

Mapping the evidence base and use of neurostimulators
(interim report)

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(interim report)

A WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT
COLLABORATION REPORT

Report commissioned by: West Midlands Specialised Commissioning Team

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Date completed: September 2008

Report Number: 70

ISBN No: 0704427192
9780704427198

WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS:

Kinga Malottki undertook the research and production of the report. Anne Fry-Smith designed search strategies and carried out searches for systematic reviews and commented on the draft of this report. David Moore led the project, contributed to and edited the final report.

ACKNOWLEDGEMENTS:

Martin Connock commented on the final draft of this report.

CONFLICTS OF INTEREST:

The authors all declare that they have no conflicts of interest.

ABBREVIATIONS AND ACRONYMS

Abbreviation/ Acronym	Definition
ARIF	Aggressive Research Intelligence Facility
HTA	Health Technology Assessment
INS	International Neuromodulation Society
IPAC	Interventional Procedures Advisory Committee
IPP	Interventional Procedures Programme
NHS	National Health Service
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Clinical Excellence

GLOSSARY

Deep brain stimulation – sending electrical impulses to specified parts of the brain using an implanted neurostimulator

Functional electrical stimulation – use of electrical impulses to stimulate the nerves and muscles, often to restore or improve certain functions (such as walking)

Gastric electrical stimulation – stimulation of the lower stomach using an implanted neurostimulator

Neuroprostheses – devices aiming at improving or replacing an impaired function, such as cochlear implants

Percutaneous electrical stimulation – stimulation involving introducing electrodes into the body through the skin and connected to an external stimulator

Pulsed electromagnetic field stimulation – stimulation utilising magnetic coils worn over the area of stimulation

Spinal cord stimulation – stimulation of a selected area of the spinal cord using an implanted neurostimulator

Tesla – unit of measurement describing a magnetic field (magnetic flux density)

Transcutaneous electrical nerve stimulation – stimulation utilising an entirely external stimulator with electrodes attached to the skin usually directly over peripheral nerves

Transcranial direct current stimulation – stimulation with two sponge electrodes attached to the patient's head, connected to a weak current generator

Transcranial magnetic field stimulation – stimulation of the brain with a device creating brief magnetic pulses

EXECUTIVE SUMMARY

Background

Neurostimulation is the utilisation of electric or magnetic impulses to alter or modulate the nerve activity. Neurostimulators are often used to relieve pain or to bring improvement in certain conditions.

There appear to be many stimulators in use or in development and they are or could be used in the treatment of numerous conditions. They include both implantable and non-invasive procedures.

The neurostimulator market in the UK is regulated by the Medicines and Healthcare products Regulatory Agency based on two Directives of the European Council.

NICE Interventional Procedures Programme has assessed some procedures involving neurostimulation. However there are so many stimulator – condition combinations only a relatively small number have been evaluated by the Programme.

Aim

The aim of this report is (i) to investigate the types of neurostimulators and their potential uses, (ii) to map the evidence on effectiveness of neurostimulator use from existing systematic reviews, (iii) to provide a stimulus for identification of priority areas where secondary evidence appraisal and/or synthesis of primary evidence should be undertaken to aid commissioning decisions.

Methods

The information provided on the website of the International Neuromodulation Society was used as a starting point for a grid combining stimulators with their indications. Broad searches in bibliographic databases were undertaken to identify systematic reviews on the use of neurostimulators (excluding cardiac pacemakers) for any indication in any population. Additionally ARIF requests on neurostimulators were scanned for references to systematic reviews. The most up to date systematic

reviews and other publications (including health technology assessments, NICE guidance, and clinical guidelines) were mapped onto the grid. The grid was also expanded to incorporate additional stimulator and indication combinations identified through the searches.

Results

At least 35 indications and 19 stimulator types were identified. 66 systematic reviews and 73 health technology assessments were identified. They covered a variety of stimulators and over 50 indications. This information was added to the map. It was evident that secondary evidence is not available for the vast majority of stimulator – indication combinations. Most existing secondary evidence concentrates on the use of spinal cord stimulation for pain relief, deep brain stimulation for movement disorders, and functional electrical stimulation for rehabilitation. At present critical appraisal of the secondary evidence for any combination has yet to be undertaken by us due to the breadth of the topic.

Conclusions

This report should be used as an overview of the existing types of neurostimulators and their applications. It also indicates areas that were covered by systematic reviews, outlines the most up to date ones, and provides references to other papers that were identified. It also identifies a large number of areas where there currently is no secondary evidence. Further effort can be concentrated in a number of areas including:

- critically appraising the secondary evidence for certain stimulator-indication combinations,
- synthesising evidence for combinations where there currently is no secondary evidence.

Due to the breadth of the topic, for each of the options to be taken forward, clear guidance is required on which are the combinations where evidence of effectiveness

is most required. This will allow appropriate and timely prioritisation of future evidence synthesis and/or appraisal.

CONTENTS

1. AIM OF THE REPORT	8
2. BACKGROUND	8
2.1 Brief overview of neurostimulators	8
2.2 Neurostimulation organisations	9
2.3 Licensing	10
2.4 NICE Interventional Procedures Programme	11
2.5 This report	12
3. METHODS	13
3.1 Search strategy	13
3.2 Inclusion and exclusion criteria	13
3.3 Mapping	14
4. RESULTS	15
4.1 Map of neurostimulators	15
4.2 Types of neurostimulators	17
4.2.1 Implantable neurostimulators	18
4.2.2 Partly implantable neurostimulators	19
4.2.3 Non-invasive neurostimulators	20
4.3 Indications for the use of neurostimulators	21
4.3.1 Pain relief	22
4.3.2 Movement disorders	23
4.3.3 Mental disorders	24
4.3.4 Rehabilitation	24
4.3.5 Voiding difficulties and/or incontinence	26
4.3.6 Sensory prosthetics	26
4.3.7 Other	27
5. DISCUSSION AND FURTHER RESEARCH RECOMMENDATIONS	28
6. APPENDICES	31
6.1 NICE Interventional Procedures Programme	31
6.2 Search strategies	33
7. REFERENCES	41

1. AIM OF THE REPORT

The aim of this report was (i) to investigate the types of neurostimulators and their potential uses, (ii) to map the evidence on effectiveness of neurostimulator use from existing systematic reviews, (iii) to provide a stimulus for identification of priority areas where secondary evidence appraisal and/or synthesis of primary evidence should be undertaken to aid commissioning decisions. The only area that was not of interest was the use of cardiac pacemakers. This brief report did not aim to systematically review primary evidence on the application of neurostimulators, nor did it undertake to critically appraise the identified evidence.

2. BACKGROUND

2.1 Brief overview of neurostimulators

The International Neuromodulation Society (INS) provides the following definition:

“neuromodulation is technology that acts directly upon nerves. It is the alteration - or modulation - of nerve activity by delivering electrical or pharmaceutical agents directly to a target area.”²¹

Although an explicit definition of neurostimulation is not provided, it can be understood that it refers only to the first component of the above definition, utilising medical devices to deliver electrical stimulation. However, there exist other definitions of neuromodulation and neurostimulation, which may differ from the one provided by the INS.

