Interventional procedure overview of intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure from high spinal cord injuries

Contents

Table 1 Abbreviations

Abbreviation	Definition
CI	Confidence interval
DPS	Diaphragm pacing system
IQR	Interquartile range

Indications and current treatment

High spinal cord injuries can damage the nerves that control breathing and cause chronic respiratory failure.

Standard care for managing chronic respiratory failure in people with high spinal cord injuries includes non-invasive forms of ventilation support (such as bi-level positive airway pressure). In advanced stages of respiratory failure, mechanical ventilation is done through a permanent tracheostomy. Phrenic nerve pacing is an alternative treatment for people who have intact phrenic nerves (the nerves that contract the diaphragm). The diaphragm is stimulated to contract by electrodes placed on the phrenic nerve in the neck or thorax

What the procedure involves

The aim of intramuscular diaphragm stimulation is to make the diaphragm contract, enabling a full or partial weaning from mechanical ventilation. This procedure needs intact phrenic nerve function. It avoids the need to access the phrenic nerve through the neck or thorax, as well as reducing the risk of phrenic nerve damage.

The procedure is done laparoscopically with general anaesthesia. Areas of the diaphragm where minimal electrical stimulation causes maximal diaphragm contraction (known as the 'motor points') are mapped. Two intramuscular electrodes are implanted on the abdominal surface of each hemi-diaphragm at the motor points. The electrode leads are tunnelled subcutaneously to an exit site in the chest where they are connected to an external battery-powered pulse generator. A reference electrode (anode) is also implanted, and the leads tunnelled with the other electrodes. Intraoperative stimulation and voltage calibration tests are done to confirm there is adequate contraction of the diaphragm. After implantation the person follows a diaphragm conditioning programme, which involves progressive use of the system for increasing periods of time with gradual weaning from the ventilator.

Outcome measures

The main outcomes included the proportion of patients using a DPS to breathe without ventilator assistance for at least 4 hours a day and the proportion of people using it for 24 hours a day.

Evidence summary

Population and studies description

This interventional procedures overview is based on approximately 500 patients from 1 prospective single-arm trial with a meta-analysis of 5 studies (Onders 2022), 3 retrospective case series (Onders 2018, Monden 2022, Wijkstra 2022), 1 systematic review (Garara 2016) and 1 case report (Dong 2021). There was some patient overlap between studies. This is a rapid review of the literature, and a flow chart of the complete selection procedure is shown in figure 1. This overview presents 6 studies as the key evidence in table 2 and table 3, and lists 23 other relevant studies in table 5.

The 6 studies included patients from the US, Canada, Iceland, Spain, Italy, the Netherlands and Brazil. In the studies that reported the recruitment period, it ranged from 2000 to 2019. The systematic review included studies published between January 2000 and June 2015. One primary study also included a meta-analysis of 4 additional studies (Onders 2022).

In the systematic review, the mean time from injury to implantation ranged from 40 days to 9.7 years. In the other 4 studies, the median time from injury to DPS surgery or the phrenic nerve test ranged from 10 to 28 months. The follow-up period was not reported for all studies. In the systematic review, 2 studies had follow-up periods of 6 months and 2 years. Of the other 4 studies, 1 had a mean follow up of 12 months, 1 was 3 years and 1 was described as long term (the actual period was not reported but the overall median survival was 22 years).

The systematic review only included adult patients. Onders et al. (2018) reported that 14 children and young people were included in the study population and the age range in Wijkstra et al. (2022) was 2 to 65 years.

Table 2 presents study details.

