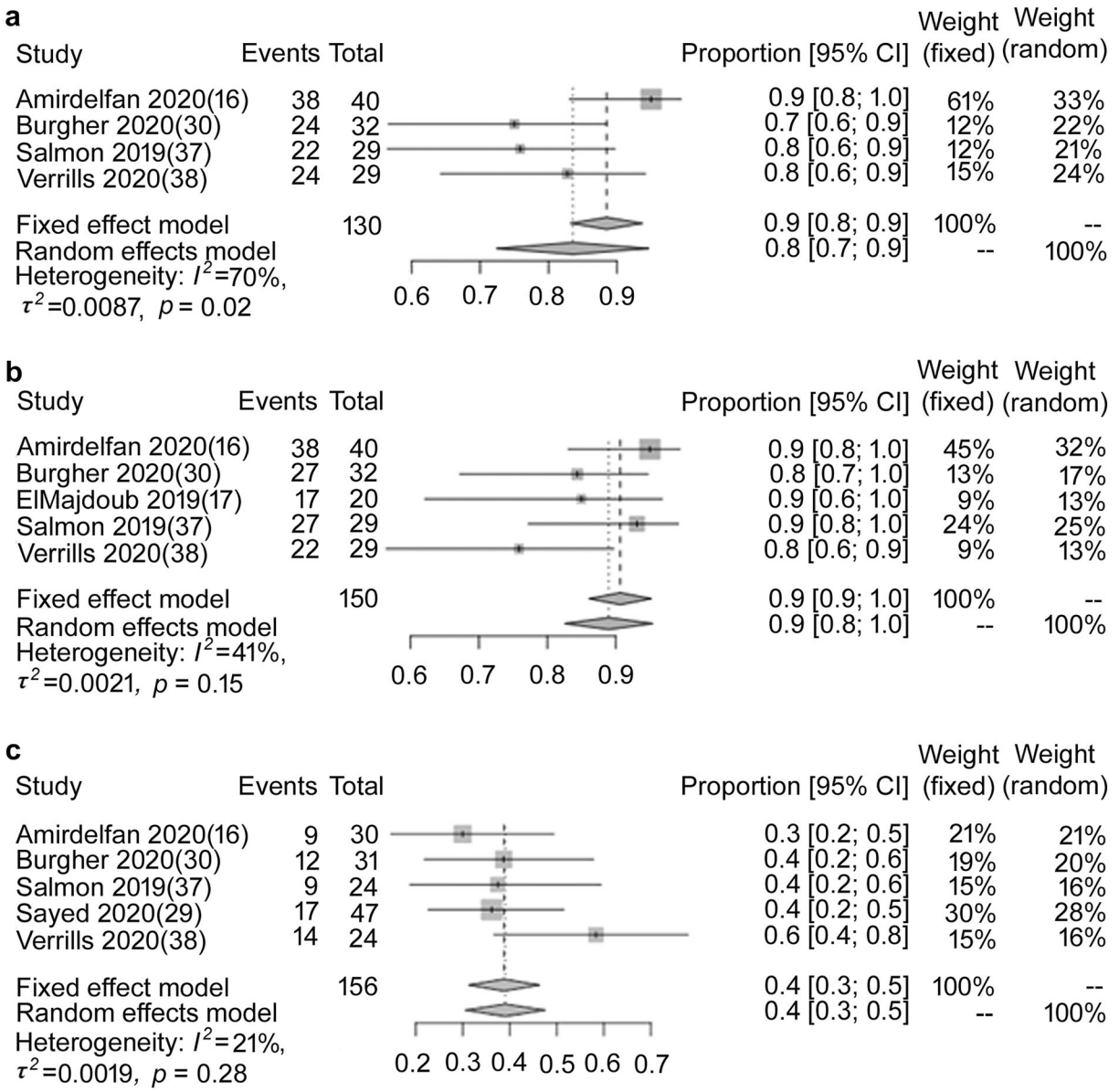


Fig. 2 Meta-analysis of quality of life outcomes at final follow-up. Forest plot of the proportion of upper limb/-neck pain patients who stated that they were "better, moderately better, or a great deal better" on the PGIC (**a**), who stated that they were "satisfied or very satisfied" with 10 kHz SCS (**b**), and patients who reduced/eliminated their medication consumption (**c**). Reference numbers for each study are included in parentheses

model and 39% (95% CI 31–48%) in the random-effects model, with an I^2 of 21% (see Fig. 2c).

