Cluster Wervelkolomgerelateerde aandoeningen

Bijlagen bij Richtlijn Wervelkolomgerelateerde pijnklachten van de lage rug

Inhoudsopgave

Bijlagen module 5 – Diagnostiek van discogene lage rugpijn

Literatuursamenvatting

Search and select

A literature question and PICO were formulated (see Table 1). However, due to the absence of a definitive reference standard for diagnosing discogenic low back pain, an exploratory search was conducted to address the clinical question.

Table 1. PICO

Literature question:	*What is the diagnostic accuracy of different diagnostic modalities in the diagnosis of discogenic low back pain?*
Patients	Patients with chronic low back pain (>3 months)
Index test	Clinical history taking, physical examination, MRI, discography, additional imaging
Comparator test	None, or (combination of) index test(s)
Reference standard	Not available
Outcomes	Clinical diagnosis, diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value)

Clinical relevance

Likelihood ratios are generally interpreted as:

- Positive likelihood ratio: 2-5 is weak evidence to rule in the condition, 5-10 moderate evidence to rule in the condition, and ≥10 strong evidence to rule in the condition
- Negative likelihood ratio: ≤0.10 strong evidence to rule out the condition, 0.1-0.2 moderate evidence to rule out the condition, and 0.2-0.5 weak evidence to rule out the condition

Search and select (Methods)

The database Embase (via Embase.com) was searched with relevant search terms from 2000 until June 26th, 2024. The detailed search strategy is available upon request. The search resulted in 582 hits. Studies were selected based on the following criteria:

- Describing the diagnosis or diagnostic modalities of discogenic low back pain
- Guidelines or reviews

Thirty-six studies were initially selected based on title and abstract screening. From these, 12 studies were selected based on full text assessment, and used to write the considerations and formulate the recommendations.

Summary of literature

As this was an exploratory search, no systematic assessment of the literature was performed. The 12 studies identified through the search were used to (re)consider the clinical process of diagnosing discogenic low back pain and are described in this section in detail. The studies (table 2), together with considerations from clinical practice, form the basis for the recommendations. See the section recommendations ("Aanbevelingen").

Table 2. Included studies from the literature search, and their designs, goals and which part of the diagnostic trajectory of discogenic low back pain they refer to.

Author, year	Study design	Study goal	Part of diagnostic trajectory
Henao Romero, 2020	Mapping review	Assess clinical and radiological signs and symptoms for the differentiation of lumbar pain of discogenic origin from other etiologies.	History taking Physical examination Additional diagnostic testing (MRI)
Petersen, 2017	SR	Develop clinical decision rules for common disorders in the lumbar spine*	Physical examination
Han, 2023	SR + MA	Determine the accuracy of diagnostic tests for disc, sacroiliac joint or facet joint as the source of low back pain*	Physical examination Additional diagnostic testing (MRI)
Chen, 2009	SR	Evaluate the comparative role (to discography) of HIZ in diagnosing discogenic low back pain	Additional diagnostic testing (MRI)
Yang, 2023	SR + MA	Investigate the correlation between HIZ and the pathogenesis of discogenic low back pain.	Additional diagnostic testing (MRI)
Herlin, 2018	SR + MA	Investigate if Modic Changes are associated with non-specific low back pain	Additional diagnostic testing (MRI)
Teraguchi, 2018	SR	Address the association of High intensity zones (HIZ) with low back pain	Additional diagnostic testing (MRI)
Carragee, 2001	Narrative review	Discuss the current uses of discography, the technique involved and its validity	Additional diagnostic testing (discography)
Carragee, 2006	Prospective study	Investigate the diagnostic validity of provocative discography for low back pain due to a primary disc lesion.	Additional diagnostic testing (discography)
Fuji, 2019	Narrative review	To describe the diagnostic criteria for discogenic back pain	History taking Additional diagnostic testing (discography, minimally invasive)
Gornet, 2024	Prospective cohort	Test the performance generalizability of magnetic resonance spectroscopy versus provocative discography in a clinical validation dataset	Additional diagnostic testing (minimally invasive)
Hirsch, 2023	Scoping review	to evaluate the potential usefulness of single photon emission computed tomography with computed tomography (SPECT/CT) as an imaging modality in guiding clinical decision-making	Additional diagnostic testing (minimally invasive)

*Only studies that evaluated discogenic low back pain are used fort his module.

Abbreviations (alphabetical): HIZ: high intensity zone, MA: meta-analysis, SR: systematic review

Prevalence

Two studies describe the prevalence of discogenic low back pain. This is important for determining the likelihood ratios of whether a particular sign or symptom is predictive of having or not having discogenic low back pain. In the study by Chen (2009), the pre-test probability (prevalence) was 39%; in the study by Han (2023), the prevalence was 46% in studies involving low back pain.

I. <u>Medical history taking</u>

Henao Romero (2020) describes in a mapping review how frequently certain signs and symptoms are mentioned in relation to discogenic low back pain. The aim of the review was not to assess the quality of the articles or to pool the data, but to investigate the frequency of reporting of various signs and symptoms. Inclusion and exclusion criteria were not reported. The study concludes (non-quantitatively) that the following findings from the medical history could be used to support the diagnosis: axial low back pain, absence of radicular pain, worsening of pain in a seated position, or worsening of pain during trunk flexion.

Fuji (2019) notes in a narrative review that red flags for cancer, infection, or trauma must be ruled out. Furthermore, Fuji (2019) describes that the localization of back pain is an important factor in the diagnosis: centralized pain has a high sensitivity for discogenic pain, whereas lateralized pain without central pain often originates from the facet joint.

A systematic review (Petersen, 2017; see the section *Physical Examination* for details) found that a history of pain crossing the midline is not a reliable measure for confirming or ruling out discogenic low back pain (sensitivity 0.27; 95% CI 0.11 to 0.52 and specificity 0.38; 95% CI 0.14 to 0.69).

II. Physical examination

The systematic review by Han (2023) was an update of an earlier review from 2007. Studies on patients with low back pain and the diagnostic value of a primary care test, published between March 2006 and January 2023, were added to the previous review. For discogenic low back pain, discography (tested at a minimum of 2 levels per patient) was used as the reference standard. Clinically relevant results were defined as a positive likelihood ratio of ≥ 2 or a negative likelihood ratio of ≤ 0.5. In total, 35 studies focused on discogenic pain. The results of Han (2023) are presented in Table 3 (for physical examination) and Table 4 (for additional diagnostic testing).

The systematic review by Petersen (2017) searched for studies (search date up to May 2015) that evaluated clinical findings for various causes of low back pain. For discogenic low back pain, discography was used as the reference standard. Clinical relevance was assessed based on diagnostic value: a positive likelihood ratio of ≥ 2 or a negative likelihood ratio of ≤ 0.5. Four studies on discogenic low back pain were identified. The results and conclusions are presented in Table 3. This study also briefly mentioned the historical finding of pain crossing the midline; see the section *Medical history taking* for details.

Henao Romero (2020) concludes through a mapping review that the following findings from physical examination are frequently reported in studies about discogenic pain: difficulty changing from sitting to standing position and centralization of pain.

Table 3. Results from studies reporting on diagnostic signs from physical examination for discogenic pain.

Test	Characteristic	Quantitative/qualitative (95% CI)	Reference test	Interpretation	Study
Centralization – level of patient	Change of pain in the furthermost whole body region	Positive LR (Individual studies): 2.1 (1.2 to 3.9) 9.4 (0.6 to 146.9) 6.9 (1.0 to 47.3) *Negative LR all >0.5*	Discography	positive test is not highly useful for ruling in the diagnosis (weak evidence for few false positives); negative test does not rule out diagnosis	Petersen 2017 (3 studies)
		Positive LR (pooled): 3.06 (1.44 to 6.50) Sensitivity 41.2% Specificity 85.9% Negative LR 0.66	Discography		Han 2023 (4 studies; 3 same as Petersen)

III. Additional diagnostic testing

MRI

Henao Romero (2020) concludes through a mapping review that Pfirrmann scale ≥2, presence of high-intensity zones (HIZ), and Modic changes (I, II or III) may indicate discogenic low back pain, as they are frequently reported.

The systematic review by Han (2023) presented pooled data on various aspects visible on MRI (disc degeneration, high-intensity zones, annular fissures, and Modic changes). Further details on the study can be found in the section *Physical Examination*, and the results are presented in Table 4.

The systematic review by Chen (2009) compared high-intensity zones (HIZ) on T2-weighted MRI with discography. Ten studies were included but not pooled (8 of these were the same studies included in Han, 2023). The positive likelihood ratios ranged from 18.37 (a positive HIZ can confirm the diagnosis) to 1.55 (HIZ has no additional value for establishing the diagnosis); the negative likelihood ratios ranged from 0.03 (a negative HIZ can exclude the diagnosis) to 0.96 (HIZ has no additional value for excluding the diagnosis). Chen (2009) concludes that – assuming a prevalence of 39% – a positive HIZ warrants further investigation with discography, while a negative test result can rule out the diagnosis of discogenic low back pain.

Another systematic review by Yang (2023) included 28 observational studies with patients experiencing low back pain who underwent T2-weighted MRI scans and discography. Of the included studies, 25 examined the relationship between HIZ and pain replication during discography. Results are shown in Table 4. The study concluded that a more advanced degree of disc degeneration on the basis of HIZ corresponded to a greater probability of discography-induced consistent pain.

The systematic review by Herlin (2018) included prospective and retrospective cohort studies as well as case-control studies involving patients with low back pain and research into Modic changes on MRI. The pathology of Modic change has been revealed to be afibrogenic and proinflammatory crosstalk between bone marrow and adjacent discs (Fuji, 2019). Herlin (2018) calculated the odds ratio between different types of Modic changes and concordant pain during provocative discography. The results are presented in Table 4. The study concludes that the association between Modic changes and low back pain is inconsistent and suggests that this relationship is influenced by disc degeneration.

The systematic review by Teraguchi (2018) included six studies that correlated the presence of HIZ with the presence of pain. The conclusions from these studies were contradictory: half found an almost doubled prevalence of HIZ in symptomatic discs, while the other half found no significant difference (see Table 4).

Table 4. Results from studies reporting on diagnostic signs from medical imaging (MRI) for discogenic pain.