It is believed that neurostimulation was used thousands of years ago as some evidence suggests the use of electric torpedo fish for pain relief and other conditions.^{21,173,182} The first record of what would be more in line with the present understanding of neurostimulation dates back to 1874 when attempts were made to stimulate the brain with electrical impulses.¹⁸² Further, in 1948 the first implantation of brain electrodes to treat a psychiatric disorder took place.¹⁸² However, the modern age of neurostimulation began in the 1960s when deep brain stimulation started to

be used to relieve chronic pain.²¹ It was shortly followed by the first spinal cord stimulation procedures in 1967.¹⁸²

In the 1970s new types of stimulators and areas of application of neurostimulation were further explored. An experiment was carried out to enable toe lifting in patients with drop foot syndrome. Further investigations were carried out in muscle stimulation to prevent further development of scoliosis in children. Applications in improving bladder control, spasticity and sustaining respiration were also investigated.¹³⁸

The devices were gradually improved, parts made smaller and user friendly systems with longer battery life were developed. This enabled the wide use of implantable devices. A trend that is likely to continue.¹⁸² Furthermore in the field of non-invasive devices, the potential for development is high and the possible uses numerous.¹⁹

The neurostimulation market is growing as more uses of neurostimulators are identified. Recent uses often cover relatively common conditions, such as chronic pain, epilepsy, depression and Parkinson's disease. The INS website provides information, based on a market study by Neurotech Reports, that the neuromodulation device industry is likely to grow from USD 3.0 billion in 2008 to USD 4.5 billion in 2010.²¹

2.2 Neurostimulation organisations

This report identified three scientific societies which are associated with neurostimulation: The International Neuromodulation Society, The International Functional Electrical Stimulation Society, and The International Society for Transcranial Stimulation.

The one with the broadest area of interest, the International Neuromodulation Society (INS) *"is a non-profit group of clinicians, scientists and engineers dedicated to the scientific development and awareness of neuromodulation..."*. INS was founded in 1989 in San Francisco and since then has developed a number of branches in different countries and regions. Since 2001 there has been a branch for

the United Kingdom and Ireland based in London. The official journal of INS is *Neuromodulation: Technology at the Neural Interface*.²¹ Further information about the INS can be found on their website www.neuromodulation.com.

The International Functional Electrical Stimulation Society has a mission to “*promote the research, application, and understanding of electrical stimulation as it is utilised in the field of medicine through meetings, tutorials, publications, and the exchange of information.*”¹⁹ Since 1999 it is formally affiliated with the INS²¹ and also recognises *Neuromodulation: Technology at the Neural Interface* as its official journal.¹⁹ Further information on the society can be found on their website: <http://www.ifess.org>.

Although the third organisation, the International Society for Transcranial Stimulation has its own website (<http://www.ists.unibe.ch>), it does not provide detailed information on the society or recent activities.⁸

2.3 Licensing

Due to the variety of types of neurostimulators (implantable, partly implantable, or non-invasive) two EU Directives apply to them:

- Active Implantable Medical Devices Directive (90/385/EEC)
- Medical Devices Directive (93/42/EEC)

Moreover, the Directive 2007/47/EC is expected to amend both, yet it does not come fully into force until 21 March 2010.¹⁴

Both current Directives provide a list of requirements that devices have to meet to enter the market. Although there is some variation according to the type of the device, the main requirement appears to be affixing a CE mark of conformity with EU requirements. Once a device is approved in this way, no obstacles exist to its marketing.^{2,3}

Both Directives require (although the formulation is to a very small degree different) the devices to be “*designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of the patients, or the safety and health of users, or, where*

applicable, other persons...". Possible side effects have to be compensated by the intended performance. It is also stated that the devices have to achieve the purpose intended by the manufacturer.^{2,3}

Both Directives provide details on various ways of affixing a CE mark. This can be carried out by any European Notified Body. The regulations on CE marking are mainly concerned with issues such as assurance of quality of the production system and product design and will not be addressed in this report.

The body responsible for marketing authorisation (overseeing granting CE mark) in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). MHRA supervises the work of UK based Notified Bodies, which undertake the actual examination of devices before they enter the market. MHRA does not undertake pre-marketing investigation itself. However, it is responsible for gathering information on the safety of devices already in use, and based on this can withdraw a device from the market.¹⁴

A Notified Body is a *"certifying organisation which the national authority (...) of a Member State designates to carry out one or more of the conformity assessment procedures described in the annexes of the Directives."* The MHRA is responsible for designating Notified Bodies in the UK. *"A Notified Body must be qualified to perform all the functions set out in any annex for which it is designated. The designation may be restricted to specified types of devices and/or Annexes."*¹²⁸

2.4 NICE Interventional Procedures Programme

The aim of the Interventional Procedures Programme (IPP) is to establish the effectiveness and safety profile of a medical procedure. It is concerned mainly with new procedures, but can also scrutinise older ones, if there is doubt about their effectiveness and/or safety. Such doubt will usually be caused by the availability of new information about a procedure.¹⁰

NICE defines an interventional procedure as one *"used for diagnosis or for treatment that involves:*

- *making a cut or a hole to gain access to the inside of a patient's body (...), or*
- *gaining access to a body cavity (...) without cutting into the body, or*
- *using electromagnetic radiation (which includes X-rays, lasers, gamma-rays and ultraviolet light)...".¹⁰*

This definition clearly places procedures involving neurostimulation within the scope of the Programme.

Procedures are considered for the IPP after a notification is made to NICE, usually by a clinician intending to use them for the first time in the NHS. If NICE decides that the procedure falls within the scope of IPP, an overview of literature is prepared.¹⁴²

Based on the overview Interventional Procedures Advisory Committee (IPAC) either issues recommendations or, if it considers the information to be insufficient, asks for a systematic review on the topic and issues recommendations after considering it.¹⁴²

Documents based on both the overview and systematic review are published on the NICE website for public consultation. After considering the recommendations of IPAC and feedback from the consultation, NICE issues guidance to England, Scotland, Wales and Northern Ireland.¹⁰

In certain circumstances a procedure can be referred to the NICE Technology Appraisal Programme. This can only happen when the effectiveness and safety of a procedure is well established. If there is any doubt about the effectiveness or safety of a procedure, it should be considered within the IPP.¹⁴²

The IPP process is currently under review and the Interventional Procedures Programme Process Guide is due to be published in early 2009.¹³

Further details on the NICE IPP can be found in [Appendix 6.1 NICE Interventional Procedures Programme](#).

2.5 This report

Individual funding requests for a range of neurostimulators have been received by commissioners. There are however few robust commissioning policies in this area. Moreover, the number and variety of indications for neurostimulation are increasing. Therefore there is a pressing need to (i) identify neurostimulators and the indications

for which they can be used, (ii) to identify the secondary evidence on neurostimulators, (iii) to map the secondary evidence onto combinations of neurostimulators and indications.