Safety Outcomes

Pain or Discomfort at the Implantable Pulse Generator (IPG)

The most commonly reported events across studies were pain or discomfort at the implantable pulse generator (IPG), with

Table 3 Summary of studies reporting medication use and safety outcomes

Study	Medication use	Safety
Al-Kaisy 2015 [15]	NR	Pain at IPG site: 27% Surgical revision: 18% Early (trial period) infection: 9% Any neurological AE: 0% Paresthesia: 0%
Al-Kaisy 2020 [28]	NR	Explantation, OR vs. traditional stimulation: 0.5 [95% CI 0.4–0.7; $p < 0.001$] (from the univariate analysis) Explantation, OR vs. traditional stimulation: 0.2 [95% CI 0.1–0.4; $p < 0.001$] (from the multivariate analysis)
Amirdelfan 2020[#] [16]	At 12 months, 7% ($n = 2$) increased their opioid intake, 63% ($n = 19$) did not change it, and 30% ($n = 9$) reduced or eliminated their opioid intake Mean daily opioid intake (ME) reduced from 63.1 at baseline to 42.1 at 12 months ($p = 0.14$)	Treatment-related serious AE: 4% Explantation: 4% Infection: 2% Extradural hematoma: 2% Lead migration: 0% Surgical revision: 0% Paresthesia: 0% Stimulation-related neurological deficit: 0%
Amirdelfan 2020 [39]	Mean daily opioid intake (MME) reduced from 73.9 at baseline to 48.9 at 12 months ($p < 0.01$) and 51% of patients reduced or eliminated their opioid intake Among the high-risk subgroup, they reduced their mean daily opioid intake (MME) from 158.8 at baseline to 99.0 at 12 months ($p < 0.05$), and 70% of patients reduced or eliminated their opioid intake	NR

Table 3 continued

Study	Medication use	Safety
Arcioni 2016 [31]	Percentage of patients overusing triptans reduced from 64% at baseline to 36% at 6 months Percentage of patients who discontinued triptans at 6 months was 29% (n = 4) Percentage of patients overusing other analgesics reduced from 36% at baseline to 14% at 6 months	Severe AE: 36% Surgical revision: 29% Discomfort at IPG site: 14% Lead migration: 14% Hypoesthesia: 7% Lead breakage: 7% Any infection: 14% Early (trial period) infection: 7% Late infection: 7% Pain or edema at IPG site: 7% Shoulder pain: 7% Any neurological AE: 0% Paresthesia: 0%
Burgher 2020[#] [30]	At 12 months, 16% increased their opioid intake, 36% did not change it, 29% reduced it, and 10% eliminated their opioid intake Mean daily opioid intake (ME) reduced from 81.8 at baseline to 61.0 at 12 months (p = 0.04)	Treatment-related AE: 9% Treatment-related serious AE: 2% Explantation: 3% Paresthesia: 0% Stimulation-related neurological deficit: 0% Lead migration: 0% Surgical revision: 0%
El Majdoub 2019 [17]	Mean morphine intake reduced from 210.0 mg/day at baseline to 160.0 mg/day at 12 months Mean oxycodone intake reduced from 440.0 mg/day at baseline to 220.0 mg/day at 12 months Mean tramadol intake reduced from 2650.0 mg/day at baseline to 900.0 mg/day at 12 months Mean ibuprofen intake reduced from 6000.0 mg/day at baseline to 1200.0 mg/day at 12 months Mean Voltaren intake reduced from 750.0 mg/day at baseline to 225.0 mg/day at 12 months	Infection: 13% Explantation: 13% (all due to infection) Lead migration: 4% Renewed neck pain: 4% (due to lead migration) Surgical revision: 4% (due to lead migration)