Test	Characteristic	Quantitative/qualitative (95% CI)	Reference test	Interpretation	Study
Disc degeneration	Pfirrmann scale Graad ≥3	Positive LR (pooled): 2.53 (1.57 to 4.07) Sensitivity 91.0% Specificity 61.3% Negative LR (pooled): **0.15 (0.09 to 0.24)**	Discography	positive test is not highly useful for ruling in the diagnosis (weak evidence); **negative test is useful for ruling out diagnosis** (few false negatives)	Han 2023 (4 studies)

	Pfirrmann scale Graad ≥4	Positive LR (pooled): 2.20 (1.61 to 3.01) Sensitivity 70.7% Specificity 66.7% Negative LR (pooled): 0.37 (0.19 to 0.73)	Discography	positive test is not highly useful for ruling in the diagnosis and negative test not highly useful for ruling out (weak evidence)	Han 2023 (3 studies)
High Intensity Zone (HIZ) (high-intensity signal located in the substance of the posterior annulus fibrosus, which is brighter than the nucleus pulposus in T2-weighted images)	Evidence of a HIZ on MRI	Positive LR (pooled): 3.10 (2.27 to 4.25) Sensitivity 95.4% Specificity 65.6% Negative LR (pooled): 0.61 (0.48 to 0.77)	Discography	positive HIZ is not highly useful for ruling in the diagnosis (weak evidence); negative HIZ does not rule out diagnosis	Han 2023 (12 studies)
	Presence of HIZ	Positive HIZ gives post-test probability of 93.1% of discogenic LBP. Negative HIZ gives post-test probability of 1.96% of discogenic LBP.	Discography	Positive and negative HIZ could be useful for clinical practice	Chen 2009 (10 studies, 8 overlap with Han 2023)
	HIZ observed on MRI	Pooled OR: 7.71 (5.29 to 11.23)	Discography	Positive HIZ more likely to be associated with pain during discography than negative HIZ	Yang 2023 (25 studies)
	HIZ observed on MRI	Prevalence of HIZ in symptomatic discs: 3-61% In asymptomatic discs: 2-32%	-	Prevalence of HIZ high in asymptomatic discs, therefore not specific for (discogenic) low back pain	Teraguchi 2018 (6 studies)
Annular fissure	Evidence of annular fissure	Positive LR (pooled): 2.88 (2.02 to 4.10) Sensitivity 61.2% Specificity 73.8% Negative LR (pooled): 0.24 (0.10 to 0.55)	Discography	positive test is not highly useful for ruling in the diagnosis and negative test not highly useful for ruling out (weak evidence)	Han 2023 (4 studies)
Modic changes	Type 1 Modic changes (high signal on T2-weighted and low/hypointense signal on T1-weighted MRI, most biologically active; represent an inflammatory reaction in the bone marrow (edema type))	Positive LR (pooled): **10.00 (4.20 to 23.82)** Sensitivity 12.9% Specificity 98.7% Negative LR: 0.84 (0.74 to 0.96)	Discography	**positive test is useful for ruling in the diagnosis** (few false positives); negative test does not rule out diagnosis	Han 2023 (4 studies)
		Pooled OR: 6.14 (2.47 to 15.27)	Discography	MC type 1 is mildly associated with concordant pain on discography	Herlin, 2018 (5 studies, 2 studies overlap with Han 2023)
	Type 2 Modic changes (high signal on T1 images and isointense or slightly hyperintense signal on T2 images; represent a fat infiltration of the bone marrow	Positive LR (pooled): **8.03 (3.23 to 19.97)** Sensitivity 12.0% Specificity 98.6% Negative LR (pooled): 0.88 (0.80 to 0.96)	Discography	**positive test is useful for ruling in the diagnosis** (few false positives); negative test does not rule out diagnosis	Han 2023 (3 studies)
		Pooled OR: 3.15 (1.00 to 9.93)	Discography	MC type 2 is mildly associated with concordant pain on discography	Herlin 2018 (5 studies; 2 studies overlap with Han 2023)
	Any modic change (1, 2 or 3; type 3 is seen as low signal on both T1 and T2 images; represent sclerotic change of the bone marrow)	Pooled OR: 4.01 (1.52 to 10.61)	Discography	Modic changes are mildly associated with concordant pain on discography	Herlin 2018 (8 studies, 2 studies overlap with Han 2023)

Discography

The narrative review by Carragee (2001) describes that the specificity of discography is influenced by patient characteristics. Discography is considered positive when the patient experiences pain at low intradiscal pressure, but many other factors can contribute to pain perception (such as psychogenic factors or the presence of chronic pain). These factors may affect the patient's ability to indicate whether the pain during discography is concordant (*i.e.*, that the discography reproduces the same quality and localization of pain as the discogenic low back pain). For instance, the specificity of discography can be as high as 90% in healthy patients without chronic pain and with a normal psychiatric profile but as low as 20% in patients with chronic pain and psychiatric risk factors.

The study by Carragee (2006) included 32 patients with low back pain and a positive discogram, using fairly strict inclusion and exclusion criteria to prevent negative clinical outcomes from being attributed to comorbidities. These patients underwent spinal fusion. The control group consisted of a matched cohort of 34 patients with unstable spondylolisthesis (grade I or II). The study aimed to use postoperative clinical outcomes as the gold standard to confirm which positive discographies were truly true-positive tests. Surgical success was the outcome measure, defined as a VAS score of ≤2 after 2 years of follow-up, an Oswestry Disability Index score of ≤15, full return to work or daily activities, and no use of pain medication (all criteria had to be met for the surgery to be considered successful; a minimally acceptable outcome allowed for slightly less stringent criteria). The results are presented in Table 5. Carragee (2006) concludes from this study that positive discography (pain occurring at a pressure of <20 psi above opening pressure) does not reliably identify isolated intradiscal lesions that cause chronic low back pain (= discogenic low back pain). The best-case positive predictive value (PPV) of discography was 50%-60%.

Table 5. Results after surgical intervention (Carragee, 2006)

Results	**Discogenic pain group (n = 32)**	**Spondylolisthesis group (n = 34)**
VAS ≤ 2	9 (30%)	27 (84.3%)
ODI ≤ 15	10 (33%)	23 (71.9%)
No medication	9 (30%)	28 (87.5%)
Full return to work/dialy activities	9 (30%)	26 (81.2%)
Total (all criteria)	*8 (26.6%)*	*23 (71.9%)*

Fuji (2019) describes in a narrative review that in nearly all international consensus statements, provocative discography or CT discography is part of the diagnostic process for discogenic low back pain, but that there is no standard diagnostic process. It is also noted that discography carries a risk of accelerated disc degeneration and herniation. Therefore, discography should be reserved for specific patients for whom surgical intervention is considered.

Minimally invasive diagnostic tests

Fuji (2019) describes in his narrative review several promising noninvasive tools for diagnosing discogenic pain:

- Serum biomarkers: Complement C3 or fibrinogen could be candidate biomarkers for discogenic low back pain. However, the specificity of these biomarkers needs to be validated, as they may also be elevated in other (systemic) diseases.
- Local biomarkers: Substance P, neurofilament, and vasoactive-intestinal peptide immunoreactive nerve fibers in the painful discs have been shown to be more extensive than in control discs.

- Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS): According to one study, MALDI-TOF-MS could differentiate between discogenic low back pain and other forms of low back pain.
- pH levels: Recent studies have shown a relationship between low pH and discogenic pain; thus, pH may serve as a metabolic biomarker for discogenic pain.

The study by Gornet (2024) describes the validation of a previously developed methodology for identifying painful or non-painful discs using Magnetic Resonance Spectroscopy (MRS), in a prospective dataset. A method for MRS was previously developed in a training cohort, using postprocessing techniques to correlate discs (painful or non-painful) with findings from provocative discography and with structural degeneration via the Pfirrmann grade. This was done using a NOCISCORE (0-10 scale) based on levels of alanine, lactate, and propionate, and an SI-SCORE, which is the proteoglycan spectral value normalized to the highest calculated level in the patient. For validation, 14 patients who underwent discography for suspected discogenic pain were included. MRS was performed on 44 discs, of which 19 discs were also subject to discography. The NOCISCORE was significantly higher in painful discs (validated with positive discography) and lower in non-painful discs (validated with negative discography). The NOCISCORE had a positive predictive value of 84% and a negative predictive value of 86%. A higher SI-SCORE was correlated with a lower Pfirrmann grade.

The narrative review by Hirsch (2024) describes studies about the value SPECT/CT in diagnosing low back pain. Four studies were found on discogenic pain; the findings were:

- The presence of increased uptake in the anterior body on SPECT/CT is correlated with degenerative disc changes on MRI and CT (in 7 patients with low back pain).
- Increased vertebral endplate uptake is more frequent in patients with low back pain than in the control group, yet one-third of patients with low back pain does not have increased endplate uptake (94 patients).
- The positive association between Modic changes on MRI and heightened activity on SPECT/CT. 71% of MRI findings resulted in scintigraphically active endplates and disc spaces on SPECT/CT (99 patients).

They concluded that SPECT/CT might have a role in the diagnosis, especially in understanding pathophysiology of discogenic pain, but that more research is needed.

Other

A poor response to facet and sacroiliac block, ruling out mechanical low back pain, could be an extra indicator for discogenic low back pain (Henao Romero, 2020).

Conclusions

No GRADE conclusions are drawn, as an exploratory search was performed to construct and support the recommendations.

Implementatietabel

Aanbeveling	Stel de waarschijnlijkheidsdiagnose discogene lage rugpijn op basis van een optelsom van factoren en exclusie van andere factoren en pathologieën Wees terughoudend met het aanbieden van behandelingen voor discogene lage rugpijn	
1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X** Ongewenste praktijkvariatie □ Nieuwe evidentie **X** Anders **Toelichting:** Er wordt veel gespeculeerd over behandelingen van discogene rugpijn, maar het is überhaupt onduidelijk hoe deze diagnose gesteld kan worden. Hier is internationaal geen consensus over.	
2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**X** < 1000 □ < 5000 □ 5000-40.000 □ > 40.000	
3. Maakt de aanbeveling deel uit van een set van interventies voor hetzelfde probleem?	**X** Ja □ Nee	
4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:	**Wat zijn mogelijke belemmerende factoren?**	**Wat zijn mogelijke bevorderende factoren?**
a. Richtlijn/ klinisch traject (innovatie)	In de literatuur wordt het begrip discogene rugklachten vaak gebruikt, echter een diagnostische basis ontbreekt	Haalbaar, geloofwaardig.
b. Zorgverleners (artsen en verpleegkundigen)	Eigen ding willen blijven doen (behandeling aanbieden ondanks dat de diagnose moeilijk gesteld kan worden)	Drive om goede en efficiente kwaliteit van zorg te bieden
c. Patiënt/ cliënt (naasten)	Het blijven zoeken naar een somatische diagnose in de rug	*Duidelijkheid dat de kans op discogene lage rugklachten moeilijk te stellen is en als enige origine van rugklachten weinig voorkomt*
d. Sociale context		Samenwerking anesthesie en rugchirurgen op dit onderwerp
e. Organisatorische context	**Meer concentratie van discografien in specifieke centra en in onderzoeksopzet.**	sluit gedeeltelijk aan bij huidige praktijk
f. **Economische/ politieke context**	**Minder interventies voor discogene lage rugklachten**	Impliceert geen extra Kosten, eerder kostenreductie
Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk?	□ Patiënt/ cliënt (naaste) **X** Professional **X** Beroepsvereniging □ Ziekenhuis(bestuurder) □ Zorgverzekeraars/ NZa □ Zorginstituut [duiding nodig]	
5. Wat zouden deze personen/ partijen moeten veranderen in hun gedrag of organisatie om de aanbeveling toe te passen?	Geen discografie buiten gespecialiseerde centra en in onderzoeksverband. Breder kijken naar de diagnose (discogene) lage rugpijn	
6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X** < 1 jaar □ < 2 jaar □ < 3 jaar Sluit grotendeels al aan bij huidige praktijk, behoeft niet veel grootschalige (organisatorische) verandering	
7. Conclusie: is er extra aandacht nodig voor implementatie van de aanbeveling (anders dan publicatie van deze richtlijnmodule)?	□ **Ja*** **X Nee** **Toelichting:** Sluit aan bij huidige praktijk, behoeft niet veel grootschalige (organisatorische) verandering	

Zoekverantwoording

Algemene informatie

Cluster/richtlijn: Cluster Wervelkolomgerelateerde aandoeningen	
Uitgangsvraag/modules: UV4 Oriënterende search: Hoe moet de diagnostiek van discogene lage rugpijn er uit zien?/ Hoe wordt de diagnose discogene lage rugpijn gesteld?	
Database: Embase.com	Datum: 26 juni 2024
Periode: vanaf 2000	Talen: geen restrictie
Literatuurspecialist: Alies Oost	Rayyan review: https://rayyan.ai/reviews/1076388
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Deduplication: voor het ontdubbelen is gebruik gemaakt van http://dedupendnote.nl/	
Toelichting: Voor deze vraag is gezocht op de elementen: discogene lage rugpijn diagnostische methoden Dit betreft een oriënterende search.	
Te gebruiken voor richtlijntekst: In de database Embase.com is op 26 juni 2024 oriënterend gezocht naar richtlijnen en systematische reviews vanaf 2000 over (bepaalde) diagnostische methoden voor discogene lage rugpijn. De literatuurzoekactie leverde 582 unieke treffers op.	