Figure 1 Flow chart of study selection

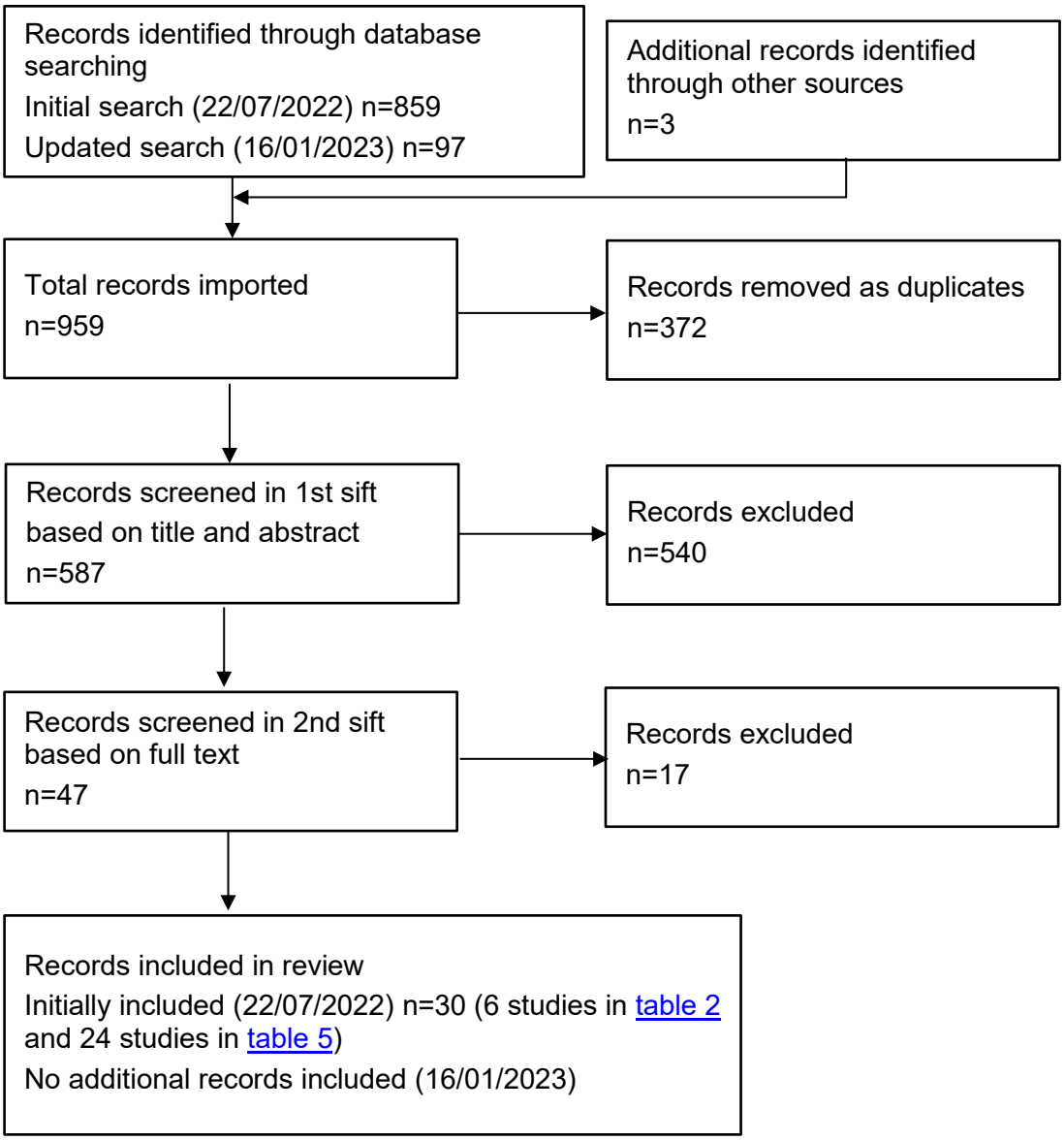

Table 2 Study details

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Onders 2022 US, Canada, Iceland	a) n=53 (41:12) b) n=192	a) Mean 36 years	a) Prospective multicentre single-arm trial b) meta-analysis of trial results with 4 additional studies	a) Clinically stable, cervical spinal cord injury with dependence on mechanical ventilation; age >18 years; clinically acceptable bilateral phrenic nerve continuity; diaphragm movement with stimulation visible under fluoroscopy and >90% oxygen saturation.	Device: NeuRx DPS (Synapse Biomedical, US)	Not reported
2	Onders 2018 US	n=92 (74:18) [including 39 patients also in study 1]	Mean age at time of injury 27 years	Retrospective case series	Patients with traumatic spinal cord injury, with stimulable diaphragms.	Device: NeuRx DPS, (Synapse Biomedical, US)	long term (unspecified follow-up period)
3	Monden 2022 US	n=28 (24:2; 2 unknown)	Mean 34 years	Retrospective case series	Patients with ventilator-dependent high tetraplegia who had a DPS implanted.	No details described	Mean 3.1 years
4	Wijkstra 2022	n=33 (24:9)	Mean 33 years (range 2 to 65)	Retrospective case series	At least 1 year old, with a cervical spinal cord injury that resulted in a complete or partial dependency on mechanical ventilation.	Device: NeuRx DPS (Synapse	12 months

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
	Spain, Italy, the Netherlands					Biomedical, USA)	
5	Garara 2016 US, Brazil	n=186	Mean 22 to 39 years (range 16 to 74 when stated)	Systematic review (including 2 multicentre retrospective studies, 8 case series and 2 case reports)	Adult patients with traumatic high cervical injury who were ventilator-dependant.	Intramuscular diaphragmatic stimulation	6 months and 2 years (only reported for 2 studies)
6	Dong 2021, US	n=1 male	22 years	Case report	The patient had rapidly progressive quadriplegia, with an acute spinal cord infarction secondary to fibrocartilaginous emboli from disc material, complicated by respiratory failure needing chronic mechanical ventilation.	Intramuscular diaphragmatic stimulation	1 month

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Onders 2022	**Proportion of patients using a DPS to breathe without ventilator assistance for at least 4 hours a day:** • Primary analysis: 96.2% (51/53); 95% CI 87.0% to 99.5% • Meta-analysis: 92.2% (95% CI 82.6% to 96.7%) **Proportion of patients using a DPS to breathe without ventilator assistance for 24 hours a day:** 58.5% (31/53); 95% CI 44.1% to 71.9% Overall, patients in the primary study were able to achieve 4 hours of continuous use in a mean of 2.6 months (95% CI 1.9 to 3.2 months) and 24 hours of continuous use in a mean of 7.6 months (95% CI 3.6 to 11.7 months). **Percentage of tidal volume over basal requirements:** for all patients 48.4% (95% CI 37.0 to 59.9%), males 42.1% (95% CI 29.0 to 55.1) and females 70.1% (95% CI 47.7 to 92.5); p<0.001 tidal volume compared with basal requirements	**Primary study** • Pneumonia: n=7.6% (4/53); 11 episodes (pacing was resumed after the pneumonia cleared, typically in 1 to 2 weeks) • Lead infection: n=3.8% (2/53) (resolved with antibiotics) There were no serious device-related adverse events reported during the course of the study. **Additional studies used in meta-analysis** Device-related adverse effects: • infection issues at the electrode wire exit site (17%) • pain with pacing (14%) • electrode wire issues involving hospitalisation (13%)
Onders 2018	**Proportion of patients using a DPS to breathe without ventilator assistance for at least 4 hours a day:** 88.0% (81/92)	• Mortality=33.7% (31/92)