Table 3 continued

Study	Medication use	Safety
Floridia 2018 [32]	Patient stopped using pain killers at 1-month follow-up	No adverse events were reported. Patient was relieved from uncomfortable paresthesia seen with LF-SCS
Gill 2019 [33]	NR	Paresthesia: 0% Any AE: 0%
Harandi 2018 [34]	The patient reduced their opioid intake (ME) from 60.0 mg/day at baseline to 0.0 mg/day at 3 months	The patient reported no paresthesia during treatment
Lambru 2016 [35]	NR	Of the four chronic migraine patients, two experienced discomfort at the IPG site, one experienced lead breakage, none experienced any stimulation-induced sensations, and none had a serious treatment-related AE Of the two SUNA patients, none had a treatment-related AE The one chronic cluster headache patient had a surgical revision due to lead migration
Salmon 2019 [37]	38% of patients (9 of 24) ceased taking strong opiates at 2.3 years Mean opioid intake (ME) reduced from 165.4 mg/day at baseline to 99.3 mg/day at 2.3 years	Additional lead placement: 17% Pain at IPG site: 17% Lead replacement: 3% Infections requiring explantation: 0% Lead displacement requiring repositioning: 0%
Sayed 2020 [29]	At 19.4 months, 4% of patients had increased medication consumption, 36% decreased, 51% maintained, and 9% provided no details	Pain at IPG site: 2% (n = 1) Overstimulation: 4% (n = 2) Ineffective therapy: 4% (n = 2) Explantation: 0%

Table 3 continued

Study	Medication use	Safety
Verrills 2020[#] [38]	At 12 months, 58% of patients reduced or eliminated their opioid consumption	Any study-related AE: 31% (n = 12) Lead migration: 10% Surgical revision: 10% Explantation: 3% Headache: 8% (n = 3) Pain at IPG site: 5% (n = 2) Infection: 5% (n = 2) Procedural nausea: 5% (n = 2) Burning sensation: 3% (n = 1) Stimulation issue: 3% (n = 1) Keloid scar: 3% (n = 1) Medical device pain: 3% (n = 1) Pain at extremity: 3% (n = 1) Swelling: 3% (n = 1) Procedural vomiting: 3% (n = 1) Vomiting: 3% (n = 1) Study-related serious AE: 3% (n = 1) Serious infection: 3% (n = 1)