3. METHODS

The approach adopted aimed at providing a clear overview of existing types of neurostimulators, their uses and the evidence base. First a search was undertaken to identify any existing frameworks which could be utilised for this purpose. Since none were found, such a framework was developed based on the information provided by the INS²¹ and on existing systematic reviews.

3.1 Search strategy

A number of broad search strategies were designed using the well established ARIF* protocol to identify systematic reviews on the use of neurostimulators. No limitations were applied with respect to the indication or population. The searches were designed to cover any type of neurostimulator apart from a cardiac pacemaker. The full search strategies can be found in the [Appendix 6.2 Search strategies](#).

Furthermore, the NICE website was searched and the most up to date relevant ARIF requests were scanned for references to secondary studies.

3.2 Inclusion and exclusion criteria

The titles and abstracts of retrieved papers were scanned to identify relevant systematic reviews based on the following criteria:

Design: systematic review (also see below)

*ARIF (Aggressive Research Intelligence Facility) “is a specialist unit based at the University of Birmingham. The role of ARIF is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region. This is achieved by helping health care workers access and interpret research evidence, particularly systematic reviews of research, in response to particular problems they are experiencing”.¹¹

Population: any

Intervention: any use of neurostimulator

Exclusion: any use of cardiac pacemakers, any primary study

If papers such as economic analyses, clinical guidelines or NICE guidelines were identified, they were also included in the list of publications, even if they were not based on a systematic review. Full copies of included articles were obtained where possible.

3.3 Mapping

The included papers were classified according to the type of publication, which included: systematic reviews, health technology assessments, NICE Guidance, NICE overview of evidence, clinical guidelines, ARIF requests, economic evaluations. The included publications were also classified according to the type of neurostimulator and indication. If the full text of the publication was not available, classification was based on the title and abstract (if available).

The next step was to design a grid to map evidence to combinations of neurostimulators and the medical conditions they can be used for. This map was designed iteratively, in the following stages (based in part on the approach utilised in a publication on “Mapping the evidence base and use of acupuncture within the NHS”¹⁷¹):

- 1) Using identified guidelines outlining types of neurostimulators and their uses (none were identified).
- 2) Using the website of the International Neuromodulation Society (www.neuromodulation.com). The Society did not claim to present a complete list, but it gave examples of stimulators and their potential uses. The main types of stimulators were derived from this website.²¹
- 3) An initial grid was constructed on which neurostimulators were paired with their proposed use for specific medical condition according to the INS.
- 4) Further indications and types of neurostimulators were added to the grid based on the results of the searches for systematic reviews and completed ARIF requests.

- 5) The most up to date evidence was mapped onto the grid.

4. RESULTS

4.1 Map of neurostimulators

The grid was developed to map the evidence identified in the searches to the appropriate combination of type of stimulator and its use. The different types of stimulators were put into columns and each row covers a different indication for neurostimulation. The most up to date secondary evidence was mapped to the relevant combinations.

A part of this table is reproduced below (Figure 1) to provide an example of how the problem was tackled.

So for example it can be seen that pain (general) has recent evidence from HTAs, systematic reviews, clinical guidelines and NICE guidelines covering its treatment by spinal cord, deep brain, motor cortex and percutaneous nerve stimulation.

Due to the great number of types of neurostimulators and their potential uses, a table summarising the results of this report could not be reproduced in this document. However, an Excel document containing the grid can be viewed:



Neurostimulators
map

Figure 1 Map of secondary evidence on neurostimulators.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q		
1	Frequently used techniques - International Neuromodulation																		
2	(latest secondary evidence)																		
3	brain and spinal cord stimulation							peripheral nerve stimulation				cranial nerve stimulation							
4			spinal cord	deep brain	motor cortex	cerebral cortex	sacral nerve	occipital nerve	pubudal nerve	sympathetic nerve	percutaneous nerve	vagus/vagal nerve	trigeminal nerve						
5	PAIN RELIEF	Pain (general)	SR 2004 HTA 2006	SR 2005	SR 2008						HTA 2007								
6			SR 2004																
7			CI G 2005 NICE 2004																
8			Pain (Ischaemia-related Angina)																
9																			
10			Pain (pelvic and/or urogenital viscera)																
11																			
12			Pain (occipital neuralgia)																
13																			
14			Pain (Phantom Limb)	ARIF 2003	ARIF 2004	ARIF 2003													
15																			
16			Pain (neuropathic)	SR 2006 HTA 2008	HTA 2001														
17		ARIF 2006																	
18	Pain (trigeminal) / Trigeminal Neuralgia		ARIF 2003																
19																			
20	Pain (back)	SR 2005									ARIF 2007								
21		CI G 2007 ARIF 2002																	
22	Pain (Ischaemic Leg)	SR 2007																	
23																			
24	Pain (Knee Osteoarthritis)																		
25																			
26	Pain (regional)	SR 2006 HTA 2003																	
27																			
28	Chronic Headache										SR 2008 NICE NA								
29																			

Columns – types of stimulators
 Rows – indications for stimulation

SR – systematic review, HTA – health technology assessment, CI G – clinical guidelines, NICE – NICE guidelines, ARIF – ARIF report

The document consists of four worksheets:

- “map” - contains a grid mapping secondary evidence on types of stimulators and their potential uses (as above). Different colours were used to indicate if a stimulator or an indication were included on the website of the INS. Only the most up to date publications were included on this grid. They are linked to their descriptions in the “references” worksheet.
- “references” - provides more detailed information on the publications that were identified. It also enables searching for included publications based on the indication, stimulator type, publication type and date of publication. However, when using the links in the “map” worksheet –data filters ought to be set to “(all)”.
- “manufacturers” - provides a list of producers of neurostimulators who were identified. It provides basic information on the indication and type of devices manufactured. Indications are not provided for non-surgical devices, as their uses depend to a large extent on the physician.
- “other indications” - provides a short list of indications that were identified, but were not referred to by the INS and were not included in systematic reviews.

4.2 Types of neurostimulators

The main types of neurostimulators in this report were based on the website of the INS. It needs to be highlighted here that in the literature there exist other ways to classify at least some of the neurostimulators.

Although new types of stimulators were added after considering the results of the searches, main categories based on the INS website remained unchanged:

- brain and spinal cord stimulation,
- peripheral nerve stimulation,
- cranial nerve stimulation,
- functional electrical stimulation,
- other.

However, when describing these devices, a higher classification based on the way they are used appears to be more adequate. This includes the following types of neurostimulators:

- implantable (which are entirely implanted into the patient's body),
- partly implantable (which involve implantation of only a part of the device, while the remaining part is external),
- non-invasive (the use of which does not involve any surgical procedures).

The following sections describe types of neurostimulators based on this higher classification with an indication of which specific types of stimulators fall within any of the categories.