Zoekopbrengst

	EMBASE
Guideline/ consensus	238
SR	344
Totaal	582*

***in Rayyan**

Zoekstrategie

Embase.com

No.	Query	Results
#1	'discogenic pain'/exp OR 'lumbar disk degeneration'/exp OR 'lumbar disk hernia'/exp OR (((lumbar OR lumbal OR lumbalis) NEAR/3 ('disc* disease*' OR 'disk* disease*' OR 'disc* degenerat*' OR 'disk* degenerat*' OR 'disc* deteriorat*' OR 'disk* deteriorat*' OR discopath* OR diskopath* OR dd OR ddd OR idd OR 'disc* displac*' OR 'disk* displac*' OR 'disc* hernia*' OR 'disk* hernia*' OR 'disc* prolaps*' OR 'disk* prolaps*' OR 'disc* protrus*' OR 'disk* protrus*' OR 'disc* ruptur*' OR 'disk* ruptur*' OR 'disc* syndrome*' OR 'disk* syndrome*')):ti,ab,kw) OR (((displace* OR degenerat* OR detoriat* OR hernia* OR prolapse* OR protrud* OR protrus* OR ruptur* OR slipped) NEAR/3 lumbar NEAR/3 (disc OR disk)):ti,ab,kw) OR (((lumbar OR lumbal OR lumbalis OR discogenic) NEAR/3 (pain* OR ache OR backpain OR backach*)):ti,ab,kw) OR ((mechanical NEAR/3 (low OR lower) NEAR/3 (backpain OR 'back pain' OR backache OR 'back ache')):ti,ab,kw) OR (((annular OR disc OR disk) NEAR/3 (tear* OR fissure OR disrupt*)):ti,ab,kw) OR (('lumbar disk'/exp OR 'intervertebral disk disease'/de OR 'intervertebral disk degeneration'/de OR 'intervertebral disk hernia'/de OR ((degenerative NEAR/3 ('disk disease*' OR 'disc disease*')):ti,ab,kw)) AND ('low back pain'/exp OR (((low OR lower) NEAR/3 (backpain OR 'back pain' OR backache OR 'back ache')):ti,ab,kw)))	32586
#2	'anamnesis'/exp OR anamnes*:ti,ab,kw OR 'history taking':ti,ab,kw OR 'physical examination'/de OR 'physical examin*':ti,ab,kw OR 'diagnostic imaging'/de OR 'diskography'/exp OR discograph*:ti,ab,kw OR diskograph*:ti,ab,kw OR discogram:ti,ab,kw OR diskogram:ti,ab,kw OR 'nuclear magnetic resonance imaging'/exp OR 'mri scanner'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR	2608541

	mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'mr imag*':ti,ab,kw OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti OR rsfmri:ti,ab,kw OR 'scintigraphy'/exp OR scintigraph*:ti,ab,kw OR scintillograph*:ti,ab,kw OR scintiphotograph*:ti,ab,kw OR scintiscan*:ti,ab,kw OR scintillation:ti,ab,kw OR laminoscintigraph*:ti,ab,kw OR 'orthopedic cast'/de OR 'plaster cast'/de OR 'walking cast'/de OR ((cast* NEAR/3 (body OR pantaloon OR plaster)):ti,ab,kw) OR corset:ti,ab,kw OR plaster:ti,ab,kw OR orthosis:ti,ab,kw OR orthoses:ti,ab,kw OR immobilis*:ti,ab,kw OR immobiliz*:ti,ab,kw OR ((facet NEAR/3 (block* OR test*)):ti,ab,kw) OR modic:ti,ab,kw OR 'disc height'/de OR 'disc height index'/de OR 'disc height':ti,ab,kw OR 'disk height':ti,ab,kw OR pfirman*:ti,ab,kw OR dallas:ti,ab,kw	
#3	#1 AND #2 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT (('adolescent'/exp OR 'child'/exp OR adolescent*:ti,ab,kw OR child*:ti,ab,kw OR schoolchild*:ti,ab,kw OR infant*:ti,ab,kw OR girl*:ti,ab,kw OR boy*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenager*:ti,ab,kw OR youth*:ti,ab,kw OR pediatr*:ti,ab,kw OR paediatr*:ti,ab,kw OR puber*:ti,ab,kw) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp OR adult*:ti,ab,kw OR man:ti,ab,kw OR men:ti,ab,kw OR woman:ti,ab,kw OR women:ti,ab,kw)) AND [2000-2024]/py	8280
#4	'practice guideline'/exp OR guideline*:ti,kw OR cpg:ti,kw OR consensus*:ti,kw OR recommend*:ti,kw OR standard*:ti,kw	1063552
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'scoping review'/exp OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	1040463
#6	#3 AND #4 – guideline/ consensus	238
#7	#3 AND #5 NOT #6 - SR	344
#8	#6 OR #7	582

Bijlagen module 6 – Persistent Spinal Pain Syndrome type 2 (PSPS-2)

Search and select

A systematic review of the literature was performed to answer the following question:
What are the effects of new forms of SCS compared with low frequency SCS (standard care) for patients with PSPS-2?

Table 1. PICO

Patients	Patients suffering from chronic (>3 months) radicular leg pain with or without back pain, for whom conservative treatment was unsuccessful and reoperation is not indicated by a spine surgeon (neurosurgeon or orthopedic surgeon). (PSPS-2)
Intervention	New forms of SCS (High frequency, new wave forms and closed-loop)
Control	Low frequency, tonic SCS (<90Hz; paresthesia based open-loop stimulation)
Outcomes	**Crucial:** pain, quality of life **Important:** function, return to work, use of pain medication, complications
Other selection criteria	Study design: systematic reviews and randomized controlled trials Minimal follow-up: 12 months

Relevant outcome measures

The working group considered pain and quality of life as **critical** outcome measures for decision making; and functioning/self-sufficiency, return to work, medication use and complications as **important** outcome measures for decision making.

The working group defined the outcome measures as follows:

Pain	NRS of VAS
Quality of life	EQ5D, SF-12, SF-36, HADS, PCS, PROMIS-29
Function	ODI, sleep (Pittsburgh sleep scale (PSQI))
Adverse Events	Complications related to the technique (e.g. migration, lead breakage, infection, reoperation)
Return to work	not pre-defined
Use of pain medication	Analgetics – specifically opioids (morfinequivalent)

The working group defined a 10% change as a minimal clinically (patient) important difference. This roughly corresponds to a difference of ten points on the Visual Analog Scale (VAS scale: 0 to 100 mm), one point on the Numeric Rating Scale (NRS scale: 0 to 10), and ten points on the Oswestry Disability Index (ODI) (scale 0 to 100).

For risk ratios and odds ratios, the thresholds of 0.91 and 1.1 are applied. Standardized Mean Difference (SMD) is classified as 0.2 (small), 0.5 (moderate), and 0.8 (large).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until August 19th, 2024. The detailed search strategy is listed under the tab 'Literature search strategy'. The systematic literature search resulted in 850 hits. Studies were selected based on the following criteria:

- Systematic reviews or randomized controlled trials
- Reported on high frequency SCS, new wave forms for neuromodulation, or closed-loop SCS as intervention
- Used low frequency SCS paresthesia based SCS as control
- Reported at least one of the outcomes from the PICO (table 1)

- Provided results over a follow-up of at least 12 months.

Initially, 42 studies were selected based on title and abstract screening. After reading the full text, 35 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 7 studies (totaling 4 study cohorts) were included.

Summary of literature

Description of studies

A total of seven studies describing four study cohorts were included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

High frequency SCS

De Andres (2017) and the SENZA cohort (Amirdelfan 2018, Kapural 2015 and Kapural 2016) compared conventional low frequency tonic stimulation SCS with high frequency SCS. Both studies included patients with chronic pain refractory to traditional treatment. De Andres (2017) only included patients with a previous back surgery (failed back surgery syndrome). However, the SENZA cohort included a mixed population since previous surgery was not an inclusion criterium. Therefore, this study did not adhere fully to the patient population in the predefined PICO. However, 75 to 79 percent of the patients in the groups of the SENZA cohort were diagnosed with PSPS-2. Thus, the working group assumed that results of this study could be generalized to the group defined in or PICO. Following the GRADE rating of evidence we downgraded the evidence found in this study for indirectness.

- Additional inclusion criteria for De Andres (2017) were: >18 years of age, mainly axial low back pain or radiating leg pain that failed to respond to other treatment, an NRS ≥5, a 50% reduction in NRS in the two-week trial period. Exclusion criteria were: unresolved issues of secondary gain or inappropriate medication use, mechanical low back pain, coexisting chronic pain conditions or neurological disease, coexisting conditions increasing procedural risk, a history of laminectomy or posterior fusion, abnormal pain behavior, unresolved psychiatric illness and a negative psychological evaluation.
- Additional inclusion criteria for SENZA were: an Oswestry Disability Index (ODI) between 41 and 80, average back pain VAS ≥50, average leg pain VAS ≥50. Exclusion criteria were: active psychological or psychiatric disorders that can impact perception of pain, mechanical spine instability and prior experience with SCS.

Differential Target Multiplex SCS

Fishman (2021) compared the effectiveness of differential target multiplexed SCS (DTM-SCS) with conventional SCS in the treatment of chronic low back and leg pain. They included adult patients that were a candidate for SCS per labeled indication with a VAS ≥50 with moderate to severe leg pain, stable pain medication for over 30 days and willingness to not increase medication for 3 months. Exclusion criteria were: unresolved legal issues or secondary gain (e.g. work related) or inappropriate medication use, a medical, anatomic, and/or psychosocial condition that contraindicate the SCS neurostimulation system, an existing active implanted device, mechanical spine instability, or an interventional procedure or surgery within 30 days of enrollment which provided pain relief.

Closed-loop SCS

The EVOKE cohort (Mekhail 2020 and 2022) compared traditional low frequency open-loop SCS with closed-loop SCS in patients with chronic intractable pain of the back and legs

refractory to conservative therapy that were a candidate for an SCS trial. Patients with and without previous back surgery were included. Therefore, this study did not adhere fully to the patient population in the predefined PICO. However, over 60 percent of the patients in the groups of the EVOKE cohort were diagnosed with PSPS-2. Therefore, the working group assumed that results of this study could be generalized to the group defined in or PICO. Following the GRADE rating of evidence, we downgraded the evidence found in this study for indirectness.