Study by Russo 2016 (no medication use or safety outcomes reported) not included

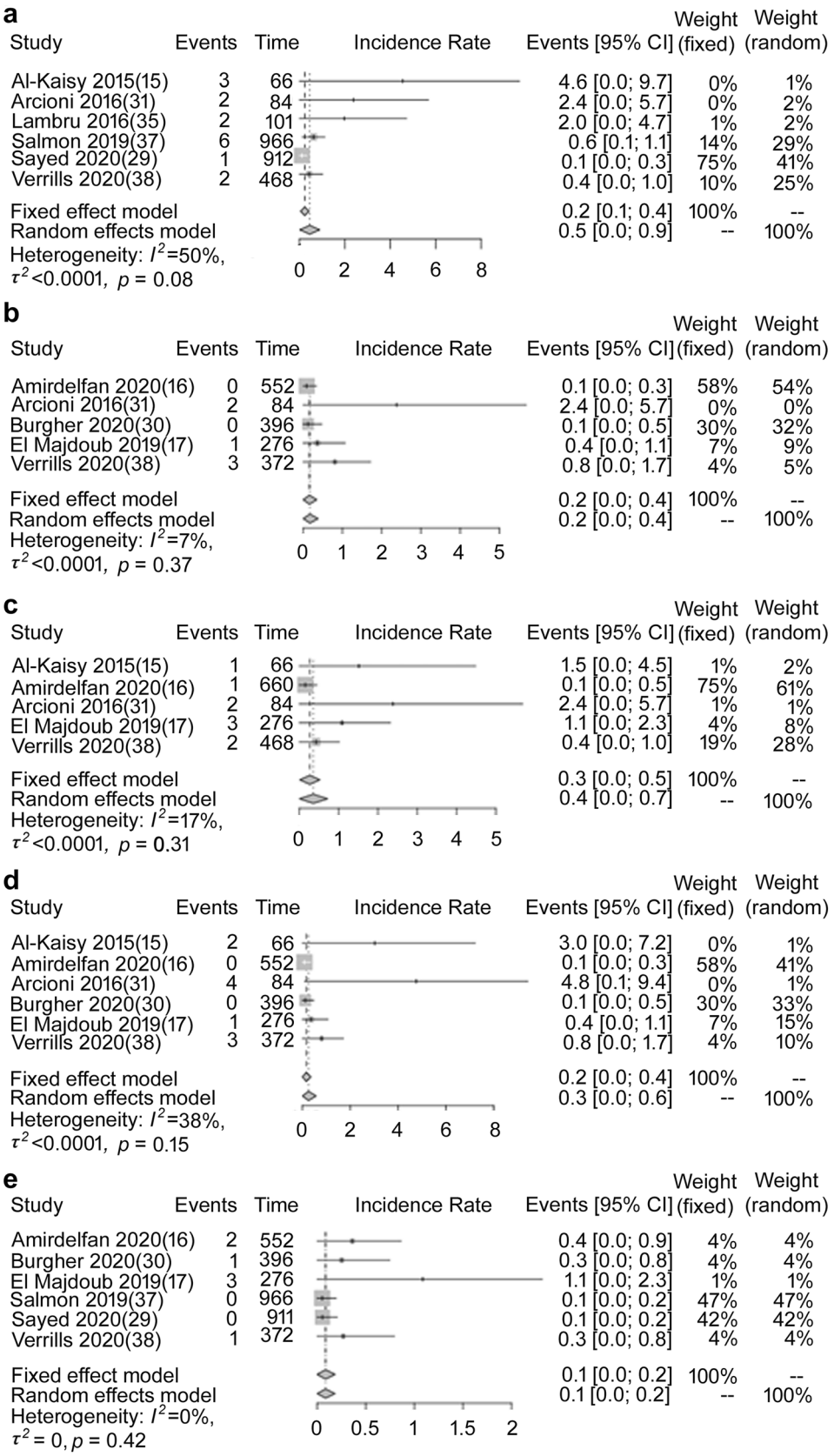
AE adverse event, *CI* confidence interval, *IPG* implantable pulse generator, *ME* morphine equivalents, *mg* milligrams, *NR* not reported, *OR* odds ratio, *SUNA* short-lasting unilateral neuralgiform headache attacks with autonomic symptoms

[#] Lead migration, explantation, and surgical revision rates were confirmed by the sponsor based on internal study data when not clearly reported in the article

incidence rates ranging from 2 to 27% of patients [15, 29, 31, 37, 38]. Meta-analysis on the incidence rates of pain or discomfort at the IPG site included six studies and 150 patients. The final follow-up was 6 months in two studies [15, 31], 12 months in one study [38], a median of 19.4 months in one study [29], a mean of 25.3 months in one study [35], and a mean of 2.3 years in another [37]. The overall pooled estimate was 0.2 (95% CI 0.1–0.4) events per 100 person-months in the fixed-effects model and 0.5 (95% CI 0.0–0.9) events per 100 person-months in the random-effects model. The I^2 was 50% (see Fig. 3a).

Lead Migration and Infection

Lead migration and infections occurred at an incidence ranging between 0 and 14% [16, 17, 30, 31, 37, 38] and 2 and 14% [15–17, 31, 37, 38] of patients, respectively. Meta-analysis on the incidence rates for lead migration included five studies and 147 patients. The final follow-up was 6 months in one study [31] and 12 months in the other four studies [16, 17, 30, 38]. The overall pooled estimate was 0.2 (95% CI 0.0–0.4) events per 100 person-months in the fixed-effects model and 0.2 (95% CI 0.0–0.4) events per 100-person months in the random-effects model. The I^2 for