4.2.1 Implantable neurostimulators

This category encompasses a wide range of stimulators:

- brain and spinal cord,
- peripheral nerve (excluding percutaneous),
- cranial nerve,
- other (gastric).

Implantable neurostimulators tend to be similar in structure and consist of electrodes, a pulse generator, wire connecting both, and a remote control. Some of the devices have their own battery (some rechargeable) – usually lasting for three to nine years.²¹ A programming platform can be also used by a physician to change various parameters of stimulation (e.g. the polarity and the number of functioning electrodes).¹⁸²

Before permanent implantation, a trial phase usually takes place to establish if the stimulator brings improvement in the condition. Only the electrodes are inserted and pulses are generated by an external stimulator. This phase can take up to a few days.⁶ If the trial phase is successful, a permanent stimulator is implanted in a comfortable position.²¹

As an example, a more detailed description of a spinal cord stimulator and of procedure for implanting it can be found on the website of eOrthopod, an information resource about orthopaedic conditions and treatment options:

http://www.eorthopod.com/public/patient_education/6952/spinal_cord_stimulators.html

An illustration of deep brain stimulation and vagus nerve stimulation can be found via the following links:

http://www.wired.com/wired/archive/15.03/images/FF_156_brain4_f.jpg

http://bp0.blogger.com/_Jrt9PxI8-

F4/RuUoLJWJhOI/AAAAAAAAAS8/QpKIQ6o0VXc/s1600-h/vns_implant.jpg

4.2.2 Partly implantable neurostimulators

Stimulators covered by this category include:

- functional electrical (excluding transcutaneous electric (or neuromuscular) and trophic electrostimulation)
- peripheral nerve (percutaneous).

It is worth mentioning that the functional electrical stimulators included in this category include mainly neuroprostheses.

A number of other neuroprostheses were identified, including widely accepted devices such as cochlear implants,¹⁵¹ as well as more “experimental” devices aiming to provide artificial vision.¹⁸ They tend to be complex devices, combining the function of registering external stimuli and subsequently providing stimulation to targeted nerves.

An example of a cochlear implant and an illustration of a device aiming at restoring vision can be viewed via the following links:

http://kidshealth.org/parent/general/eyes/images_61903/P_cochlear-noConsole.jpg

<http://www.medgadget.com/archives/img/65234ss2.jpg>

Percutaneous nerve stimulation, although falling under the same category, tends to be a less complicated technology, compared to sensory prostheses. The electrodes

are introduced into the body through the skin and the open end of the wire is connected to an external stimulator.^{9,114}

An example of a percutaneous neurostimulator can be viewed at:

http://neurosofthellas.gr/images/women_ear.jpg

4.2.3 Non-invasive neurostimulators

Non-invasive neurostimulators include a wide range of devices:

- functional: transcutaneous electric (or neuromuscular),
- other: trophic electric, transcranial direct current stimulation, transcranial magnetic field, pulsed electromagnetic field.

Transcutaneous stimulators are frequently used for rehabilitation. They consist of electrodes that are usually attached to the skin surface directly over peripheral nerves. Electrodes are connected to a stimulator using leads.¹⁷⁶ Trophic stimulators have a similar structure, but are applied to influence muscles by mimicking healthy motor activity.¹⁵⁴

An example of a transcutaneous stimulator can be found at:

<http://www.guardianoffers.co.uk/mall/popupimage.cfm?productid=638&storename=GOTensor>

For transcranial direct current stimulation two relatively large (20-35 cm²) sponge electrodes, soaked in saline, are attached to the patient's head. These are connected to a current generator, which delivers a weak constant electrical current of up to 2 mA. The procedure usually takes from a few minutes up to half an hour.¹⁷⁹

A transcranial direct current stimulator can be viewed at:

http://bp1.blogger.com/_Jrt9PxI8-F4/Ru0cHwkT_h/AAAAAAAAAUk/Co1mMdYfIHs/s1600-h/tdcs.jpg

For transcranial magnetic field stimulation, a stimulator is needed to which different coils can be connected (usually two connected circular coils are used to achieve focal stimulation). They are placed next to the patients head and brief (<1ms) magnetic pulses of up to several Tesla are applied.¹⁷⁹

An illustration of the device and of its application is available at:

<http://www.medgadget.com/archives/img/98633tms.jpg>

http://content.revolutionhealth.com/contentimages/images-image_popup-dn7_transcranial.jpg

Pulsed electromagnetic field stimulator “*consists of external current-carrying coils driven by a signal generator*”. The coils are worn across the area of stimulation.⁷⁹

An example of such a device and of potential uses can be found at:

<http://www.geocities.com/kbeb3234/HomeUseMedicalDevice/PulseEMF/image006.jpg>

[g](http://www.geocities.com/kbeb3234/HomeUseMedicalDevice/PulseEMF/image009.gif)

<http://www.geocities.com/kbeb3234/HomeUseMedicalDevice/PulseEMF/image009.gif>

[f](http://www.geocities.com/kbeb3234/HomeUseMedicalDevice/PulseEMF/image009.gif)

It also needs to be mentioned that occipital cortex implantation was not placed in any class of stimulator. Although the INS referred to it as an investigational use of neurostimulation for improvement of eyesight,²¹ no further information was found. There was however some information on visual cortex implantation, which would place it in the partly implantable category with other sensory prostheses.¹⁵¹

4.3 Indications for the use of neurostimulators

Using the information from the INS website and our searches, more than 50 uses of neurostimulators were identified.

These indications can be grouped into seven main categories:

- pain relief,
- movement disorders,
- mental disorders,
- rehabilitation,
- voiding difficulties and/or incontinence,
- sensory prosthetics,
- other.

There is a difficulty in providing an exact number or list of uses, since some of the indications overlap. A good example might be the use of neurostimulation for stroke recovery and in rehabilitation of paralysed patients – which could occur both in stroke and other conditions.

It also needs to be borne in mind that these indications were based on the INS website and searches for systematic reviews. It is possible that more indications could be found if the searches were broadened to include other study designs.

Overviews of indications using the above categories are given below, including the types and amount of secondary evidence identified by our searches.

4.3.1 Pain relief

Pain relief, the first condition that modern neurostimulation was used for, was covered by a high number of publications. Altogether, 17 systematic reviews,^{44,55,68,82,105,115,116,119,120,131,159,187-189,192,194,195} 11 HTAs,^{9,23,39,95,96,121,153,161,177,181,199} and eight clinical guidelines^{5,48,49,83,107,152,180} were identified. Seven ARIF requests that addressed pain relief with neurostimulation were included in this report.^{24,26,27,29,31,33,35}

The searches identified evidence on three general categories: reviews on pain relief without specifying the type of pain, on regional pain, and neuropathic pain. Moreover a number of publications addressed more specific indications.

Specific indications provided by the INS website included the following pain types:

- ischaemia-related angina,
- pelvic and/or urogenital viscera,
- occipital neuralgia,
- trigeminal,
- migraineous headaches.