Additional inclusion criteria were: 18 to 80 years of age, overall VAS, back pain VAS ánd leg pain VAS ≥60 cm, an ODI between 41 and 80, stable pain medication and no previous SCS therapy. Exclusion criteria were: active disruptive psychological or psychiatric disorder, medical condition that could interfere with accurate pain reporting, not a surgical candidate, existing implantable device and prior experience with SCS.

Table 2. Characteristics of included studies

Study	Participants	Intervention	Control	Outcomes	Comments	Risk of bias *
High versus low frequency						
De Andres 2017 *Spain, Multidisciplinary Pain Management Department of a hospital*	N I: 26 | C: 29 Sex (% female) I: 42.3 | C: 62.1 Age (mean ± SD) I: 53.8 ±11.5 | C: 51.6 ± 9.3 NRS (mean ± SD) I: 7.69 ± 1.17 | C: 7.60 ± 1.06 ODI (mean ± SD) I: 26.96 ± 5.18 | C: 27.18 ± 5.21	High frequency SCS - initial pulse width 30 µs - initial amplitude 1.5 mA (max 5 mA) - frequency: 10.000 Hz	Low frequency SCS stimulation patterns tested for optimal overlap between paresthesia and the region of the subjects's back and leg pain covering the entire area of pain. - max amplitude 8 volts - initial pulse width 300 µs (max 450 µs) - initial frequency 40 Hz	*After 12 months:* Pain (NRS) Quality of Life (SF-12, HAD) Function (ODI) Adverse events (device related AEs)	Excluded patients from trial and analysis that had an unsuccessful trial phase (<50% NRS improvement)	LOW Pain, Quality of Life, Function, LOW Adverse events
SENZA (Amirdelfan 2018, Kapural 2015 and 2016) *United States, multicenter (mainly pain centers).*	N I: 92 | C: 87 Sex (% female) I: 62.0| C: 58.6 Age (mean ± SD) I: 54.6 ± 12.4 | C: 55.2 ± 13.4 Duration of pain (years; mean ± SD) I: 13.0 ± 10.4 | C: 14.2 ± 12.2 FBSS (%) I: 79.3 | C: 74.7 Previous back surgery (n,%) I: 87.0 | C: 86.2	High frequency SCS - 30 µs pulses delivered at 10,000 Hz with amplitude adjusted to optimal analgesic response (min, max ±SD: 1.6 ± 1.1, 3.8 ± 3.4 mA). No intraoperative testing Adjusted as needed based on patient feedback	Low frequency SCS. Adjusted to optimally overlap paresthesia with the region of the subject's back and leg pain. (min, max ±SD: 39.2 ± 15.0, 77.3 ± 133.5 Hz; amplitude 3.6 ± 2.8, 8.5 ± 4.0 mA; pulse width 347 ± 148, 591 ± 214 µ) Intraoperative testing Adjusted as needed based on patient feedback	*After 12 and 24 months:* Pain (>50%VAS improvement, VAS leg and back) Function (ODI) Quality of Life (PSQI, SF-12) Adverse Events	Excluded subjects with unsuccessful trial phase: only patients with ≥50% or greater back pain reduction from baseline were eligible to proceed to permanent implantation.	HIGH

Study	Participants	Intervention	Control	Outcomes	Comments	Risk of bias *
	VAS (mm, mean ± SD) *back pain* I: 7.4 ± 1.2 | C: 7.8 ± 1.2 *Leg pain* I: 7.1 ± 1.5 | C: 7.6 ± 1.4					
Differential Target Multiplexed (DTM)						
Fishman, 2021 *United States,* *12 'investigational sites*	N I: 67 | C: 61 Sex (% female) I: 50.7 | C: 55.7 Age (mean ± SD) I: 61.28 ± 12.16 | C: 60.66 ± 11.77 VAS (mean ± SD) *Back pain* I: 7.3 ± 1.5| C: 7.4 ± 1.3 *Leg pain* I: 6.2 ± 2.6 | C: 6.6 ± 2.1 Spine surgeries (mean ± SD) I: 1.5 ± 1.3 | C: 1.4 ± 1.1 Years since onset symptoms (mean ± SD) I: 12.64 ± 13.05 | C: 12.89 ±11.25	DTM SCS 4 possible programs, intensity adjusted for optimal use. Possible settings: - 50 Hz 200 µs - 300 Hz 170 µs Subjects could adjust stimulation intensity and selected DTM SCS options based on optimal pain relief.	Traditional SCS *"subjects were programmed according to the labeling/manual"*	*After 12 months:* Pain (NRS) Quality of Life (PROMIS) Function (ODI) Adverse events	Included patients in ITT analysis that had an unsuccessful trial phase (<40% VAS improvement)	HIGH
Closed-loop SCS						
EVOKE (Mekhail 2020 and 2022) *United States, 12 sites: specialist clinics, academic centers and hospitals*	N I: 67 | C: 67 Sex (% female) I: 48 | C: 49 Age (mean ± SD) I: 55.9 ± 11.6	Fixed-output, open-loop SCS	Closed-loop SCS	*After 12 months:* Pain (≥50% improvement in VAS*, VAS) Quality of Life (EQ-5d-5L*, SF 12*)	(1) Previous surgery was not an inclusion criterium (not adhering fully to PICO) (2) Excluded highest functioning patients (ODI 41-80)	HIGH

Study	Participants	Intervention	Control	Outcomes	Comments	Risk of bias *
	C: 54.6 ± 9.7 <u>Duration of pain (years; mean ± SD)</u> I: 11.2 ± 9.9 | C: 13.6 ± 9.6 <u>FBSS (n (%))</u> I: 41 (61) | C: 38 (57) <u>Previous back surgery (n,%)</u> I: 41 (61) | C: 39 (58) <u>VAS (mm, mean ± SD)</u> *Overall* I: 82.3 ± 8.8 | C: 81.9 ± 10.6 *Back pain* I: 80.4 ± 11.2 | C: 81.4 ± 10.2 *Leg pain* I: 80.0 ± 9.9 | C: 82.2 ± 8.8			Function (ODI*, PSQI*) Adverse events (AE serious/ non serious) Use of pain medication (daily morphine equivalents) **also change scores after 24 months*	(3) Included patients in analysis that had an unsuccessful trial phase (<50% VAS improvement). However, the study excluded patients that withdrew voluntarily, unrelated to device.	
Abbreviations: C- control; DTM SCS - Differential Target Multiplexed spinal cord stimulation; FBSS – failed back surgery syndrome; HAD – Hospital Anxiety and Depression Scale – intervention; NRS numeric rating scale; ODI – Oswestry Disability Index; SCS spinal cord stimulation; SF-12- 12-Item Short Form Survey; VAS – visual analogue scale;						

*For further details, see risk of bias table in the appendix

Results

Results are presented separately for three different types of new-form SCS: high frequency SCS, differential targeted multiplexed (DTM) SCS and closed-loop SCS.

1. High frequency SCS

Pain (crucial)

Pain intensity was reported with an 11-point pain intensity numeric rating scale (NRS) or visual analogue scale (VAS), where 0 represents no pain and 10cm (or 100mm) represents the worst possible pain. When VAS scores were presented in millimeters, they were divided by 10 to make comparison between studies possible.

De Andres (2017) reported pain intensity with the NRS at 12 months and did not specify pain location. SENZA reported VAS back pain and leg pain at 24 months. Pain scores are reported in Table 3.

Table 3. Pain - high frequency SCS

Study	Pain type	Intervention	Control	MD [95% CI]	Follow-up
SENZA	Back pain (at follow-up)	2.4±2.3	4.5 ± 2.9	-2.10 [-2.89 to -1.31]*	24 months
	Back pain (change from baseline)	-5.0 ± 2.5	-3.2 ± 3.0		
	Leg pain (at follow-up)	2.4±2.5	3.9 ± 2.8	-1.50 [-2.30 to -0.70]*	24 months
	Leg pain (change from baseline)	-4.7 ± 2.8	-3.7 ± 3.0		
De Andres (2017)	Not specified (at follow-up)	6.06 ± 2.13	5.86 ± 2.46	0.20 [-1.01 to 0.41]	12 months
	Not specified (change from baseline)	-1.82 ± 2.45	-1.44 ± 2.28		

** clinically relevant*

Abbreviations: CI – confidence interval; MD – mean difference; SCS – spinal cord stimulation

Quality of life (crucial)

De Andres (2017) reports on quality of life with the Hospital Anxiety and Depression Scale (HADS) and the mental health component of the Short Form-12 (Table 4). The HADS is a self-assessment scale detecting states of depression, anxiety, and emotional distress. Scales range from 0 to 21 with higher scores indicating greater anxiety, depression, or mood disorders.

The (SF-12) questionnaire results in a physical component summary and a mental component summary. A score above 50 on the SF-12 indicates better functioning than average whereas scores below 50 indicate lower than average quality of life. De Andres (2017) reports the mental health component.

Table 4. Quality of life – high frequency SCS

Study	Subscale	Intervention	Control	MD [95% CI]	Follow-up
De Andres (2017)	HADS anxiety (at follow-up)	8.69 ± 5.08	8.54 ± 5.67	0.15 [-2.69 to 2.99]	12 months
	HADS anxiety (change from baseline)	-1.62 ± 4.07	-2.04 ± 5.82		
	HADS depression (at follow-up)	8.19 ± 5.00	7.21 ± 4.97	0.98 [-1.66 to 3.62]	
	HADS depression (change from baseline)	-0.77 ± 4.5	-2.00 ± 5.38		
	SF-12 Mental health (at follow-up)	49.64 ± 24.3	48.46 ± 24.8	1.18 [-11.79 to 14.15]	
	SF-12 Mental health	5.77 ± 23.9	10.6 ± 32.0		

** clinically relevant*

Abbreviations: CI – confidence interval; HADS - Hospital Anxiety and Depression Scale; MD – mean difference; SF-12 – Short form -12;

Function (important)

De Andres (2017) and Senza report on function with the Oswestry Disability Index (ODI). The ODI is condition-specific outcome measures used in the management of spinal disorders. The score ranges from 0 to a 100 with 0 representing no disability and a 100 representing total disability. ODI scores by De Andres (2017) are reported in Table 5.

Table 5. Function reported by De Andres – high frequency SCS

Study	Outcome measure	Intervention	Control	MD [95% CI]	Follow-up
De Andres (2017)	ODI (at follow-up)	22.96 ±7.06	22.07 ± 7.85	0.89 ± -3.05 to 4.83	12 months
	ODI (change from baseline)	-4.04 ± 5.77	-4.14 ± 8.76		

** clinically relevant*

Abbreviations: CI – confidence interval; MD – mean difference; ODI – Oswestry Disability Index

SENZA reported ODI in categories (Table 6).

Table 6. Function reported by Senza – high frequency SCS

	Intervention		Control	
ODI category	baseline n=89	Follow-up n=85	Baseline (n=80)	Follow-up (n=71)
Minimal (%)	0.0	23.5	0.0	9.9
Moderate (%)	9.4	41.2	1.4	39.4
Severe (%)	69.4	30.6	77.5	42.3
Bedbound (%)	21.2	4.7	21.1	8.5

Abbreviations: ODI – Oswestry Disability Index

Adverse events (important)

De Andres (2017) reported one lead migration with replacement (3.4%) after twelve months in the high frequency SCS group compared to two (6.5%) in the conventional low frequency SCS group. They reported no infection or complains of pain at implant site.