a
Study Events Time Incidence Rate Events [95% CI] Weight (fixed) Weight (random)
Al-Kaisy 2015(15) 3 66 4.6 [0.0; 9.7] 0% 1%
Arcioni 2016(31) 2 84 2.4 [0.0; 5.7] 0% 2%
Lambru 2016(35) 2 101 2.0 [0.0; 4.7] 1% 2%
Salmon 2019(37) 6 966 0.6 [0.1; 1.1] 14% 29%
Sayed 2020(29) 1 912 0.1 [0.0; 0.3] 75% 41%
Verrills 2020(38) 2 468 0.4 [0.0; 1.0] 10% 25%
Fixed effect model 0.2 [0.1; 0.4] 100% --
Random effects model 0.5 [0.0; 0.9] -- 100%
Heterogeneity: I^2=50%, τ^2<0.0001, p = 0.08
0 2 4 6 8
b
Study Events Time Incidence Rate Events [95% CI] Weight (fixed) Weight (random)
Amirdelfan 2020(16) 0 552 0.1 [0.0; 0.3] 58% 54%
Arcioni 2016(31) 2 84 2.4 [0.0; 5.7] 0% 0%
Burgher 2020(30) 0 396 0.1 [0.0; 0.5] 30% 32%
El Majdoub 2019(17) 1 276 0.4 [0.0; 1.1] 7% 9%
Verrills 2020(38) 3 372 0.8 [0.0; 1.7] 4% 5%
Fixed effect model 0.2 [0.0; 0.4] 100% --
Random effects model 0.2 [0.0; 0.4] -- 100%
Heterogeneity: I^2=7%, τ^2<0.0001, p = 0.37
0 1 2 3 4 5
c
Study Events Time Incidence Rate Events [95% CI] Weight (fixed) Weight (random)
Al-Kaisy 2015(15) 1 66 1.5 [0.0; 4.5] 1% 2%
Amirdelfan 2020(16) 1 660 0.1 [0.0; 0.5] 75% 61%
Arcioni 2016(31) 2 84 2.4 [0.0; 5.7] 1% 1%
El Majdoub 2019(17) 3 276 1.1 [0.0; 2.3] 4% 8%
Verrills 2020(38) 2 468 0.4 [0.0; 1.0] 19% 28%
Fixed effect model 0.3 [0.0; 0.5] 100% --
Random effects model 0.4 [0.0; 0.7] -- 100%
Heterogeneity: I^2=17%, τ^2<0.0001, p = 0.31
0 1 2 3 4 5
d
Study Events Time Incidence Rate Events [95% CI] Weight (fixed) Weight (random)
Al-Kaisy 2015(15) 2 66 3.0 [0.0; 7.2] 0% 1%
Amirdelfan 2020(16) 0 552 0.1 [0.0; 0.3] 58% 41%
Arcioni 2016(31) 4 84 4.8 [0.1; 9.4] 0% 1%
Burgher 2020(30) 0 396 0.1 [0.0; 0.5] 30% 33%
El Majdoub 2019(17) 1 276 0.4 [0.0; 1.1] 7% 15%
Verrills 2020(38) 3 372 0.8 [0.0; 1.7] 4% 10%
Fixed effect model 0.2 [0.0; 0.4] 100% --
Random effects model 0.3 [0.0; 0.6] -- 100%
Heterogeneity: I^2=38%, τ^2<0.0001, p = 0.15
0 2 4 6 8
e
Study Events Time Incidence Rate Events [95% CI] Weight (fixed) Weight (random)
Amirdelfan 2020(16) 2 552 0.4 [0.0; 0.9] 4% 4%
Burgher 2020(30) 1 396 0.3 [0.0; 0.8] 4% 4%
El Majdoub 2019(17) 3 276 1.1 [0.0; 2.3] 1% 1%
Salmon 2019(37) 0 966 0.1 [0.0; 0.2] 47% 47%
Sayed 2020(29) 0 911 0.1 [0.0; 0.2] 42% 42%
Verrills 2020(38) 1 372 0.3 [0.0; 0.8] 4% 4%
Fixed effect model 0.1 [0.0; 0.2] 100% --
Random effects model 0.1 [0.0; 0.2] -- 100%
Heterogeneity: I^2=0%, τ^2 = 0, p = 0.42
0 0.5 1 1.5 2

◀**Fig. 3** Meta-analysis of safety outcomes. Forest plot of the incidence rates (events per 100 person-months) of pain or discomfort at the implant pulse generator site (**a**), lead migration (**b**), infection (**c**), surgical revision (**d**), explants (**e**). Reference numbers for each study are included in parentheses

heterogeneity was 7% (see Fig. 3b). Meta-analysis on the incidence rates for infection included six studies and 177 patients. The final follow-up was 12 months in three studies [16, 17, 38], 6 months in two studies [15, 31], and a mean of 2.3 years in one study [37]. The overall pooled estimate was 0.3 (95% CI 0.0–0.5) events per 100 person-months in the fixed-effects model and 0.4 (95% CI 0.0–0.7) events per 100 person-months in the random-effects model. The I^2 was 17% (see Fig. 3c).