Searches for systematic reviews provided further specific pain types that can be relieved with neurostimulation:

- back,
- ischaemic leg,

- phantom limb,
- knee osteoarthritis,
- chronic headache,
- whiplash associated disorder.

The main areas of stimulation were brain and spinal cord using implantable devices. In some cases, however, other areas were targeted and other types of stimulators were investigated.

Searches on the NICE website provided information that spinal cord stimulation was considered for IPP, but it was decided that this *“procedure is considered standard clinical practice with risks and benefits that are sufficiently well-known.”*¹⁷⁷ A NICE overview was also prepared on occipital nerve stimulation for intractable headache, and the guidance is due to be issued in Autumn 2008.¹⁶ One of the HTAs referred to above was a Technology Assessment prepared for NICE on spinal cord stimulation for chronic pain of neuropathic or ischaemic origin.¹⁷⁷ Guidance is expected to be issued in November 2008.¹⁷

4.3.2 Movement disorders

Movement disorders, especially Parkinson’s disease, are another area in which neurostimulation is often utilised. The searches identified seven systematic reviews,^{78,84,101,108,112,158,191} one protocol of a systematic review,¹³⁶ ten HTAs^{43,47,56,102,110,125,127,149,155,164} and one project of an HTA¹²⁴ on the use of neurostimulators in movement disorders. Two ARIF requests were included.^{30,34}

The INS pointed to the following conditions where the use of neurostimulation can be of benefit to the patient:

- Parkinson’s disease,
- dystonia,
- essential tremor,
- Tourette’s syndrome.

Searches provided additionally literature on tremor in general – not confined to essential tremor.

Systematic reviews on the treatment of these conditions by deep brain stimulation were identified. The INS also pointed at the possible application of spinal cord stimulation, but no systematic reviews were identified. One systematic review assessed the effectiveness of transcranial magnetic field stimulation in Parkinson's disease.⁷⁸

NICE Guidance on movement disorders (Parkinson's disease and dystonia)^{144,148} and a NICE Guideline on Parkinson's disease including management with deep brain stimulation¹⁴⁰ were also identified.

4.3.3 Mental disorders

Two systematic reviews^{117,118} and six HTAs^{37,45,46,87,93,193} were found on the treatment of mental disorders by neurostimulation. This report also included an ARIF request on vagal nerve stimulation for depression.³² Furthermore, NICE Guidance on the use of transcranial magnetic field stimulation for depression was identified.¹⁴³

The INS website provided information on the use of neurostimulation in patients with depression and obsessive-compulsive disorder. Searches did not add more indications.

However, it appears that some new indications for the use of neurostimulators can be expected in this field in the near future. Neurostimulation has already been used in a research setting to influence the course of disorders such as schizophrenia and mania.⁵⁰ Further to this a patent was identified for a stimulator which can be used in patients with schizophrenia, borderline personality disorder and probably other "*neuropsychiatric disorders*".²⁰

4.3.4 Rehabilitation

Neurostimulation appears to be extensively used in rehabilitation. It is also one of the more problematic areas as far as classification is concerned.

The INS pointed at the possible use of neurostimulation in rehabilitation of stroke patients. It was also indicated that neurostimulation could be of benefit to patients

with traumatic brain injury and severe motor impairment – but in terms of a future area of development of the therapy.

The searches provided some further uses of neurostimulation for rehabilitation in/after:

- paralysis,
- muscle weakness,
- drop foot syndrome,
- cerebral palsy,
- Bell's palsy,
- spinal cord injury,
- hip fracture surgery,
- soft tissue injuries of the knee,
- ligament injury.

The searches identified 19 systematic reviews,^{41,71,80,81,85,106,109,130,134,150,154,165-167,169,170,190,198,200} two protocols of systematic reviews^{132,135} and a NICE Guidance in progress on the use of functional electrical stimulation in drop foot syndrome.¹² An ARIF request addressing trophic electrical stimulation for facial paralysis following treatment of brain tumour was also included.²⁸

Most of the evidence investigated the use of functional electrical stimulation. Although this class of devices can be further divided into specific types of stimulators (e.g. transcutaneous electric/ neuromuscular, or diaphragm (phrenic) pacing), a lot of publications referred to functional electrical stimulation rather than the type of stimulator.

While some reviews tend to address complex rehabilitation in specified conditions (e.g. stroke), others describe the potential use of neurostimulators in rehabilitation of a specific disability which can be observed in a number of conditions (e.g. muscle weakness). Thus the indications in this section cannot necessarily be perceived as mutually exclusive.

4.3.5 Voiding difficulties and/or incontinence

Neurostimulation can be also used in patients with urinary and bowel voiding difficulties or incontinence. These uses were indicated on the website of the INS and searches identified evidence on them.

Seven systematic reviews^{51,52,77,104,137,160,175} were found to address these indications. Two of the systematic reviews were carried out for NICE IPP^{52,77} and guidance was issued taking them into account on sacral nerve stimulation for urinary urge incontinence and urgency frequency and for faecal incontinence.^{145,146} Two protocols for systematic reviews^{42,100} and nine HTAs^{54,57,75,89,111,122,123,126,156} were also identified.

4.3.6 Sensory prosthetics

Another area where neurostimulation can be applied is sensory prosthetics. As mentioned in section [4.2.2 Partly implantable neurostimulators](#), this includes well established uses, such as cochlear implants for improvement of hearing, and very novel ones, such as an investigational device which was developed to improve or return eyesight.

The INS provided the following indications:

- blinded (retinitis pigmentosa or macular degeneration),
- improvement of eyesight,
- hearing loss,
- tinnitus.

All of the above apart from hearing loss were referred to as investigational. Searches provided no further indications in this area.

On hearing loss: five systematic reviews,^{36,63,139,174,178} 23 HTAs,^{38,40,58,61,64-67,69,72,73,76,86,92,97-99,113,163,172,184,186,197} one project of a NICE Technology Appraisal (cochlear implants for severe to profound deafness in children and adults)¹ and a clinical guideline⁴ were identified. No evidence was found for the remaining indications, probably due to their investigational character.

4.3.7 Other

Apart from the above categories some other uses were identified. Based on the INS website, the following conditions were included as possibly treatable with neurostimulation:

- spasticity,
- epilepsy,
- chronic respiratory insufficiency.

The INS also provided the following investigational uses:

- obesity,
- spastic cough reflexes,
- induction of memory,
- induction of plasticity and learning.

Searches for systematic reviews have further extended the list of indications to include:

- angina pectoris,
- chronic critical leg ischaemia,
- gastroparesis,
- temporomandibular disorder,
- dysphagia.