SENZA reported six study-related adverse events (5.0%) in the high-frequency group compared to eight (7.2%) in the traditional SCS group. They reported that lead migration resulting in surgical revision occurred in 3.0% of high frequency SCS therapy subjects and 5.2% of traditional SCS.

Return to work (important)

None of the included studies reported on return to work.

Use of pain-medication (important)

SENZA reported decreased or eliminated opioid use in 35.5% of the intervention group compared to 26.4% in the traditional SCS group. They also reported on daily morphine equivalents for individuals who were taking opioids at baseline (Table 7).

Table 7. Morphine equivalents – high frequency SCS

	Outcome measure	Intervention	Control	Mean Difference [95% CI]	Follow-up
SENZA	ME (at follow-up)	87.9 ± 85.3	118.0 ± 113.2	-30.10 [-61.61 to 1.41]*	12 months
	ME (change from baseline)	-24.8	-7.3		

** clinically relevant*

Abbreviations: CI – confidence interval; ME: morphine Equivalents in mg/day

2. Differential Targeted Multiplexed (DTM) SCS

Pain (crucial)

Pain intensity was reported with a visual analogue scale (VAS), where 0 represents no pain and 10cm (or 100mm) represents the worst possible. When VAS scores were presented in millimeters, they were divided by 10 to make comparison possible.

Fishman (2021) reports VAS reduction in leg pain and back pain at 12 months (Table 8). No absolute values of pain at follow-up were reported. However a clinicalyl relevant change is VAS is observed for leg and back pain in both the intervention and control condition.

Table 8. Pain reported by Fishman – DTM SCS

Study	Oucome measure	Intervention	Control	Follow-up
Fishman (2021)	Leg pain (change from baseline)	-5.53±2.79	-4.95 ± 2.38	12 months
	Back pain (change from baseline	-5.48±2.41	-3.62 ± 2.53	

Quality of life

None of the included studies on DTM-SCS reported on quality of life.

Function (important)

Fisman (2021) reports on function with the Oswestry Disability Index (ODI). The ODI is condition-specific outcome measures used in the management of spinal disorders. The score ranges from 0 to a 100 with 0 representing no disability and a 100 representing total disability. Fishman (2021) reports on the ODI in categories (Table 9).

Table 9. Function reported by Fishman –DTM SCS

Study	ODI category	Intervention		Control	
		Baseline	Follow-up	Baseline	Follow-up
Fishman (2021)	Minimal (%)	0.0	31.0	0	32.4
	Moderate (%)	26.9	45.2	24.6	29.7
	Severe (%)	56.7	21.4	55.7	37.8
	Bedbound (%)	16.4	2.4	19.7	0.0

Abbreviations: CI – confidence interval; DTM SCS- differential target multiplexed spinal cord stimulation; ODI: Oswestry Disability Index

Adverse events (important)

Fishman (2021) reported four adverse events (6.0%) in the DTM-SCS group compared to eight (13.1%) in the traditional SCS group. Of the adverse events in the DTM SCS-group, two were lead dislodgements. Two serious adverse events (medical device site pain and site infection) occurred in the traditional SCS group (3.3%) of which the infection (1.6%) led to system explant in the trial phase.

Return to work (important)

None of the included studies on DTM-SCS reported on return to work.

Use of pain-medication (important)

None of the included studies on DTM-SCS reported on the use of pain medication.

3. Closed-loop SCS

Pain (crucial)

EVOKE reports on VAS overall back and leg pain at 24 months. Pain scores are reported in Table 10.

Table 10. Pain – Closed-loop SCS

Study	Outcome measure	Intervention	Control	MD [95% CI]	Follow-up
EVOKE	Overall back and leg pain (at follow-up)	2.64±2.6	3.83 ± 2.97	-1.19 [-2.20 to 0.18]*	24 months
	Overall back and leg pain (change from baseline)	-5.56 ± NR	-4.39 ± NR		

** clinically relevant*

Abbreviations: CI – confidence interval; DTM SCS- differential target multiplexed spinal cord stimulation; HF – high frequency; MD – mean difference; SCS – spinal cord stimulation

Quality of life (crucial)

EVOKE reports on quality of life with the SF-12 for the physical and the mental health component and the European Quality of Life Five-Dimensional Five-Level Index score (EQ-5D 5L) at 24 months follow-up.

The (SF-12) questionnaire results in a physical component summary (PCS) and a mental component summary (MCS). A score above 50 on the SF-12 indicates better functioning than average whereas scores below 50 indicate lower than average quality of life. The EQ-5D-DL score ranges from 0 to 1, with 1 representing best health. Quality of life scores are reported in Table 11.

Table 11. Quality of life – closed-loop SCS

Study	Outcome measure	Intervention	Control	Follow-up
EVOKE	SF-12 Physical health (change from baseline)	10.1 ± 11.0	11.0 ± 10.0	24 months
	SF-12 Mental health (change from baseline)	6.7 ± 11.6	-1.4 ± 10.0	
	EQ-5D-5L (change from baseline)	0.25 ± 0.16	0.21 ± 0.16	

Abbreviations: EQ-5D-5L - European Quality of Life Five-Dimensional Five-Level Index score; SF-12 – Short form -12;

Function (important)

EVOKE report on function with the Oswestry Disability Index (ODI) and the Pittsburgh Sleep Quality Index (PSQI) (Table 12). The ODI is condition-specific outcome measures used in the management of spinal disorders. The score ranges from 0 to a 100 with 0 representing no disability and a 100 representing total disability). The PSQI is designed to measure sleep problems and sleep disorders. The score ranges from zero to 21 with lower scores representing better sleep quality. EVOKE only reported change scores for function. No intention to treat analysis was performed. Results are reported in Table 12.

Table 12. Function – closed-loop SCS

Study	Outcome measure	Intervention	Control	Follow-up
EVOKE	ODI (change from baseline)	22.96 ± 7.06	22.07 ± 7.86	24 months
	PSQI (change from baseline)	-4.1 ± 4.3	-4.1 ± 4.7	

Abbreviations: ODI - Oswestry Disability Index; PSQI - Pittsburgh Sleep Quality Index

Adverse events (important)

EVOKE reported two explants (3%) due to procedure-related infections in the closed-loop group, compared to one (1.5%) in the open-loop group. Furthermore, they reported two

explants (3%) due to loss of efficacy in the open-loop group compared to zero in the closed-loop group.

Return to work (important)

None of the included studies reported on return to work.

Use of pain-medication (important)

EVOKE reported on voluntary opioid reduction or elimination of patients who were taking opioids at baseline and on daily morphine milligram equivalents. EVOKE reported a reduction in 18 out of 27 (66.7%) patients in the closed-loop group compared to 14 out of 23 (60.9%) patients in the open-loop group. MME is reported in table 13.

Table 13. Use of pain medication – Closed-loop SCS

Study	Outcome measure	Intervention	Control	Mean Difference [95% CI]	Follow up
EVOKE	MME (at follow-up)	41.9 ± 47.3	42.2 ± 41.5	-0.30 [-24.92 to 24.32]	24 mo
	MME (change from baseline)	-38.2 ± NR	-24.2 ± NR		

Abbreviations: CI – confidence interval; MME – daily morphine milligram equivalents; NR- not reported

Summary of Findings

Summary of Findings table: High frequency SCS compared with traditional SCS in PSPS-2

Outcome	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Conclusions**
		High freq SCS	**Low freq SCS**		
Pain (crucial)	Measured by: VAS and NRS Both have a scale from 0 to 10 (higher scores indicating higher pain) Based on data from 2 studies. (*De Andres, 2017; SENZA)*	SENZA reported a **mean difference (VAS)** - in back pain of -2.10 (95%CI -2.89 to -1.31) - in leg pain of -1.50 (95%CI -2.30 to -0.70). Both in favor of the intervention group. De Andres (2017) reported a **mean difference (NRS)** of 0.20 (95%CI [-1.01 to 0.41]) in favor of the control group.		**Very low** Due to very serious risk of bias, serious inconsistency and serious imprecision[1]	The evidence is very uncertain about the effect of high frequency SCS on pain when compared with low frequency SCS in patients with PSPS-2.
Quality of life (crucial)	Measured by: HADS and SF-12 mental health subscale Based on data from 1 study (*De Andres, 2017)*	See result section for details.		**Low** Due to very serious imprecision[2]	High frequency SCS may lead to little or no difference in quality of life when compared with low frequency SCS in patients with PSPS-2.
Function (important)	Measured by ODI Scale 0 to 100 (higher scores indicating higher disability) Based on data from 1 study with 55 participants *(De Andres, 2017)*	22.96 ± 7.06	22.07 ±7 .86	**Low** Due to very serious imprecision[3]	High frequency SCS may lead to little or no difference in function when compared with low frequency SCS in patients with PSPS-2.
		Difference: **MD 0.89 higher** (CI 95% 3.05 lower to 4.83 higher)			
Adverse events	Based on data from 2 studies *(De Andres, 2017; SENZA)*	Adverse events were reported as lead migration, infection and complaints of pain at implant site by De Andres (2017). SENZA reported on study-related adverse events and lead migration resulting in surgical revision. See result section for details.		**Very low** Due to very serious risk of bias, serious imprecision, and serious indirectness[4]	The evidence is very uncertain about the effect of high frequency SCS on pain when compared with low frequency SCS in patients with PSPS-2.
Return to work (important)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of high frequency SCS on return to work when compared with traditional SCS in patients with PSPS-2.
Use of pain-medication (important)	Measured by: morphine equivalent Based on 1 study on 158 participants *(SENZA)*	87.9±85.3	118.0±113.2	**Very Low** Due to very serious risk of bias, serious imprecision, and serious indirectness[5]	The evidence is very uncertain about the effect of high frequency SCS use of pain medication when compared with low frequency SCS in patients with PSPS-2.
		Difference: **MD 30.10 lower** (CI 95% 61.61 lower to 1.41 higher)			
Abbreviations: CI – confidence interval; HADS – Hospital anxiety and depression scale; MD – mean difference; NRS – Numeric Rating Scale; ODI – Oswestry Disability Index; PSPS – Persistent Spinal Pain Syndrome; SCS – spinal cord stimulation; VAS- Visual Analogue Score					

1. **Risk of Bias: very serious.** Due to lack of blinding, due to study sponsoring by manufacturer. **Imprecision: serious.** Due to overlap of the upper limit of the 95% confidence interval with the minimal clinically important difference. **Inconsistency:** serious. Due to conflicting results. Indirectness: serious. Due to broader patient inclusion than PICO.
2. **Imprecision**: very serious. Due to overlap of the limits of the 95% confidence interval with the minimal clinically important difference.
3. **Imprecision**: very serious. Due to not reaching the optimal information size.
4. **Risk of Bias: very serious.** Due to lack of blinding, due to study sponsoring by manufacturer. **Imprecision: serious.** Due to a small number of events. Indirectness: serious. Due to broader patient inclusion than PICO.
5. **Risk of Bias: very serious.** Due to lack of blinding, due to study sponsoring by manufacturer. **Imprecision: serious.** Due to overlap of the lower limit of the 95% confidence interval with the minimal clinically important difference. Indirectness: serious. Due to broader patient inclusion than PICO.