Surgical Revision

Surgical revision rates ranged from 0 to 29% across six studies [15–17, 30, 31, 35, 38]. Meta-analysis on these data included 158 patients. The final follow-up was 6 months in two studies [15, 31] and 12 months in the other four [16, 17, 30, 38]. The overall pooled estimate was 0.2 (95% CI 0.0–0.4) events per 100 person-months in the fixed-effects model and 0.3 (95% CI 0.0–0.6) events per 100 person-months in the random-effects model. The I^2 was 38% (see Fig. 3d).

Explantation

Explant rates ranged between 0 and 13% of patients across six studies [16, 17, 28–30, 37, 38]. Additionally, Al-Kaisy et al. [18] found that 10 kHz SCS devices were significantly less likely to be explanted relative to traditional stimulation [28]. The study noted loss of efficacy as the main reason for explant, followed by infection, MRI requirement, remission of pain, and device-related complications. Meta-analysis on the explant incidence rates included six studies and 215 patients. The final follow-up was 12 months in four studies [16, 17, 30, 38], a median of 19.4 months in one study [29], a mean of 2.3 years in one study [37], and over 11 years in one study [28]. In both the fixed- and random-effects models, the overall pooled estimate was 0.1 (95% CI 0.0–0.2) events per 100 person-months, with an I^2 of 0% (see Fig. 3e).

Neurological Injury or Paresthesia

No patients reported a neurological event or paresthesia following 10 kHz SCS in the studies included in this review (see Table 3) [16, 17, 28–38].

Risk of Bias and Quality of Evidence

The risk of bias assessment for each outcome category is summarized in Supplementary Table S5. Of the nine studies reporting pain outcomes, six were deemed moderate risk and three were serious risk. Of the seven studies reporting functional outcomes, five were considered moderate risk and two were serious risk. Of the five studies reporting QoL, four were moderate risk and one was serious risk. Of the six studies reporting patient satisfaction, five were deemed moderate risk and one was serious risk. Of the six studies reporting medication use, four were considered moderate risk and two were serious risk. Lastly, of the 11 studies reporting safety data, seven were moderate risk and four were serious risk. The reasons for elevated risk of bias were the variability in disease diagnosis and pain etiologies, variability in follow-up periods, incomplete data, and unblinded outcomes assessment.

Based on the included evidence and their risk of bias, the overall quality of evidence was graded as "moderate" for pain and patient satisfaction outcomes according to the GRADE criteria. The baseline GRADE for observational studies was "low." Pain and patient satisfaction were upgraded to "moderate" quality of evidence based on the magnitude, consistency, and precision of the treatment effects exhibited across trials. All other outcomes were graded as "low."

DISCUSSION

The purpose of this systematic review was to identify and evaluate the clinical evidence of the use of 10 kHz SCS in patients with upper

limb or neck pain indications. The evidence was derived from 15 studies (1693 total patients; 317 upper limb or neck pain patients) which consistently demonstrated favorable outcomes in terms of pain reductions, improvements in function, QoL, patient satisfaction, reductions in medication use, and an acceptable safety profile. These findings were seen across a range of different upper limb and neck pain indications and over multiple months to years of treatment. Future research on this topic should focus on its comparative effects against other therapies indicated for this patient population, its effects within more specific patient populations and diagnoses, and if lead placement level influences patient outcomes.

Efficacy of Cervical 10 kHz SCS

Traditional SCS has been used in clinical practice for decades for the treatment of chronic back and leg pain, and the NACC has made recommendations on the use of traditional cervical SCS for neuropathic pain syndromes affecting the upper extremities [11, 12]. The studies included in the review showed that 10 kHz SCS was associated with pain relief and decreases in the consumption of opioid medications. In fact, based on the reported data, it is estimated that over one third of patients reduced or eliminated their opioid medications following 10 kHz SCS. Interestingly, over three quarters of patients in the studies included in this review were reportedly satisfied or very satisfied with 10 kHz SCS treatment and rated their overall improvement to be better, moderately better, or a great deal better. Furthermore, studies also documented improvements in disability, QoL, and sleep.