Nine systematic reviews^{53,59,60,62,70,129,168,196,201}, ten HTAs,^{70,74,88,90,91,94,133,157,162,185} two HTA projects,^{22,103} NICE Guidance on application of neurostimulation to refractory epilepsy in children¹⁴⁷ and gastroparesis¹⁴¹ were identified. Information was also found that deep brain stimulation in epilepsy was considered outside of the scope of NICE IPP, as it was only used in research settings.⁷ A NICE guideline on epilepsy including vagus nerve stimulation was also found.¹⁸³ This report also included an ARIF request on vagal nerve stimulation for epilepsy.²⁵

Background reading provided a number of potential additional applications of neurostimulators. Some of them included:

- sleep apnoea,

- heart failure,
- hypertension (modulation of blood pressure),
- chronic memory disorders (which arise from, “*for example, Alzheimer's Disease, encephalitis, cerebral palsy, Wernicke-Korsakoff (alcohol-related) syndrome, brain injury, post-temporal lobectomy, Binswanger disease, Parkinson's disease, Pick's disease, stroke, multi-stroke dementia, multiple sclerosis, post arrest hypoxic injury, near drowning, etc.*”¹⁵).

It has to be however borne in mind that this report was not aimed at identifying emerging uses of neurostimulators and no specific searches were undertaken for this purpose. Furthermore, it appears that different types of stimulators might have been used in research settings for a number of other conditions. Therefore it is highly possible that searches for publications such as case reports could provide a variety of indications that were not identified by this report.

5. DISCUSSION AND FURTHER RESEARCH RECOMMENDATIONS

The aim of this report was to map the secondary evidence on neurostimulation. In order to do this a framework needed to be created on which to place the identified evidence. This framework was created by an iterative process, using the following sources: INS, identified secondary evidence, and the most up to date ARIF requests. The framework grid allows a stimulator (and location of a stimulator) to be cross referenced to an indication for which it is being applied. The framework is large due to the breadth and complexity of the topic and as such neither the list of stimulators or indications can be considered exhaustive.

This report identified 66 systematic reviews and 73 HTAs addressing different types and uses of neurostimulators. In the map only the most up to date publications were included. References to the remaining ones are however provided.

The report did not undertake to critically appraise any of the identified papers. Moreover, due to constraints not all of the papers could be obtained and in the case of doubt if they meet the inclusion criteria, papers were included.

The searches were aimed at identifying systematic reviews. However documents of other types (such as clinical guidelines) – if found – were also included in the report. It has to be however highlighted that searches were not targeted at their identification and these references were included only as examples.

It needs to be further stressed that, although some additional uses of neurostimulators were identified in the course of background reading, no systematic searches were undertaken for this purpose. It is likely that such searches could identify a wide range of additional applications, as neurostimulation could have been used in a number of conditions only in a research setting. The identified patents also suggest that there might be a number of emerging indications for neurostimulation.

The iterative process employed allows for expansion of the framework, including the addition of current experimental uses of neurostimulators. It is a good framework on which to map secondary evidence, as in this report, but also if necessary to add primary evidence or other information.

As the report is not a review of effectiveness, it does not cover the important subject of adverse events of the use of neurostimulators. This could be an important issue especially with regard to the implanted and partly implanted stimulators where there are some safety considerations associated with surgery. Moreover the possible undesired impact on functions other than intended can be of importance in some cases.

One of the major problems encountered in mapping the potential uses of neurostimulators was the overlap in the range of medical conditions which can be targeted. A good example would be drop foot syndrome – which can occur in patients with a number of conditions including stroke, cerebral palsy, spinal cord injury or multiple sclerosis.

It is clear from the evidence mapped on the framework that (i) there is a number of indication-stimulator combinations covered by secondary evidence, (ii) at present no secondary evidence exists on many of possible combinations.

This leads to the following options for further work:

- expanding the framework by undertaking searches for primary evidence in order to identify additional combinations of indications and neurostimulators;
- critically appraising existing systematic reviews in a specified area (or areas) of interest;
- critically appraising existing systematic reviews in a specified area (or areas) of interest and, if necessary, updating them.

Guidance is required on which of these options should be undertaken.

6. APPENDICES

6.1 NICE Interventional Procedures Programme

The first step is notification of a procedure to NICE. Most often it is notified by a clinician who wants to use this procedure for the first time in the NHS outside of a research setting. It is also possible that for example patients or organisations notify procedures to NICE.¹⁴²

Such a notification has to provide information concerning:

- *“contact details of the notifier,*
- *name of the interventional procedure,*
- *description of the interventional procedure,*
- *indications, any other procedure that the new procedure is likely to replace,*
- *if the notifier is not a clinician, the name of a clinician for NICE to contact in connection with the notification.”¹⁴²*

NICE decides whether the notified procedure falls within the scope of the Programme. This is based on a set of criteria which state that the procedure must:

- *“involve an incision or a puncture or entry into a body cavity, or the use of ionising, electromagnetic or acoustic energy, and*
- *be available within the NHS or about to be used for the first time in the NHS, outside formal research, and*
- *either not yet be generally considered standard clinical practice, or*
- *be a standard clinical procedure, the safety or efficacy of which has been called into question by new information”¹⁴²*

If the procedure is considered to fall within the scope of the Programme, NICE prepares an “overview” of the procedure. This document includes results of a brief literature search and opinions of at least three clinical experts (Specialist Advisors nominated by professional healthcare bodies). It provides information on the *“nature and purpose of the procedure, results of the most valid studies found in a rapid review of the literature, key safety and efficacy issues”*.¹⁴²

The next step is for the Interventional Procedures Advisory Committee (IPAC) to consider the evidence included in the overview and then to either produce guidance or that more information is needed.¹⁴²

If no further evidence is needed, IPAC produces a draft document which is placed on the NICE website for a four week consultation. Following that, IPAC reviews its document and issues recommendations for the procedure. Based on that, NICE issues guidance to the NHS in England, Scotland, Wales and Northern Ireland.¹⁰

If IPAC, however, considers the information in the “overview” to be insufficient, the procedure is further referred to a consortium of three universities and a teaching hospital NHS Trust (Review Body). Parallel to that a document for consultation is placed on the NICE website for a period of four weeks. The Review Body carries out a systematic review and if it is considered necessary, organises data collection in collaboration with relevant professional organisations. Based on this, an evaluation report is produced. IPAC considers the report, as well as comments from stakeholders, and issues a second consultation document which is placed on the NICE website for another four weeks consultation. Afterwards, the same procedure as described above (when no further information was needed) follows.¹⁴²

In certain circumstances a procedure can be referred to NICE Technology Appraisal Programme. This can only happen when the effectiveness and safety of a procedure is well established. Moreover it is more likely for a procedure to be considered for a Technology Appraisal if the procedure:

- *“is indicated in a common health problem,*
- *has important advantages over existing treatment(s),*
- *is the only existing treatment, and/or*
- *is potential for rapid diffusion,*
- *has differing costs from existing treatment(s),*
- *is connected to government priority”.*¹⁴²

6.2 Search strategies

Searches were undertaken in accordance with the ARIF protocol

Spinal cord / dorsal column stimulation

Source Cochrane Library 2008 Issue 2

- #1 spinal next cord next stimulat*
- #2 spinal next column next stimulat*
- #3 scs
- #4 dorsal next cord next stimulat*
- #5 dorsal next column next stimulat*
- #6 (#1 OR #3 OR #5)
- #7 MeSH descriptor Spinal Cord, this term only
- #8 MeSH descriptor Electric Stimulation, this term only
- #9 MeSH descriptor Electric Stimulation Therapy, this term only
- #10 (#8 OR #9)
- #11 (#7 AND #10)
- #12 (#6 OR #11)