Summary of Findings table: DTM - SCS compared with traditional SCS in PSPS-2

Outcome	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Conclusions**
		DTM-SCS	**Low freq SCS**		
Pain (crucial)	Based on data from 1 study with 128 participants. *(Fishman 2021)*	Pain was reported by Fishman (2021) as back and leg pain VAS change from baseline. They report a mean difference in change: - in back pain of 1.86 (95%CI -2.72 to -1.00) - in leg pain of -0.58 (95%CI -1.48 to 0.32). Both in favor of the intervention group.		**Very low** Due to very serious risk of bias and serious imprecision[1]	The evidence is very uncertain about the effect of DTM-SCS on pain when compared with low frequency SCS in patients with PSPS-2.
Quality of life (crucial)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of DTM-SCS on quality of life when compared with traditional SCS in patients with PSPS-2.
Adverse events	Based on data from 1 study with 128 participants. . *(Fishman 2021)*	Fishman (2021) reports four out of 67 (6.0%) adverse events in the DTM-SCS group compared to eight out of 61 (13.1%) in the traditional SCS group. Two were lead dislodgements which both occurred in the DTM SCS-group. See results for more detail.		**Very low** Due to very serious risk of bias, serious inconsistency and very serious imprecision[2]	The evidence is very uncertain about the effect of DTM-SCS on adverse events when compared with low frequency SCS in patients with PSPS-2.
Function; Return to work; Use of Pain medication (important)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of DTM-SCS on function, return to work or use of pain medication when compared with traditional SCS in patients with PSPS-2.
Abbreviations: CI – confidence interval; DTM-SCS - differential target multiplexed SCS; HADS – Hospital anxiety and depression scale; MD – mean difference; NRS – Numeric Rating Scale; ODI – Oswestry Disability Index; PSPS – Persistent Spinal Pain Syndrome; SCS – spinal cord stimulation; VAS- Visual Analogue Score					

1. **Risk of Bias: very serious.** Due to lack of blinding, due to study sponsoring by manufacturer. **Imprecision: serious.** Due to overlap of the upper limit of the 95% confidence interval with the minimal clinically important difference.
2. **Risk of Bias: very serious.** Due to lack of blinding, due to study sponsoring by manufacturer. **Imprecision**: very serious. Due to overlap of the limits of the 95% confidence interval with the minimal clinically important difference.

Summary of Findings table: Closed-loop SCS compared with traditional open-loop SCS in PSPS-2

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Conclusions
		Closed-loop SCS	Open-loop SCS		
Pain (crucial)	Pain Measured by: VAS Scale from 0 to 10 (higher scores indicating higher pain) Based on data from 1 study (EVOKE).	2.64 ± 2.6	3.83 ± 2.97	**Very low** Due to very serious risk of bias, serious indirectness and serious imprecision[1]	The evidence is very uncertain about the effect of DTM-SCS on pain when compared with low frequency SCS in patients with PSPS-2.
		Difference: **MD 1.19 lower** (CI 95% 2.20 lower - 0.18 lower)			
Quality of life (crucial)	-	EVOKE reported on quality of life as the change from baseline in SF-12 and the EQ-5D-5L. See results for more detail.		**Very low** Due to very serious risk of bias, serious indirectness and serious imprecision[2]	The evidence is very uncertain about the effect of DTM-SCS on quality of life when compared with low frequency SCS in patients with PSPS-2.
Function (important)	Based on data from 1 study with 171 participants (EVOKE).	EVOKE reported on function as change of baseline in ODI and change of baseline in PSQI. - **Ook Mean difference ODI** was 2.80 (CI 95% -8.55 to 0.95) in favor of the DTM-SCS group. - **Mean difference PSQI** was 0.00 (CI 95% -1.53 to 1.53)		**Very low** Due to very serious risk of bias, serious indirectness and serious imprecision[3]	The evidence is very uncertain about the effect of DTM-SCS on function when compared with low frequency SCS in patients with PSPS-2.
Adverse events	Based on data from 1 study (EVOKE).	EVOKE reported on adverse events as procedure related infections leading to explants. **Risk ratio** 1.68 (CI 95% 0.16 to 17.88) in favor of traditional SCS.		**Very low** Due to very serious risk of bias, serious indirectness and very serious imprecision[3]	The evidence is very uncertain about the effect of DTM-SCS on adverse events when compared with low frequency SCS in patients with PSPS-2.*)*
Return to work (important)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of DTM-SCS on return to work when compared with traditional SCS in patients with PSPS-2.
Use of pain-medication (important)	Measured by: morphine equivalents Based on 1 study on 158 participants (EVOKE).	41.9 ± 47.3	42.2 ± 41.5	**Very Low** Due to very serious risk of bias, due to due to serious imprecision, due to serious indirectness[3]	The evidence is very uncertain about the effect of DTM-SCS on use of pain medication when compared with low frequency SCS in patients with PSPS-2.
		Difference: **MD 0.30 lower** (CI 95% 24.92 lower to 24.32 higher)			
Abbreviations: CI – confidence interval; DTM-SCS - differential target multiplexed SCS; HADS – Hospital anxiety and depression scale; MD – mean difference; NRS – Numeric Rating Scale; ODI – Oswestry Disability Index; PSPS – Persistent Spinal Pain Syndrome; SCS – spinal cord stimulation; VAS- Visual Analogue Score					

1. **Risk of Bias: very serious.** Due to lack of blinding, due to study sponsoring by manufacturer. **Imprecision: serious.** Due to not reaching the optimal information size. Indirectness: serious. Due to broader patient inclusion than PICO.
2. **Risk of Bias: very serious.** Due to lack of blinding, due to study sponsoring by manufacturer. **Imprecision**: very serious. Due to overlap of the limits of the 95% confidence interval with the minimal clinically important difference. Indirectness: serious. Due to broader patient inclusion than PICO.
3. **Risk of Bias: very serious.** Due to lack of blinding, due to study sponsoring by manufacturer. **Imprecision**: very serious. Due to overlap of the limits of the 95% confidence interval with the minimal clinically important difference. Indirectness: serious. Due to broader patient inclusion than PICO.

Implementatietabel

Aanbeveling – 1 en subaanbeveling	Op basis van de beschikbare evidentie en ervaring uit de praktijk kon er onvoldoende richting aan de besluitvorming worden gegeven. Om die reden is er geen beschrijving van belemmeringen en kansen voor implementatie van de aanbeveling toegevoegd. Disseminatie van de kennis in deze module verloopt via de standaard route. De module wordt gepubliceerd op de Richtlijnendatabase.

Risk of Bias tables

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?**	**Was the allocation adequately concealed?**	**Blinding: Was knowledge of the allocated interventions adequately prevented? | Were patients/healthcare providers/data collectors/outcome assessors / data analysts blinded?**	**Was loss to follow-up (missing outcome data) infrequent?**	**Are reports of the study free of selective outcome reporting?**	**Was the study apparently free of other problems that could put it at a risk of bias?**	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
De Andres, 2017	Probably yes; Reason: Computerized list of randomized numbers	Definitely yes; Reason: Investigators were blinded from assignment until after allocation	Definitely no; Reason: Open label trial. Outcome assessors were blinded, patients were not, but were unaware of hypothesis. (blinding of data analysts not reported)	Probably yes; Reason: There was no loss to follow-up reported.	Definitely yes; Reason: All relevant outcomes were reported	Definitely yes; Reason: No other problems noted	**LOW**
SENZA trial (Amirdelfan 2018, Kapural 2015 and 2016)	Definitely yes; Reason: Stratified randomization administered cen trally with each study site assigned randomly chosen alternating blocks of sizes 2, 4, and 6	No information	Definitely no; Reason: open-label trial – subjects and investigators were not blinded.			Definitely no; Authors received personal fees from device manufacturer Sample size for noninferiority (not for comparison). One-sided sign. Testing. Higher pain score in the control group at baseline.	**HIGH** Reason: Open label trial, Industry sponsored study. Baseline differences between groups in favor of intervention.

Fishman, 2022	Definitely yes; Reason: Central block randomization after with computer generated random numbers	No information	**Definitely no;** Reason: Open-label trial (patients and health care providers not blinded), outcome assessors blinded (blinding of data collectors and analysts not reported)	Probably yes Reason: *Loss to follow-up was infrequent in intervention and control group. Adequate imputation methods (multiple imputation) were used*	Definitely yes R*eason: All relevant outcomes were reported;*	Definitely no; *Reason: Industry sponsored authors (Medtronic). Study sponsored by Stimgenics (now acquired by Medtronic) which is the manufacturer of the DTM device.*	**HIGH** **Reason:** Open label trial, industry sponsored study.
Mekhail (2020) and Mekhail (2022) EVOKE – trial	Definitely yes Reason: Computer generetad blocked and stratified randomization by an independent statistician	Definitely yes; Reason: Treat ment allocation was concealed from the patients, investigator, and site staff		Probably no; Reason: No ITT analysis for secondary outcomes. Significant loss to follow up, 25% in the closed-loop (C) and 37% in the open-loop. (I)	Probably no; Reason: Only change scores are reported. For some measures no SD is reported. However, all outcome measures are reported.	Definitely no; Reason: Industry sponsored study (Saluda Medical, manufacturer of EVOKE system) Several authors are employees of the device manufacturer. Many outcomes reported on a relatively small group.	**HIGH** Reason: No ITT analysis for secondary outcomes at 24 months. Industry sponsored study.