First author, date	Efficacy outcomes	Safety outcomes
	Proportion of patients using a DPS to breathe without ventilator assistance for 24 hours a day: 60.9% (56/92) This was higher in patients who had the procedure within 1 year of injury (72.7% [24/33]) compared with those who had the procedure after 2 years (51.2% [22/43]). **Full recovery of breathing with subsequent diaphragm pacing removal:** 5.4% (5/92); all 5 patients had the procedure within 6 months of injury. **Unsuccessful weaning off mechanical ventilation:** 5.4% (5/92); 1 patient had been on the ventilator for 25 years and had significant scoliosis. **Overall median survival:** 22.2 years	Cause of death was unknown in 14 patients. For the remaining 17 patients, cause of death included myocardial infarction (n=2), homicide (n=1), systemic mastocytosis (n=1), pulmonary embolism (n=2), overdose (n=1), Guillain-Barre syndrome (n=1), ventilator disconnect (was not pacing at the time; n=1), seizures (n=1), heat stroke (n=1), osteomyelitis sepsis (n=1), stroke (n=1), pneumonia (n=1), malignant hyperthermia (n=1), and withdrawal of care (n=2).
Monden 2022	**Median time spent using the DPS per day:** 15.0 hours (IQR 6.0 to 23.5 hours). 14.3% (4/28) of patients had returned to independent breathing, without diaphragmatic pacing and mechanical ventilation, at the time of the interview, spending a median time of 5.5 hours (IQR 1.0 to 14.5 hours) breathing independently	• Complications within 2 weeks of a DPS implant=17.9% (5/28); broken lead/wrong lead placement (n=2), extra time to heal from surgery (n=1), pneumothorax (n=1), adverse reaction to DPS (n=1) • Additional surgery needed for complications or DPS malfunction=25.0% (7/28); repairs or

First author, date	Efficacy outcomes	Safety outcomes
	per day. Most patients still used mechanical ventilation when not using their DPS. **Effect of a DPS on participation and quality of life:** • Activities improved by DPS=60.7% (17/28) • Easier to travel=40.7% (11/28) • Harder to travel=7.4% (2/28) • Employment/productivity made easier=35.7% (10/28) • No change in employment/productivity=64.3% (18/28) When patients were asked to report what they disliked about the DPS, 5 patients described its negative effect on speech (limiting the number of words a patient could speak without pausing, poor voice quality, not being able to speak). Most patients (96%) were happy that they had the DPS implanted and 86% reported that they were satisfied with it (some patients had since returned to mechanical ventilation but appreciated the opportunity to try a DPS).	repositioning of wires (n=5), removal of DPS (n=1), pneumothorax (n=1) • Ongoing complications (beyond 2 weeks) ○ Pain=14.3% (4/28) ○ Infection at wire sites=14.3% (4/28) ○ Pneumonia/aspiration=21.4% (6/28) ○ Spasticity=17.8% (5/28) Frequency of aspiration episodes was lower in 2 patients, higher in 1 patient and the same in 24 patients. Frequency of infection or pneumonia was lower in 4 patients, higher in 3 patients and the same in 20 patients.
Wijkstra 2022	**Median time spent using the DPS per day:** • 6 months=11 hours (IQR 2 to 18 hours; n=26)	**Adverse events**

First author, date	Efficacy outcomes	Safety outcomes
	• 12 months=14 hours (IQR 4 to 24 hours; n=22) **Proportion of patients using a DPS for at least 4 hours a day:** • 6 months=73.1% (19/26) • 12 months=77.3% (17/22) **Proportion of patients using a DPS for at least 15 hours a day:** • 6 months=42.3% (11/26) • 12 months=50.0% (11/22) **Proportion of patients using a DPS for 24 hours a day, with complete liberation from mechanical ventilation:** • 6 months=23.1% (6/26) • 12 months=36.4% (8/22) **Proportion of patients using a DPS for night-time stimulation:** • 6 months=46.2% (12/26) • 12 months=57.1% (12/21)	• Death=24.2% (8/33; 2 euthanasia, 2 pneumonia, fever of unknown origin) • Hospitalisation=15.2% (5/33; 3 pneumonia, 1 pleural drainage for infection, 1 deep vein thrombosis) • Respiratory events not related to procedure or device=45.5% (15/33; 9 pneumonia, 2 pneumothorax, 2 atelectasis, 1 bronchial congestion, 1 respiratory arrest) • Device or procedure-related events=21.2% (7/33); 2 capnothorax, 1 pneumothorax, 1 revision of DPS needing hospitalisation, 1 DPS wire eruption, 1 access site haemorrhage, 1 co-contraction of abdominal muscle.
Garara 2016	**Technical success:** • The procedure failed in 1 patient, attributed to false positive preoperative phrenic nerve conduction studies.	• Safety issues reported include capnothorax and pneumothorax postoperatively in up to 42% of patients. All were treated successfully