Source - Ovid MEDLINE(R) 1950 to June Week 3 2008

- 1 spinal cord stimulat\$.mp.
- 2 spinal column stimulat\$.mp.
- 3 dorsal cord stimulat\$.mp.
- 4 dorsal column stimulat\$.mp.
- 5 spinal cord/
- 6 electric stimulation/
- 7 electric stimulation therapy/
- 8 6 or 7
- 9 5 and 8
- 10 1 or 2 or 3 or 4 or 9
- 11 scs.mp.
- 12 10 or 11
- 13 limit 12 to "reviews (specificity)"

Source – EMBASE (Ovid) 1980 to June 2008

- 1 spinal cord stimulat\$.mp.
- 2 spinal column stimulat\$.mp.
- 3 dorsal column stimulat\$.mp.
- 4 dorsal cord stimulat\$.mp.
- 5 spinal cord/
- 6 electrostimulation/
- 7 1 or 2 or 3 or 4
- 8 5 and 6
- 9 7 or 8
- 10 limit 9 to "reviews (1 term high specificity)"

Deep brain stimulation

Source – Cochrane Library 2008 Issue 2

- #1 deep next brain next stimulation
- #2 pallidotomy

- #3 subthalamotomy
- #4 subthalamic next stimulation
- #5 MeSH descriptor Subthalamic Nucleus, this term only
- #6 MeSH descriptor Electric Stimulation, this term only
- #7 MeSH descriptor Electric Stimulation Therapy explode all trees
- #8 (#6 OR #7)
- #9 (#5 AND #8)
- #10 (#1 OR #2 OR #3 OR #4 OR #9)

Source - Ovid MEDLINE(R) 1950 to June Week 2 2008

- 1 pallidotomy.mp.
- 2 subthalamotomy.mp.
- 3 subthalamic stimulation.mp.
- 4 subthalamic nucleus/
- 5 electrical stimulation/
- 6 electric stimulation therapy/
- 7 deep brain stimulation.mp.
- 8 5 or 6
- 9 4 and 8
- 10 1 or 2 or 3 or 7 or 9
- 11 limit 10 to "reviews (specificity)"

Source - EMBASE (Ovid) 1980 to June 2008

- 1 deep brain stimulation.mp.
- 2 pallidotomy.mp.
- 3 subthalamotomy.mp.
- 4 subthalamic stimulation.mp.
- 5 subthalamic nucleus/
- 6 electrostimulation/
- 7 5 and 6
- 8 1 or 2 or 3 or 4
- 9 7 and 8
- 10 limit 9 to "reviews (1 term high specificity)"

Motor cortex stimulation

Source - Cochrane Library 2008 Issue 2

- #1 motor next cortex next stimulat*
- #2 cortical next stimulat*
- #3 (#1 OR #2)
- #4 MeSH descriptor Motor Cortex, this term only
- #5 MeSH descriptor Electric Stimulation, this term only
- #6 MeSH descriptor Electric Stimulation Therapy, this term only
- #7 (#5 OR #6)
- #8 (#4 AND #7)
- #9 (#3 OR #8)

Source - Ovid MEDLINE(R) 1950 to June Week 3 2008

- 1 motor cortex stimulat\$.mp.
- 2 cortical stimulat\$.mp.
- 3 Motor Cortex/
- 4 electric stimulation/
- 5 electric stimulation therapy/
- 6 4 or 5
- 7 3 and 6
- 8 1 or 2 or 7

9 limit 8 to "reviews (specificity)"

Source - EMBASE (Ovid) 1980 to June 2008

- 1 motor cortex stimulat\$.mp.
- 2 cortical stimulat\$.mp.
- 3 Motor Cortex/
- 4 Electrostimulation/
- 5 3 and 4
- 6 1 or 2
- 7 5 or 6
- 8 limit 7 to "reviews (2 or more terms high specificity)"

Sacral nerve stimulation

Source – Cochrane Library 2008 Issue 2

- #1 sacral next nerve next stimulat*
- #2 MeSH descriptor sacrum, this term only
- #3 MeSH descriptor Electric Stimulation, this term only
- #4 MeSH descriptor Electric Stimulation Therapy, this term only
- #5 (#3 OR #4)
- #6 (#2 AND #5)
- #7 (#1 OR #6)

Source - Ovid MEDLINE(R) 1950 to June Week 3 2008

- 1 sacral nerve stimulat\$.mp.
- 2 sacrum/
- 3 electric stimulation/
- 4 electric stimulation therapy/
- 5 3 or 4
- 6 2 and 5
- 7 1 or 6
- 8 limit 7 to "reviews (specificity)"
- 9 limit 7 to "reviews (optimized)"

Source – EMBASE (Ovid) 1980 to June 2008

- 1 sacral nerve stimulat\$.mp.
- 2 SACRUM/
- 3 electrostimulation/
- 4 2 and 3
- 5 1 or 4
- 6 limit 5 to "reviews (1 term high specificity)"

Peripheral nerve stimulation

Source – Cochrane Library 2008 Issue 2

- #1 peripheral next nerve next stimulation
- #2 pudendal next nerve next stimulation
- #3 sympathetic nerve stimulation
- #4 (#1 or #2 or #3)
- #5 MeSH descriptor Peripheral Nerves, this term only
- #6 MeSH descriptor Sympathetic Nervous System, this term only
- #7 MeSH descriptor Electric Stimulation, this term only
- #8 MeSH descriptor Electric Stimulation Therapy, this term only
- #9 (#7 or #8)
- #10 (#5 or #6)

#11 (#9 and #10)

Source - Ovid MEDLINE(R) 1950 to June Week 3 2008

- 1 peripheral nerve stimulation.mp.
- 2 pudendal nerve stimulation.mp.
- 3 sympathetic nerve stimulation.mp.
- 4 1 or 2 or 3
- 5 limit 4 to "reviews (specificity)"
- 6 from 5 keep 1
- 7 peripheral nerves/
- 8 sympathetic nervous system/
- 9 electric stimulation/
- 10 electric stimulation therapy/
- 11 7 or 8
- 12 9 or 10
- 13 11 and 12
- 14 limit 13 to "reviews (specificity)"

Source - EMBASE (Ovid) 1980 to June 2008

- 1 peripheral nerve stimulation.mp.
- 2 pudendal nerve stimulation.mp.
- 3 sympathetic nerve stimulation.mp.
- 4 1 or 2 or 3
- 5 Peripheral Nerve/
- 6 Sympathetic Nerve/
- 7 electrostimulation/
- 8 5 or 6
- 9 7 and 8
- 10 4 or 9
- 11 limit 10 to "reviews (1 term high specificity)"

Percutaneous nerve stimulation

Source - Ovid MEDLINE(R) 1950 to June Week 2 2008

- 1 pens.tw.
- 2 percutaneous electric\$ neurostimulation.mp.
- 3 Electric Stimulation Therapy/
- 4 percutaneous electric\$ nerve stimulation.mp.
- 5 percutaneous electric\$ neuromodulation.mp.
- 6 limit 1 to "reviews (optimized)"
- 7 3 or 4
- 8 limit 7 to "reviews (optimized)"
- 9 limit 7 to "reviews (specificity)"

Source – Cochrane Library 2008 Issue 2

- #1 PENS
- #2 percutaneous next electric* next neurostimulation
- #3 percutaneous next electric* next nerve next stimulation
- #4 percutaneous next nerve next neuromodulation
- #5 (#1 OR #2 OR #3 OR #4)

Source – EMBASE (Ovid) 1980 – June 2008

- 1 pens.mp.
- 2 percutaneous electric\$ neurostimulation.mp.