Table of excluded studies

Reference	Reason for exclusion
Braun E, Khatri N, Kim B, Nazir N, Orr WN, Ballew A, Latif U, Sack A, Sowder T, Canova K, Clark S, Grace P, Khan TW. A Prospective, Randomized Single-Blind Crossover Study Comparing High-Frequency 10,000 Hz and Burst Spinal Cord Stimulation. Neuromodulation. 2023 Jul;26(5):1023-1029. doi: 10.1016/j.neurom.2022.10.054. Epub 2022 Dec 7. PMID: 36494306.	Crossover design, follow-up too short.
Breel J, Wille F, Wensing AGCL, Kallewaard JW, Pelleboer H, Zuidema X, Bürger K, de Graaf S, Hollmann MW. A Comparison of 1000 Hz to 30 Hz Spinal Cord Stimulation Strategies in Patients with Unilateral Neuropathic Leg Pain Due to Failed Back Surgery Syndrome: A Multicenter, Randomized, Double-Blinded, Crossover Clinical Study (HALO). Pain Ther. 2021 Dec;10(2):1189-1202. doi: 10.1007/s40122-021-00268-7. Epub 2021 Jun 6. PMID: 34091818; PMCID: PMC8586063.	Crossover design, follow-up too short.
Conger A, Sperry BP, Cheney CW, Burnham TM, Mahan MA, Onofrei LV, Cushman DM, Wagner GE, Shipman H, Teramoto M, McCormick ZL. The Effectiveness of Spinal Cord Stimulation for the Treatment of Axial Low Back Pain: A Systematic Review with Narrative Synthesis. Pain Med. 2020 Nov 1;21(11):2699-2712. doi: 10.1093/pm/pnaa142. PMID: 32472130.	Review without meta-analysis
De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World Neurosurg. 2013 Nov;80(5):642-649.e1. doi: 10.1016/j.wneu.2013.01.040. Epub 2013 Jan 12. PMID: 23321375.	Follow-up too short
De Ridder D, Lenders MW, De Vos CC, Dijkstra-Scholten C, Wolters R, Vancamp T, Van Looy P, Van Havenbergh T, Vanneste S. A 2-center comparative study on tonic versus burst spinal cord stimulation: amount of responders and amount of pain suppression. Clin J Pain. 2015 May;31(5):433-7. doi: 10.1097/AJP.0000000000000129. PMID: 24977394.	Wrong study design: retrospectieve study
Deer T, Slavin KV, Amirdelfan K, North RB, Burton AW, Yearwood TL, Tavel E, Staats P, Falowski S, Pope J, Justiz R, Fabi AY, Taghva A, Paicius R, Houden T, Wilson D. Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation. 2018 Jan;21(1):56-66. doi: 10.1111/ner.12698. Epub 2017 Sep 29. PMID: 28961366.	Crossover design, follow-up too short.
Do TT, Smet I, Jerjir A, Vandamme K, Devos M, Van Buyten JP. Real-World Analysis: Long-Term Effect of Spinal Cord Stimulation With Different Waveforms for Patients With Failed Back Surgery Syndrome. Pain Pract. 2021 Feb;21(2):215-225. doi: 10.1111/papr.12952. Epub 2020 Oct 21. PMID: 32964562.	Non-randomized study
D'Souza RS, Strand N. Neuromodulation With Burst and Tonic Stimulation Decreases Opioid Consumption: A Post Hoc Analysis of the Success Using Neuromodulation With BURST (SUNBURST) Randomized Controlled Trial. Neuromodulation. 2021 Jan;24(1):135-141. doi: 10.1111/ner.13273. Epub 2020 Sep 14. PMID: 32929783.	Crossover design, follow-up too short.
Duarte RV, McNicol E, Colloca L, Taylor RS, North RB, Eldabe S. Randomized Placebo-/Sham-Controlled Trials of Spinal Cord Stimulation: A Systematic Review and Methodological Appraisal. Neuromodulation. 2020 Jan;23(1):10-18. doi: 10.1111/ner.13018. Epub 2019 Jul 15. PMID: 31305001; PMCID: PMC7004207.	Review without meta-analysis
Duse G, Reverberi C, Dario A. Effects of Multiple Waveforms on Patient Preferences and Clinical Outcomes in Patients Treated With Spinal Cord Stimulation for Leg and/or Back Pain. Neuromodulation. 2019 Feb;22(2):200-207. doi: 10.1111/ner.12899. Epub 2018 Dec 11. PMID: 30548106.	Crossover design, follow-up too short. Wrong comparison
Eldabe S, Duarte R, Gulve A, Williams H, Garner F, Brookes M, Madzinga G, Buchser E, Batterham AM. Analgesic Efficacy of "Burst" and Tonic (500 Hz) Spinal Cord Stimulation Patterns: A Randomized Placebo-Controlled Crossover Study. Neuromodulation. 2021 Apr;24(3):471-478. doi: 10.1111/ner.13321. Epub 2020 Nov 29. PMID: 33251662.	Crossover design, follow-up too short. Wrong comparison (placebo)
Gallego H, Arango S, Combalia A, Fuster S, Jaramillo C, Herrera AM. Treatment Options for Failed Back Surgery Syndrome: An Umbrella Systematic Review of Systematic Reviews on the Effectiveness of Therapeutic Interventions. Spine Surg Relat Res. 2023 Aug 10;8(2):143-154. doi: 10.22603/ssrr.2023-0032. PMID: 38618223; PMCID: PMC11007241.	Umbrella review, two relevant reviews appeared in search and were considered separately.
Goudman L, De Smedt A, Eldabe S, Rigoard P, Linderoth B, De Jaeger M, Moens M; Discover Consortium. High-dose spinal cord stimulation for patients with failed back surgery syndrome: a multicenter effectiveness and prediction study. Pain. 2021 Feb 1;162(2):582-590. doi: 10.1097/j.pain.0000000000002035. PMID: 32910099.	Wrong study design: prospective cohort stuy.
Grider JS, Manchikanti L, Carayannopoulos A, Sharma ML, Balog CC, Harned ME, Grami V, Justiz R, Nouri KH, Hayek SM, Vallejo R, Christo PJ. Effectiveness of Spinal Cord Stimulation in Chronic Spinal Pain: A Systematic Review. Pain Physician. 2016 Jan;19(1):E33-54. PMID: 26752493.	Review without meta-analysis, no recent search.

Hara S, Andresen H, Solheim O, Carlsen SM, Sundstrøm T, Lønne G, Lønne VV, Taraldsen K, Tronvik EA, Øie LR, Gulati AM, Sagberg LM, Jakola AS, Solberg TK, Nygaard ØP, Salvesen ØO, Gulati S. Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery: A Randomized Clinical Trial. JAMA. 2022 Oct 18;328(15):1506-1514. doi: 10.1001/jama.2022.18231. PMID: 36255427; PMCID: PMC9579901.	Crossover design, follow-up too short. Wrong comparison (placebo)
Head J, Mazza J, Sabourin V, Turpin J, Hoelscher C, Wu C, Sharan A. Waves of Pain Relief: A Systematic Review of Clinical Trials in Spinal Cord Stimulation Waveforms for the Treatment of Chronic Neuropathic Low Back and Leg Pain. World Neurosurg. 2019 Nov;131:264-274.e3. doi: 10.1016/j.wneu.2019.07.167. Epub 2019 Jul 30. PMID: 31369885.	Systematic review of insufficient quality
Hou S, Kemp K, Grabois M. A Systematic Evaluation of Burst Spinal Cord Stimulation for Chronic Back and Limb Pain. Neuromodulation. 2016 Jun;19(4):398-405. doi: 10.1111/ner.12440. Epub 2016 May 3. PMID: 27139915.	Review without meta-analysis
Kallewaard JW, Billet B, Van Paesschen R, Smet I, Mendiola A, Peña I, López P, Carceller J, Tornero C, Zuidema X, Vesper J, Lehmberg J, Laloo W, Cedeño DL, Vallejo R. European randomized controlled trial evaluating differential target multiplexed spinal cord stimulation and conventional medical management in subjects with persistent back pain ineligible for spine surgery: 24-month results. Eur J Pain. 2024 Nov;28(10):1745-1761. doi: 10.1002/ejp.2306. Epub 2024 Jun 28. PMID: 38943239.	Wrong comparison (conventional medical management)
Kapural L, Mekhail NA, Costandi S, Gilmore C, Pope JE, Li S, Hunter CW, Poree L, Staats PS, Taylor RS, Eldabe S, Kallewaard JW, Thomson S, Petersen EA, Sayed D, Deer TR, Antony A, Budwany R, Leitner A, Soliday N, Duarte RV, Levy RM. Durable multimodal and holistic response for physiologic closed-loop spinal cord stimulation supported by objective evidence from the EVOKE double-blind randomized controlled trial. Reg Anesth Pain Med. 2024 Apr 2;49(4):233-240. doi: 10.1136/rapm-2023-104639. PMID: 37491149; PMCID: PMC11041592.	No absolute outcome measures reported.
Kapural L, Patterson DG, Li S, Hatheway J, Hunter C, Rosen S, Fishman M, Gupta M, Sayed D, Christopher A, Burgher A, McJunkin T, Ross EL, Provenzano D, Amirdelfan K. Multiphase Spinal Cord Stimulation in Participants With Chronic Back or Leg Pain: Results of the BENEFIT-02 Randomized Clinical Trial. Neuromodulation. 2023 Oct;26(7):1400-1411. doi: 10.1016/j.neurom.2023.05.006. Epub 2023 Aug 16. PMID: 37589641.	Wrong comparison (both interventions are high frequency SCS)
Karri J, Orhurhu V, Wahezi S, Tang T, Deer T, Abd-Elsayed A. Comparison of Spinal Cord Stimulation Waveforms for Treating Chronic Low Back Pain: Systematic Review and Meta-Analysis. Pain Physician. 2020 Sep;23(5):451-460. Erratum in: Pain Physician. 2022 Mar;25(2):221. PMID: 32967388.	Systematic review of insufficient quality without sub analysis for relevant patient group.
Lamer TJ, Moeschler SM, Gazelka HM, Hooten WM, Bendel MA, Murad MH. Spinal Stimulation for the Treatment of Intractable Spine and Limb Pain: A Systematic Review of RCTs and Meta-Analysis. Mayo Clin Proc. 2019 Aug;94(8):1475-1487. doi: 10.1016/j.mayocp.2018.12.037. Epub 2019 Jul 3. PMID: 31279543.	Review without recent search. Relevant RCTs appeared in search and were considered separately.
Luecke T, Edgar D, Huse D. 10 kHz spinal cord stimulation for the treatment of chronic back and/or leg pain: Summary of clinical studies. SAGE Open Med. 2020 Aug 20;8:2050312120951369. doi: 10.1177/2050312120951369. PMID: 32913650; PMCID: PMC7444111.	Only includes one relevant RCT which was assessed separately.
Mekhail NA, Levy RM, Deer TR, Kapural L, Li S, Amirdelfan K, Pope JE, Hunter CW, Rosen SM, Costandi SJ, Falowski SM, Burgher AH, Gilmore CA, Qureshi FA, Staats PS, Scowcroft J, McJunkin T, Carlson J, Kim CK, Yang MI, Stauss T, Petersen EA, Hagedorn JM, Rauck R, Kallewaard JW, Baranidharan G, Taylor RS, Poree L, Brounstein D, Duarte RV, Gmel GE, Gorman R, Gould I, Hanson E, Karantonis DM, Khurram A, Leitner A, Mugan D, Obradovic M, Ouyang Z, Parker J, Single P, Soliday N; EVOKE Study Group. ECAP-controlled closed-loop versus open-loop SCS for the treatment of chronic pain: 36-month results of the EVOKE blinded randomized clinical trial. Reg Anesth Pain Med. 2024 May 7;49(5):346-354. doi: 10.1136/rapm-2023-104751. PMID: 37640452; PMCID: PMC11103285.	RCT results reported after possibility for cross-over.
Metzger CS, Hammond MB, Pyles ST, Washabaugh EP 3rd, Waghmarae R, Berg AP, North JM, Pei Y, Jain R. Pain relief outcomes using an SCS device capable of delivering combination therapy with advanced waveforms and field shapes. Expert Rev Med Devices. 2020 Sep;17(9):951-957. doi: 10.1080/17434440.2020.1812383. Epub 2020 Sep 21. PMID: 32883126.	Wrong study design: case-series
Mong MSA, Lai MYC, Cheng LJ, Lau Y. Novel Spinal Cord Stimulation Waveforms for Treating Back and Leg Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Neuromodulation. 2023 Jul;26(5):905-916. doi: 10.1016/j.neurom.2022.11.003. Epub 2022 Dec 11. PMID: 36517255.	No meta-analysis for relevant group.