First author, date	Efficacy outcomes	Safety outcomes
	Complete liberation from mechanical ventilation: • Between 40% and 72.7% of patients were completely free of ventilator support after conditioning (excluding the case reports).	with observation, simple aspiration, or a chest drain. • Postoperative infection, n=2 (1 superficial wound infection treated by oral antibiotics, and by shortening and terminating the tunnelled electrodes, and 1 delayed wound infection from a suture granuloma at the superficial wire connection site, which was treated by externalising the electrodes.) • DPS interacting with a pre-existing internal cardiac pacemaker, n=1. • Intermittent aspiration of food during meals that was attributed to contraction of the diaphragm causing large negative airway pressure, n=1 (A Passy-Muir speaking valve was used to successfully manage the symptoms.)
Dong 2021	The device was successfully implanted with no complications.	Two months after DPS implantation, the patient developed frequent premature ventricular contractions followed by ventricular fibrillation and cardiac arrest. Return of spontaneous circulation was achieved after prolonged cardiopulmonary resuscitation by advanced cardiac life support algorithm including numerous shocks. A single chamber implantable cardiac defibrillator was implanted and the voltage for the DPS was reduced.

Procedure technique

Of the 6 studies, 3 reported that the NeuRx DPS (Synapse Biomedical, US) device was used.

Efficacy

Proportion of patients using a DPS to breathe without ventilator assistance for at least 4 hours a day

The proportion of patients using a DPS to breathe without ventilator assistance for at least 4 hours a day was reported by 3 studies and ranged from 77% to 96% (Onders 2022, Onders 2018, Wijkstra 2022). In 1 study, this was compared with a predefined objective performance goal of 45% (Onders 2022).

Proportion of patients using a DPS to breathe without ventilator assistance for 24 hours a day

The proportion of patients using a DPS to breathe without ventilator assistance for 24 hours a day was reported by 3 studies and ranged from 36% to 61% (Onders 2022, Onders 2018, Wijkstra 2022). In 1 study, it was reported that this was higher in patients who had the procedure within 1 year of injury (73% [24/33]) compared with those who had the procedure after 2 years (51% [22/43]; Onders 2018). In a systematic review of 12 studies, between 40% and 73% of patients were completely free of ventilator support after conditioning (Garara 2016).

Median time spent using a DPS per day

In 2 studies, the median time spent using a DPS per day was 15 hours (IQR 6 to 24 hours) and 14 hours (IQR 4 to 24 hours; Monden 2022, Wijkstra 2022).

Full recovery of breathing

In 1 study, 5% (5/92) of patients had full recovery of breathing with subsequent diaphragm pacing removal. All 5 patients had the procedure within 6 months of their spinal cord injury (Onders 2018). In 1 study, 14% (4/28) of patients had returned to independent breathing, without diaphragmatic pacing and mechanical ventilation, at the time of the interview, spending a median time of 5.5 hours (IQR 1.0 to 14.5 hours) breathing independently (Monden 2022).

Quality of life and patient satisfaction

The effect of a DPS on participation and quality of life was reported in 1 study. Of the 28 patients, 17 (61%) reported that activities were improved by a DPS, 11 (41%) reported that it was easier to travel, 2 (7%) reported that it was harder to travel, 10 (36%) reported that employment or productivity was easier and 18 (64%) reported no change in employment or productivity. Most patients (96%) were happy that they had the DPS implanted and 86% reported that they were satisfied with it (Monden 2022).

Safety

Capnothorax or pneumothorax

Capnothorax or pneumothorax was reported in up to 42% of patients after the procedure, in the systematic review of 12 studies (Garara 2016). All reported cases were treated successfully with observation, simple aspiration, or a chest drain. In the study by Monden (2022), pneumothorax needing additional surgery was reported in 1 patient within 2 weeks of the DPS implantation procedure. In the study by Wijkstra (2022), pneumothorax was reported in 9% (3/33) of patients, 1 of which was reported to be related to the device or procedure and was treated by thoracocentesis. In the same study, 6% (2/33) of patients had device or procedure-related capnothorax.

Pneumonia

Four studies reported pneumonia, although this was not necessarily related to the procedure. In the study by Onders (2022), pneumonia was reported in 8% (4/53) of patients and pacing was resumed after the pneumonia cleared. In the study by Monden (2022), pneumonia or aspiration was reported as an ongoing complication (beyond 2 weeks of the procedure) in 21% (6/28) of patients. In the study by Wijkstra (2022), there were 2 deaths attributed to pneumonia and 3 patients were hospitalised for it. A further 27% (9/33) of patients had pneumonia but it was reported not to be related to the procedure or device. In the study by Onders (2018), the cause of death was reported to be pneumonia in 1 patient.