- 3 percutaneous electric\$ nerve stimulation.mp.
- 4 percutaneous electric\$ neuromodulation.mp.
- 5 1 or 2 or 3 or 4
- 6 Limit 5 to "reviews (1 term high specificity)

Vagal nerve stimulation

Source – Cochrane Library 2008 Issue 2

- #1 vagal nerve stimulation
- #2 vagus nerve stimulation
- #3 MeSH descriptor Vagus Nerve, this term only
- #4 MeSH descriptor Electric Stimulation, this term only
- #5 MeSH descriptor Electric Stimulation Therapy, this term only
- #6 (#3 OR #4)
- #7 (#3 AND #6)
- #8 (#1 OR #2)
- #9 (#7 OR #8)

Source - Ovid MEDLINE(R) 1950 to June 2008

- 1 vagal nerve stimulation.mp.
- 2 vagus nerve stimulation.mp.
- 3 vagus nerve/
- 4 electric stimulation therapy/
- 5 electric stimulation/
- 6 1 or 2
- 7 4 or 5
- 8 3 and 7
- 9 6 or 8
- 10 limit 9 to "reviews (specificity)"

Source – EMBASE (Ovid) 1980 to June

- 1 vagal nerve stimulation.tw.
- 2 vagus nerve stimulation.tw.
- 3 Vagus Nerve/
- 4 Electrostimulation/
- 5 3 and 4
- 6 1 or 2 or 5
- 7 limit 6 to "reviews (1 term high specificity)"

Functional electrical stimulation

Source – Cochrane Library 2008 Issue 2

- #1 functional electric* next stimulat*

Source - Ovid MEDLINE(R) 1950 to June Week 3 2008

- 1 functional electric\$ stimulat\$.mp)
- 2 limit 1 to "reviews (specificity)"

Source – EMBASE (Ovid) 1980 to 2008

- 1 functional electric\$ stimulat\$.mp.
- 2 limit 1 to "reviews (1 term high specificity)"

Neuromuscular electrical stimulation

Source – Cochrane Library 2008 Issue 2

#1 neuromuscular next electric* next stimulat*

Source - Ovid MEDLINE(R) 1950 to July Week 4 2008

- 1 neuromuscular electrical stimulation.mp.
- 2 limit 2 to "reviews (optimized)"

Source – EMBASE (Ovid) 1980 to 2008 Week 30

- 1 neuromuscular electrical stimulation.mp.
- 2 limit 1 to "reviews (2 or more terms high specificity)"
- 3 limit 1 to "reviews (2 or more terms min difference)"

Pulsed magnetic fields

Source – Cochrane Library 2008 Issue 2

#1 pulsed next magnetic next field*

Source - Ovid MEDLINE(R) 1950 to June Week 3 2008

- 1 pulsed magnetic field.mp.
- 2 limit 1 to "reviews (specificity)"

Source – EMBASE (Ovid) 1950 to June Week 3 2008

- 1 pulsed magnetic field.mp.
- 2 limit 1 to "reviews (1 term high specificity)"

Gastric electrical stimulation

Source – Cochrane Library 2008 Issue 2

#1 gastric next electrical next stimulation

Source - Ovid MEDLINE(R) 1950 to July Week 4 2008

- 1 gastric electrical stimulation.mp.
- 2 limit 1 to "reviews (optimized)"

Source – EMBASE (Ovid) 1980 – July 2008

- 1 gastric electrical stimulation.mp.
- 2 limit 1 to "reviews (1 term high specificity)"

Cochlear implantation

Source – Cochrane Library 2008 Issue 2

#1 cochlear next implant*
#2 auditive next implant*
#3 MeSH descriptor Cochlear Implants, this term only
#4 (#1 OR #2 OR #3)

Source - Ovid MEDLINE(R) 1950 to June Week 3 2008

- 1 cochlear implant\$.mp.
- 2 auditive implant\$.mp.

- 3 Cochlear Implantation/
- 4 cochlear implants/
- 5 1 or 2 or 3 or 4
- 6 limit 5 to "reviews (specificity)"

Source – EMBASE (Ovid) 1980 to 2008 Week 32

- 1 cochlear implant\$.mp.
- 2 auditive implant\$.mp.
- 3 cochlea prosthesis/
- 4 1 or 2 or 3
- 5 limit 4 to "reviews (2 or more terms high specificity)"

Retinal stimulation

Source – Cochrane Library 2008 Issue 2

- #1 MeSH descriptor Retina, this term only
- #2 MeSH descriptor Electric Stimulation, this term only
- #3 MeSH descriptor Electric Stimulation Therapy, this term only
- #4 retinal next stimulat*
- #5 (#2 OR #3)
- #6 (#1 AND #5)
- #7 (#4 OR #6)

Source – MEDLINE (Ovid) 1950 to July 2008

- 1 Retina/
- 2 Electric stimulation/
- 3 Electric stimulation therapy/
- 4 Retinal stimulat\$.mp.
- 5 2 or 3
- 6 1 and 5
- 7 4 or 6

Source – EMBASE (Ovid) 1980 to July 2008

- 1 Retina/
- 2 Electrostimulation/
- 3 1 and 2
- 4 Retinal stimulat\$.mp.
- 5 3 or 4

Closed loop peripheral stimulation

Source – Cochrane Library 2008 Issue 3

- #1 closed next loop next peripheral

Source – Ovid MEDLINE 1950 – July 2008

- 1 closed loop peripheral.mp.

Source – EMBASE (Ovid) 1980 – July 2008

- 1 closed loop peripheral.mp.

Diaphragm pacing

Source – Cochrane Library 2008 Issue 3

#1 diaphragm next pacing

#2 phrenic next pacing

Source – Ovid MEDLINE 1950 – July 2008

1 diaphragm pacing.mp.

2 phrenic pacing.mp.

Source – EMBASE (Ovid) 1980 – July 2008

1 diaphragm pacing.mp.

2 phrenic pacing.mp.

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ISBN No: 07044 27192
9780704427198

Price: £15.00