Muhammad S, Roeske S, Chaudhry SR, Kinfe TM. Burst or High-Frequency (10 kHz) Spinal Cord Stimulation in Failed Back Surgery Syndrome Patients With Predominant Back Pain: One Year Comparative Data. Neuromodulation. 2017 Oct;20(7):661-667. doi: 10.1111/ner.12611. Epub 2017 May 24. PMID: 28544182.	Non-randomized study and not the right comparison
Papalia GF, Russo F, Vadalà G, Pascarella G, De Salvatore S, Ambrosio L, Di Martino S, Sammartini D, Sammartini E, Carassiti M, Papalia R, Denaro V. Non-Invasive Treatments for Failed Back Surgery Syndrome: A Systematic Review. Global Spine J. 2023 May;13(4):1153-1162. doi: 10.1177/21925682221141385. Epub 2022 Nov 22. PMID: 36412047; PMCID: PMC10189334.	Review without meta-analysis
Paz-Solís J, Thomson S, Jain R, Chen L, Huertas I, Doan Q. Exploration of High- and Low-Frequency Options for Subperception Spinal Cord Stimulation Using Neural Dosing Parameter Relationships: The HALO Study. Neuromodulation. 2022 Jan;25(1):94-102. doi: 10.1111/ner.13390. PMID: 35041592.	Wrong study design: case-series
Pollard EM, Lamer TJ, Moeschler SM, Gazelka HM, Hooten WM, Bendel MA, Warner NS, Murad MH. The effect of spinal cord stimulation on pain medication reduction in intractable spine and limb pain: a systematic review of randomized controlled trials and meta-analysis. J Pain Res. 2019 Apr 30;12:1311-1324. doi: 10.2147/JPR.S186662. PMID: 31118751; PMCID: PMC6502439.	Review without recent search. Relevant RCTs appeared in search and were considered separately.
Provenzano DA, Park N, Edgar D, Bovinet C, Tate J. High-frequency (10 kHz) spinal cord stimulation (SCS) as a salvage therapy for failed traditional SCS: A narrative review of the available evidence. Pain Pract. 2023 Mar;23(3):301-312. doi: 10.1111/papr.13184. Epub 2022 Dec 8. PMID: 36409060.	Review without meta-analysis
Rigoard P, Ounajim A, Moens M, Goudman L, Roulaud M, Lorgeoux B, Baron S, Nivole K, Many M, Lampert L, David R, Billot M. Should we Oppose or Combine Waveforms for Spinal Cord Stimulation in PSPS-T2 Patients? A Prospective Randomized Crossover Trial (MULTIWAVE Study). J Pain. 2023 Dec;24(12):2319-2339. doi: 10.1016/j.jpain.2023.07.015. Epub 2023 Jul 18. PMID: 37473903.	
Sammak SE, Mualem W, Michalopoulos GD, Romero JM, Ha CT, Hunt CL, Bydon M. Rescue therapy with novel waveform spinal cord stimulation for patients with failed back surgery syndrome refractory to conventional stimulation: a systematic review and meta-analysis. J Neurosurg Spine. 2022 Jun 3;37(5):670-679. doi: 10.3171/2022.4.SPINE22331. PMID: 36303477.	Systematic review, wrong population and only 1 RCT included.
Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. Neuromodulation. 2014 Jul;17(5):443-50. doi: 10.1111/ner.12197. Epub 2014 Jun 19. PMID: 24945621.	Crossover design, follow-up too short.
Sokal P, Malukiewicz A, Kierońska S, Murawska J, Guzowski C, Rudaś M, Paczkowski D, Rusinek M, Krakowiak M. Sub-Perception and Supra-Perception Spinal Cord Stimulation in Chronic Pain Syndrome: A Randomized, Semi-Double-Blind, Crossover, Placebo-Controlled Trial. J Clin Med. 2020 Aug 31;9(9):2810. doi: 10.3390/jcm9092810. PMID: 32878061; PMCID: PMC7563558.	Follow-up too short.
Zheng Y, Liu CW, Hui Chan DX, Kai Ong DW, Xin Ker JR, Ng WH, Wan KR. Neurostimulation for Chronic Pain: A Systematic Review of High-Quality Randomized Controlled Trials With Long-Term Follow-Up. Neuromodulation. 2023 Oct;26(7):1276-1294. doi: 10.1016/j.neurom.2023.05.003. Epub 2023 Jul 10. PMID: 37436342.	Review without meta-analysis

Literature search strategy

Algemene informatie

Cluster/richtlijn: Cluster Wervelkolomgerelateerde aandoeningen	
Uitgangsvraag/modules: UV5 Wat is de aanbevolen strategie voor het toepassen van SCS bij patiënten met PSPS-2 om kwaliteit van leven te verbeteren en pijn te verminderen?	
Database(s): Embase.com, Ovid/Medline	Datum: 19 augustus 2024
Periode: vanaf 2010	Talen: geen restrictie
BMI-zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Deduplication: voor het ontdubbelen is gebruik gemaakt van http://dedupendnote.nl/	
Toelichting: Voor deze vraag is gezocht op de elementen: - Persistent Spinal Pain Syndrome (PSPS-2) - Spinal cord stimulation (SCS) De sleutelartikelen worden gevonden met deze search.	
Te gebruiken voor richtlijntekst: In de databases Embase.com en Ovid/Medline is op 19 augustus 2024 systematisch gezocht naar systematische reviews, RCTs en observationele studies vanaf 2010 over spinal cord stimulation (SCS) voor Persistent Spinal Pain Syndrome (PSPS-2). De literatuurzoekactie leverde 850 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SR	138	105	153
RCT	332	234	373
Observationele studies	318	246	324
Totaal	788	585	**850***

in Rayyan

Zoekstrategie

Embase.com

No.	Query	Results
#1	'failed back surgery syndrome'/exp OR (('leg pain'/de OR (((leg OR limb* OR 'lower extremit*') NEAR/6 pain*):ti,ab,kw)) AND ('refractory disease'/de OR 'intractable pain'/exp OR 'radiculopathy'/exp OR radiculopath*:ti,ab,kw OR polyradiculopath*:ti,ab,kw OR radiculalgia:ti,ab,kw OR radicular:ti,ab,kw OR 'nerve root*':ti,ab,kw OR neuropathic:ti,ab,kw OR chronic:ti,ab,kw OR intractable:ti,ab,kw OR refractory:ti,ab,kw)) OR 'chronic refractory pain':ti,ab,kw OR 'failed back surgery':ti,ab,kw OR (('failed back' NEAR/3 syndrome*):ti,ab,kw) OR fbss:ti,ab,kw OR (((postdiscectom* OR 'post discectom*' OR postlaminectom* OR 'post laminectom*' OR 'post lumbar surger*') NEAR/3 syndrome*):ti,ab,kw) OR psps2:ti,ab,kw OR (((psps OR 'persistent spinal pain') NEAR/3 (2 OR ii OR t2 OR syndrome*)):ti,ab,kw)	18788
#2	'spinal cord stimulation'/exp OR 'spinal cord stimulator'/exp OR 'waveform'/de OR (((spinal OR lumbal OR sacral OR lumbosacral OR 'dorsal column') NEAR/3 stimulat*):ti,ab,kw) OR scs:ti,ab,kw OR eses:ti,ab,kw OR dcs:ti,ab,kw OR electrostimulat*:ti,ab,kw OR neurostimulat*:ti,ab,kw OR neuromodulation:ti,ab,kw OR sunburst:ti,ab,kw OR senza:ti,ab,kw OR evoke:ti,ab,kw OR microburst:ti,ab,kw OR 'closed loop':ti,ab,kw OR waveform*:ti,ab,kw OR 'wave form*':ti,ab,kw OR burst*:ti,ab,kw OR 'differential target* multiplex*':ti,ab,kw OR dtm:ti,ab,kw OR '10 khz':ti,ab,kw OR 10khz:ti,ab,kw OR hf10:ti,ab,kw OR 'hf 10':ti,ab,kw	299719
#3	#1 AND #2 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT (('adolescent'/exp OR 'child'/exp OR adolescent*:ti,ab,kw OR child*:ti,ab,kw OR schoolchild*:ti,ab,kw OR infant*:ti,ab,kw OR girl*:ti,ab,kw OR boy*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenager*:ti,ab,kw OR youth*:ti,ab,kw OR pediatr*:ti,ab,kw OR paediatr*:ti,ab,kw OR puber*:ti,ab,kw) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp OR adult*:ti,ab,kw OR man:ti,ab,kw OR men:ti,ab,kw OR woman:ti,ab,kw OR women:ti,ab,kw))	1544
#4	#3 AND [2010-2024]/py	1219
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR	1054403

	systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4090717
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	8367442
#8	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	15324709
#9	#4 AND #5 - SR	138
#10	#4 AND #6 NOT #9 - RCT	332
#11	#4 AND (#7 OR #8) NOT (#9 OR #10) - observationeel	318
#12	#9 OR #10 OR #11	788

Ovid/Medline

#	Searches	Results
1	Failed Back Surgery Syndrome/ or ((((Lower Extremity/ or Leg/) and Pain/) or ((leg or limb* or 'lower extremit*') adj6 pain*).ti,ab,kf.) and (exp Pain, Intractable/ or Chronic Pain/ or exp Radiculopathy/ or radiculopath*.ti,ab,kf. or polyradiculopath*.ti,ab,kf. or radiculalgia.ti,ab,kf. or radicular.ti,ab,kf. or 'nerve root*'.ti,ab,kf. or neuropathic.ti,ab,kf. or chronic.ti,ab,kf. or intractable.ti,ab,kf. or refractory.ti,ab,kf.)) or 'chronic refractory pain'.ti,ab,kf. or 'failed back surgery'.ti,ab,kf. or ('failed back' adj3 syndrome*).ti,ab,kf. or fbss.ti,ab,kf. or ((postdiscectom* or 'post discectom*' or postlaminectom* or 'post laminectom*' or 'post lumbar surger*') adj3 syndrome*).ti,ab,kf. or psps2.ti,ab,kf. or ((psps or 'persistent spinal pain') adj3 ("2" or II or t2 or syndrome*)).ti,ab,kf.	9223
2	exp Spinal Cord Stimulation/ or ((spinal or lumbal or sacral or lumbosacral or 'dorsal column') adj3 stimulat*).ti,ab,kf. or scs.ti,ab,kf. or eses.ti,ab,kf. or dcs.ti,ab,kf. or electrostimulat*.ti,ab,kf. or neurostimulat*.ti,ab,kf. or neuromodulation.ti,ab,kf. or sunburst.ti,ab,kf. or senza.ti,ab,kf. or evoke.ti,ab,kf. or microburst.ti,ab,kf. or 'closed loop'.ti,ab,kf. or waveform*.ti,ab,kf. or 'wave form*'.ti,ab,kf. or	222870

	burst*.ti,ab,kf. or 'differential target* multiplex*'.ti,ab,kf. or dtm.ti,ab,kf. or '10 khz'.ti,ab,kf. or 10khz.ti,ab,kf. or hf10.ti,ab,kf. or 'hf 10'.ti,ab,kf.	
3	(1 and 2) not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/) not ((Adolescent/ or Child/ or Infant/ or adolescen*.ti,ab,kf. or child*.ti,ab,kf. or schoolchild*.ti,ab,kf. or infant*.ti,ab,kf. or girl*.ti,ab,kf. or boy*.ti,ab,kf. or teen.ti,ab,kf. or teens.ti,ab,kf. or teenager*.ti,ab,kf. or youth*.ti,ab,kf. or pediatr*.ti,ab,kf. or paediatr*.ti,ab,kf. or puber*.ti,ab,kf.) not (Adult/ or adult*.ti,ab,kf. or man.ti,ab,kf. or men.ti,ab,kf. or woman.ti,ab,kf. or women.ti,ab,kf.))	1150
4	limit 3 to yr="2010 -Current"	914
5	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	768262
6	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2765507
7	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4804244
8	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5763079
9	4 and 5 - SR	105
10	(4 and 6) not 9 - RCT	234
11	(4 and (7 or 8)) not (9 or 10) - observationeel	246
12	9 or 10 or 11	585