Infection

Infection was reported in 4 studies. Infection at the wire sites was reported in 14% (4/28) and 4% (2/53) of patients in 2 studies (Monden 2022, Onders 2022). In the meta-analysis reported in Onders (2022), infection issues at the electrode wire site were reported in 17% of patients. In the systematic review by Garara (2016), 2 patients had a postoperative wound infection, both of which were treated by adjusting the electrode wires. In the study by Wijkstra (2022), 1 patient had pleural drainage for infection.

Pain

In the meta-analysis reported in Onders (2022), pain with pacing was reported in 14% of patients. Ongoing pain (beyond 2 weeks of the procedure) was reported in 14% (4/28) of patients in the study by Monden (2022).

Device complications

In the meta-analysis reported in Onders (2022), electrode wire issues involving hospitalisation was reported in 13% of patients. In the study by Monden (2022), broken or wrong lead placement was reported in 7% (2/28) of patients and repairs or repositioning of wires was reported in 18% (5/28) of patients. In the study by Wijkstra (2022), 1 patient needed hospitalisation for revision of the DPS and 1 patient had a DPS wire eruption.

Cardiac complications

In the systematic review by Garara (2016), the DPS interacted with a pre-existing internal cardiac pacemaker in 1 patient.

Ventricular tachycardia leading to cardiac arrest was described in 1 patient who had a DPS in a case report. A single chamber implantable cardiac defibrillator was implanted and the DPS was continued at a lower voltage (Dong 2021).

Other

In the systematic review by Garara (2016), intermittent aspiration of food during meals was reported in 1 patient. Co-contraction of abdominal muscles and access site haemorrhage were reported in 1 patient each in the study by Wijkstra (2022). In the study by Monden (2022), spasticity was reported in 18% (5/28) of patients. In the same study, 1 patient had an adverse reaction to the DPS within 2 weeks of the procedure.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if

they thought there were other adverse events that might possibly occur, even if they have never happened (theoretical).

They did not describe any anecdotal or theoretical adverse events.

Two professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- No comparative studies were identified.
- Most of the studies had a small sample size.
- Only 1 prospective study was included (Onders 2022).
- The study by Monden et al. (2022) was a self-report questionnaire about experiences over the previous year and may be subject to recall bias.
- Of the 5 studies, 2 specifically stated that only adults were within the inclusion criteria (Onders 2022, Garara 2016).
- Follow-up periods were not reported for all studies. One study had a mean follow up of 3 years (Monden 2022) and 1 had long-term follow up, of an unspecified period. The study that reported outcomes at 6 and 12 months showed that the success rate was higher after 12 months (Wijkstra 2022).
- Evidence was only included on patients with chronic respiratory failure, but the length of time on mechanical ventilation varied between and within studies. Almost all the included articles in the systematic review reported implantation several years after injury. There was some evidence to suggest that patients who had the procedure sooner after their spinal cord injury may have better outcomes.

- The mechanism of spinal cord injury varied and this is likely to affect the outcome of the procedure. One paper noted that the procedure had a lower success rate for patients who had a violent injury, such as a gunshot wound (Onders 2018).
- Post operative weaning programmes varied between studies.
- Many patients were on home ventilation, and the weaning process was done by family members and caregivers. Other patients were weaned in hospital.
- A potential conflict of interest was declared by authors of 2 papers (Onders 2018 and Onders 2022) and 2 studies reported funding from Synapse Biomedical, the company that makes the device (Onders 2022 and Wijkstra 2022).

Related NICE guidance

Interventional procedures

- NICE's interventional procedures guidance on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease (Recommendation: this procedure should not be used).

NICE guidelines

- NICE guideline on rehabilitation after traumatic injury.

Professional societies

- Association of British Neurologists
- Society of British Neurological Surgeons
- British Association of Spinal Cord Injury Specialists
- British Association of Spinal Surgeons

- Association of Laparoscopic Surgeons of Great Britain & Ireland
- British Society of Rehabilitation Medicine
- Intensive Care Society
- Faculty of Intensive Care Medicine
- British Thoracic Society.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

1. Onders RP, Khansarinia S, Ingvarsson PE et al. (2022) Diaphragm pacing in spinal cord injury can significantly decrease mechanical ventilation in multicenter prospective evaluation. Artificial Organs DOI: 10.1111/aor.14221
2. Onders RP, Elmo MJ, Kaplan C et al. (2018) Long-term experience with diaphragm pacing for traumatic spinal cord injury: Early implantation should be considered. Surgery 164: 705–711
3. Monden KR, Coker J, Charlifue S et al. (2021) Long-term follow-up of patients with ventilator-dependent high tetraplegia managed with diaphragmatic pacing systems. Archives of Physical Medicine and Rehabilitation 103: 773–78
4. Wijkstra PJ, Van Der Aa H, Hofker HS et al. (2021) Diaphragm pacing in patients with spinal cord injury: a European experience. Respiration 101:18–24
5. Garara B, Wood A, Marcus HJ et al. (2016) Intramuscular diaphragmatic stimulation for patients with traumatic high cervical injuries and ventilator dependent respiratory failure: A systematic review of safety and effectiveness. Injury 47: 539–44

6. Dong T, Chami T, Janus S et al. (2021) Diaphragmatic pacemaker-induced ventricular tachycardia leading to cardiac arrest: A case report. European Heart Journal - Case Reports 5: ytab352