The Senza SCS system has already been approved by the FDA in the management of chronic intractable pain of the trunk or limbs associated with failed back surgery syndrome or intractable low back or leg pain. Prior systematic reviews support the use of any SCS in this particular indication; however, they have also found evidence suggesting that 10 kHz SCS devices demonstrate more favorable outcomes relative to traditional devices [41–46]. More specifically, the reviews by Vallejo et al. and Conger et al. found similar values for the percentage of patients who experienced $\geq$ 50% reduction in pain following 10 kHz SCS as estimated in the current meta-analysis on those with upper limb or neck pain (i.e., 83% [95% CI 77–89%]) [41, 46]. In terms of pain medication consumption, Pollard et al. found that 10 kHz SCS resulted in increased odds of reducing opioid use and greater mean medication dose reduction compared to traditional SCS in patients with intractable spine and limb pain, though there was limited evidence and the results were not statistically significant [45]. In addition, a systematic review by Raghu et al. concluded that traditional SCS should be a standard treatment for patients with painful diabetic neuropathy, while also highlighting the emergence of promising evidence for 10 kHz SCS [47]. Though these studies are not limited to the current population of interest (i.e., upper limb or neck pain), they provide evidence supporting the broader use of 10 kHz SCS, and their results are consistent with the current review, suggesting 10 kHz SCS also has a place in the management of those with upper limb or neck pain.

Safety of 10 kHz SCS

The results of this review demonstrated that 10 kHz SCS is a relatively safe procedure given its comparable risk of pain or discomfort at the IPG site, lead migration, and infection [3, 4, 48–51]. These events are not usually considered serious and can be resolved, if needed, with surgical revision or explantation [12, 15–17, 35, 39]. A reason why the NACC supports the use of neurostimulation is due to its lack of medication-related side effects, and highlights the incidence of its device-related complications as becoming less frequent as technology and the surgical skills required to implant the device improve [12]. This notion may be reflected in the study by Al-Kaisy et al. [18], where 10 kHz SCS devices were significantly less likely to be explanted relative to traditional stimulation [28]. Additionally, another potential concern with cervical SCS is

the occurrence of neurological complications due to the complex anatomy surrounding the cervical spine [7, 10]. None of the studies included in this review reported occurrence of neurological complications, indicating that such risks are minimal with 10 kHz SCS.

Study Limitations and Future Directions

To generate comprehensive insight into the efficacy and safety of cervical 10 kHz SCS in this systematic review, a combination of narrative synthesis, meta-analysis, and bias assessment were performed. However, we acknowledge this review was limited by the quality of the included studies. Indeed, they were predominantly observational with relatively small sample sizes, including patients with a range of diagnoses and pain etiologies. In addition, due to their observational design, they did not have a comparison or control group, meaning the results should be carefully interpreted. Not all the studies reported safety outcomes, and the retrospective studies also included patients with a range of different follow-up periods and reported outcomes, making it difficult to generate a holistic account of the long-term effects of cervical 10 kHz SCS. However, findings consistently suggested that cervical 10 kHz SCS was effective and safe in this patient cohort.

To improve the evidence for cervical 10 kHz SCS, future research should consider quantifying patient-reported outcomes and systematically report adverse events (AEs) at specific time points. This would provide more valuable and interpretable results, especially when synthesizing the data and grading the quality of evidence.

CONCLUSION

Findings from this systematic review suggest 10 kHz SCS has an acceptable safety profile in patients with upper limb and neck pain indications and was associated with improvements in pain, function, QoL, and medication consumption. Importantly, patients reported high satisfaction with the therapy, reinforcing the benefits patients experience with cervical 10 kHz SCS. Neurological injury and paresthesias were not reported in any of the studies included. Overall, the current evidence suggests 10 kHz SCS is a promising, suitable, and minimally invasive therapy for managing chronic upper limb and neck pain indications.

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