Methods

NICE identified studies and reviews relevant to intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by high spinal cord injuries from the medical literature. The following databases were searched between the date they started to 16 January 2023: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients with ventilator-dependent chronic respiratory failure caused by high spinal cord injuries.
- Intervention or test: intramuscular diaphragm stimulation.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	16/01/2023	1946 to January 13, 2023
MEDLINE In-Process (Ovid)	16/01/2023	1946 to January 13, 2023
MEDLINE Epubs ahead of print (Ovid)	16/01/2023	January 13, 2023
EMBASE (Ovid)	16/01/2023	1974 to 2023 January 13
EMBASE Conference (Ovid)	16/01/2023	1974 to 2023 January 13
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	16/01/2023	Issue 1 of 12, January 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	16/01/2023	Issue 12 of 12, December 2022
International HTA database (INAHTA)	16/01/2023	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 (diaphragm* adj4 (stimulat* or technique* or system*)).tw.
2 (diaphragm* adj4 pac*).tw.
3 IDS.tw.
4 DPS.tw
5 (respirat* adj4 stimulat* adj4 system*).tw.
6 or/1-5
7 diaphragm/
8 diaphrag*.tw.
9 Respiration/
10 breathing/
11 respirat*.tw.
12 or/7-11
13 Electric Stimulation Therapy/
14 electrotherapy/
15 (electric* adj4 stimulat* adj4 therap*).tw.
16 electrotherap*.tw.

17 or/13-16
18 12 and 17
19 6 or 18
20 respiratory failure/
21 Respiratory Paralysis/
22 Respiratory Insufficiency/
23 ((Respirator* or ventilat* or diaphrag*) adj4 (insufficien* or weakness* or deficienc* or paralysis* or fail*)).tw.
24 spinal cord disease/
25 (spin* adj4 cord* adj4 injur*).tw.
26 amyotrophic lateral sclerosis/
27 (Amyotrophic* adj4 Latera* adj4 Sclero*).tw.
28 ALS.tw.
29 (gehrig* adj4 diseas*).tw.
30 motor neuron disease/
31 (motor* adj4 neuron* adj4 diseas*).tw.
32 exp multiple sclerosis/
33 (multipl* adj4 scleros*).tw.
34 MS.tw.
35 quadriplegia/
36 paraplegia/
37 (Quadripleg* or parapleg* or tetrapleg*).tw.
38 or/20-37
39 19 and 38
40 Animals/ not Humans/
41 39 not 40

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Alshekhlee A, Onders RP, Syed TU et al. (2008) Phrenic nerve conduction studies in spinal cord injury: applications for diaphragmatic pacing. Muscle Nerve 38:1546–52	Case series n=26	Of 26 implanted patients, 25 (96%) were able to pace and tolerate being off the ventilator for more than 4 hours per day.	Study is included in systematic review by Garara et al. (2016).
Dean JM, Onders RP, Elmo MJ (2018) Diaphragm pacers in pediatric patients with cervical spinal cord injury: a review and implications for inpatient rehabilitation. Current Physical and Medical Rehabilitation Reports 6: 257–263	Review n=22 children	Implantation of a DPS is a safe and effective alternative to long-term positive pressure ventilation in children with high level tetraplegia and respiratory insufficiency and failure related to spinal cord disease. Implantation of a DPS can be done at any time after injury. There is evidence that shows early implantation is associated with faster wean times.	Review
DiMarco AF, Geertman RT, Tabbaa K et al. (2019) Complete	Case series n=3	Complete restoration of respiratory muscle function can be safely and effectively	Larger or more recent studies are included.

restoration of respiratory muscle function in three subjects with spinal cord injury: pilot interventional clinical trial. American Journal of Physical Medicine & Rehabilitation 98: 43–50		achieved in the same individuals with spinal cord injury. Spinal cord stimulation results in peak expiratory airflow and airway pressure generation characteristic of a normal cough, whereas diaphragm pacing was successful in maintaining patients off mechanical ventilation.	
DiMarco, Anthony F (2018) Diaphragm Pacing. Clinics in chest medicine 39: 459–71	Review	Benefits of diaphragm pacing include improved mobility, speech, olfaction, and quality of life.	General review of diaphragm pacing.
DiMarco AF, Onders RP, Ignagni A et al. (2005) Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. Chest 127: 671–8	Case series n=5	In 4 of the 5 patients, initial bilateral diaphragm stimulation resulted in inspired volumes between 430 and 1,060 ml. Reconditioning of the diaphragm over several weeks resulted in increases in inspired volumes to 1,100 to 1,240 ml. These patients were comfortably maintained without mechanical ventilatory support for prolonged time periods by diaphragm pacing, by full-time ventilatory support in 3 patients, and 20 hours per day, in 1 patient. No response to stimulation was observed in 1 patient, most likely secondary to denervation atrophy.	Study is included in systematic review by Garara et al. (2016). Same population as Onders et al. (2004) and Onders et al. (2005)

DiMarco AF, Onders RP, Ignagni A et al. (2006) Inspiratory muscle pacing in spinal cord injury: case report and clinical commentary. Journal of Spinal Cord Medicine 29: 95–108	Case report n=1	A case report of an individual who successfully had a DPS using intramuscular diaphragm electrodes.	Study is included in systematic review by Garara et al. (2016).
Hazwani TR, Alotaibi B, Alqahtani W et al. (2019) Pediatric diaphragmatic pacing. Pediatric Reports 11: 7973	Case report n=1	A 4-year-old child with a spinal cord injury had a diaphragmatic pacing procedure, which helped start gradual weaning from mechanical ventilation.	Case report
Hill TM, Onugha O (2019) Diaphragmatic pacing: is there a benefit? Surgical Technology International 35: 265–70	Review	Diaphragm pacing is a therapeutic option for diaphragm dysfunction in patients with spinal cord injuries.	General review of diaphragm pacing.
Karacam V, Sanli A, Ulugun I et al. (2018) A practical technique in laparoscopic diaphragm pacing surgery: Retrospective analyse of 43 patients. Journal of Minimal Access Surgery 14: 273–6	Case series n=43 (5 with spinal cord injury)	The DPS implantation procedure duration may vary depending on the patient characteristics and the surgeon's experience. This study demonstrated that minimal modification in DPS implantation procedure could shorten the duration of the surgery. Shorter implantation duration can provide lower intraoperative and postoperative complications.	Study describes a modified technique for implanting the device. Only a small proportion of patients had spinal cord injury as an indication for the procedure.
Kerwin A, Yorkgitis B, Ebler D et al. (2018) Use of	Non-randomised comparative study	Diaphragm pacing system implantation in patients with acute	The study describes patients with

diaphragm pacing in the management of acute cervical spinal cord injury. Journal of Trauma and Acute Care Surgery 85: 928–31	n=101	cervical spinal cord injury can be 1 part of a comprehensive critical care program to improve outcomes. However, the association of a DPS with the marked improved mortality seen on bivariate analysis may be due solely to improvements in critical care throughout the study period.	acute spinal cord injury rather than chronic respiratory failure. The study is included in the meta-analysis by Onders et al. (2022).
Lammertse D, Charlifue S, Berliner J (2016) Longitudinal follow up of individuals with implanted diaphragm pacing systems. American Spinal Injury Association Annual Scientific Meeting. Philadelphia, US.	Case series n=31	24/28 (86%) patients were still using a DPS (4 to 24 hours) at the time of follow up (mean 16 hours, median 16 hours). 7/28 patients (25%) were pacing 24 hours a day.	Study reported only as conference abstract but included in the meta-analysis by Onders et al. (2022).
Onders RP, Elmo MJ, Stepien C et al. (2021) Spinal cord injury level and phrenic nerve conduction studies do not predict diaphragm pacing success or failure-all patients should undergo diagnostic laparoscopy. American Journal of Surgery 221: 585–8	Case series n=50	Phrenic nerve conduction studies are inadequate preoperative studies. Direct laparoscopic evaluation should be offered for all spinal cord injury patients to receive the benefit of diaphragm pacing.	The study assesses the use of phrenic nerve conduction studies in patient selection.
Onders RP, Ponsky TA, Elmo MJ et al. (2011) First reported experience with intramuscular	Case series n=6	In all patients, a DPS provided tidal volumes above basal needs. Five of the patients underwent a home-	Larger or more recent studies are included.

diaphragm pacing in replacing positive pressure mechanical ventilators in children. Journal of Pediatric Surgery 46: 72–6		based weaning program, whereas 1 patient who was implanted only 11 days after spinal cord injury never returned to the ventilator with DPS use. Another patient was weaned from the ventilator full time but died of complications of his underlying brain stem tumour. The remaining patients weaned from the ventilator for over 14 hours a day or are actively conditioning their diaphragms.	
Onders RP, Khansarinia S, Weiser T et al. (2010) Multicenter analysis of diaphragm pacing in tetraplegics with cardiac pacemakers: positive implications for ventilator weaning in intensive care units. Surgery 148:893–7	Case series n=20	A DPS can be safely implanted in tetraplegics with cardiac pacemakers. Applications for temporary use of a DPS to maintain diaphragm type 1 muscle fibre and improve posterior lobe ventilation may benefit complex critical care patients.	Study is included in systematic review by Garara et al. (2016).
Onders RP, Elmo M, Khansarinia S et al. (2009) Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients. Surgical	Case series n=88 (50 with spinal cord injury)	In the patients with spinal cord injury, 96% were able to use a DPS to provide ventilation replacing their mechanical ventilators.	Study is included in systematic review by Garara et al. (2016).

Endoscopy 23:1433-40			
Onders RP, Elmo MJ, Ignagni AR (2007) Diaphragm pacing stimulation system for tetraplegia in individuals injured during childhood or adolescence. Journal of Spinal Cord Medicine 30: S25–9	Case series n=10 (injured as children or adolescents)	Four patients use a DPS continuously, 4 pace daytime only, and 2 patients are still actively conditioning their diaphragms. Two patients needed surgical correction of scoliosis before implantation. All patients prefer breathing with the DPS and would recommend it to others; 4 patients specifically identified that attending college or church without a ventilator eases their integration into society.	Study is included in systematic review by Garara et al. (2016).
Onders RP, DiMarco AF, Ignagni AR et al. (2005) The learning curve for investigational surgery: lessons learned from laparoscopic diaphragm pacing for chronic ventilator dependence. Surgical Endoscopy 19: 633–7	Case series n=6	One procedure was unsuccessful because of a nonfunctioning phrenic nerve. All 5 of the successfully implanted patients could be maintained on prolonged ventilatory support with the device.	Study is included in systematic review by Garara et al. (2016). Same population as Onders et al. (2004) and DiMarco et al. (2005)
Onders RP, Dimarco AF, Ignagni AR et al. (2004) Mapping the phrenic nerve motor point: the key to a successful laparoscopic diaphragm pacing system in the first human series. Surgery 136: 819–26	Case series n=6 (with spinal cord injury)	5 of 6 patients had electrodes successfully implanted at the motor point to produce adequate tidal volumes. The 1 failure caused a change in the inclusion criteria to include fluoroscopic confirmation of diaphragm movement during surface nerve	Study is included in systematic review by Garara et al. (2016). Same population as Onders et al. (2005) and

		stimulation. Three patients were completely free of the ventilator, and the other 2 were progressively increasing their time off the ventilator with conditioning.	DiMarco et al. (2005)
Posluszny JA, Onders R, Kerwin AJ et al. (2014) Multicenter review of diaphragm pacing in spinal cord injury: successful not only in weaning from ventilators but also in bridging to independent respiration. Journal of Trauma and Acute Care Surgery 76: 303–9	Case series n=29	Of the [AS1]patients who could have stimulation, who had a DPS, 72% (16/22) were completely free of ventilator support in an average of 10 days. For the remaining 6 patients, 2 had delayed weans of 180 days, 3 had partial weans and 1 patient went to a long-term acute care hospital and had life-prolonging measures withdrawn. Eight patients (36%) had complete recovery of respiration, and the DPS wires were removed.	Study is included in systematic review by Garara et al. (2016) and in the meta-analysis included in Onders et al. (2022).
Tedde ML, Onders RP, Teixeira MJ et al. (2012) Electric ventilation: indications for and technical aspects of diaphragm pacing stimulation surgical implantation. Jornal brasileiro de pneumologia: publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia 38: 566–72	Case series n=5 Follow up=6 months	Of the 5 patients, 3 could breathe using a DPS alone for more than 24 hours, 1 could do so for more than 6 hours, and one could not do so at all.	Study is included in systematic review by Garara et al. (2016). Includes the same patients as the study below.

Tedde ML, Vasconcelos Filho P, Hajjar LA et al. (2012) Diaphragmatic pacing stimulation in spinal cord injury: anesthetic and perioperative management. Clinics 67:1265–9	Case series n=5 Follow up=6 months	The diaphragmatic pacemaker placement was successful in all patients. Two patients presented with capnothorax during the perioperative period, which resolved without consequences. After 6 months, 3 patients achieved continuous use of the diaphragm pacing system, and 1 could be removed from mechanical ventilation for more than 4 hours per day.	Study is included in systematic review by Garara et al. (2016). Includes the same patients as the study above.
Watt J, Wiredu E, Silva P et al. (2011) Survival after short- or long-term ventilation after acute spinal cord injury: a single-centre 25-year retrospective study. Spinal Cord 49: 404–410	n=189 (19 patients used diaphragm pacing)	Mean survival in patients who used diaphragm pacing (full or part time) was 19.2 years for those aged 0 to 30 (n=13), 13.1 years for those aged 31 to 45 (n=3) and 10.3 years for those aged 46 and above (n=3). Mean survival for patients on mechanical ventilation was 17.4 years for those aged 0 to 30 (n=12), 9.9 years for those aged 31 to 45 (n=12) and 7.9 years for those aged 46 and above (n=12).	Retrospective study with a small number of patients who had diaphragm pacing. This group of patients was not described in enough detail to warrant inclusion in the main evidence summary.
Woo A La, Tchoe Ha Jin, Shin Hae Won et al. (2020) Assisted breathing with a diaphragm pacing system: a systematic review. Yonsei Medical Journal 61: 1024–33	Systematic review n=289 10 studies (82 patients [5 studies] with spinal cord injury)	The studies involving patients with spinal cord injury found that survival duration was not significantly different between diaphragm pacing and no diaphragm pacing. The rate of mechanical	The review only included 5 relevant studies, all of which have been described in the key evidence summary or appendix of the

		ventilation weaning in patients with spinal cord injury was reported in 1 cohort study as 33% and 1 case series as 96%. However, given that 1 study was only a case series, the results remain inconclusive. Additional well-designed studies are needed to ascertain the efficacy of a DPS in patients with spinal cord injuries.	overview. There was no meta-analysis.
Yokota K, Masuda M, Koga R et al. (2022) Diaphragm pacing implantation in Japan for a patient with cervical spinal cord injury: A case report. Medicine 101: e29719	Case report n=1	At 1.5 years after injury, a DPS was surgically implanted to support the patient's respiratory function. The mechanical ventilator support was successfully withdrawn from the patient 14 weeks after implantation. Both the vital capacity and tidal volume of the patient were significantly promoted after implantation. The patient finally returned to daily life without any mechanical support.	Case report