SYLLABUS

TC35: Pain

Wednesday, November 16, 2011 09:00 - 12:30 Hall J

Marrakesh, Morocco, November 12-17, 2011

XXth WORLD CONGRESS OF NEUROLOGY

XXth WCN 2011 MARRAKESH World Congress of Neurology

WFN

SMN SOCIETE MAROCAINE DE NEUROLOGIE

WCN Education Program

Wednesday, 16 November, 2011

09:00-12:30

PAIN

Chairperson: **Giorgio Cruccu**, *Italy*

NEUROPATHIC PAIN AND ITS MECHANISMS
Praveen Anand, *UK*

CLINICAL CHARACTERISTICS AND DIAGNOSTIC INVESTIGATIONS
Claudia Sommer, *Germany*

TREATMENT OF NEUROPATHIC PAIN
Giorgio Cruccu, *Italy*

10:30-11:00 *Coffee Break*

TREATMENT OF NEUROPATHIC PAIN

G. CRUCCU
EFNS Panel Neuropathic Pain, Vienna
Dept. Neurology & Psychiatry, Rome


AAN-EFNS Guidelines on Trigeminal Neuralgia 2008

European Journal of Neurology 2008, 15: 1013–1028 doi:10.1111/j.1468-1331.2008.02185.x
EFNS GUIDELINES/CME ARTICLE

AAN-EFNS guidelines on trigeminal neuralgia management

G. Cruccu[a], G. Gronseth[b], J. Alksne[c], C. Argoff[d], M. Brainin[e], K. Burchiel[f], T. Nurmikko[g] and J. M. Zakrzewska[h]

[a]Department of Neurological Sciences, La Sapienza University, Rome, Italy; [b]Department of Neurology, University of Kansas, Kansas City, USA; [c]Division of Neurosurgery, School of Medicine, University of California, San Diego, USA; [d]New York University School of Medicine and Cohn Pain Management Center, North Shore University Hospital, Manhasset, USA; [e]Clinical Neurosciences, Department of Clinical Medicine and Prevention, Donau-Universität Krems, Krems, Austria; [f]Department of Neurological Surgery, Oregon Health & Science University, Portland, USA; [g]Pain Research Institute, Division of Neurological Science, School of Clinical Sciences, University of Liverpool, Liverpool, UK; [h]University College London Hospitals Eastman Dental Hospital, London, UK

EFNS=European Federation of Neurological Societies; NP=Neuropathic pain.

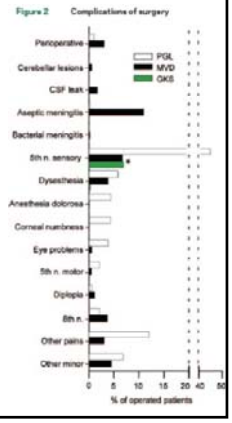
Recommendations for trigeminal neuralgia

The two drugs to consider as first-line therapy in CTN are CBZ (200–1200 mg/day) and OXC (600–1800 mg/day). Although the evidence for CBZ is stronger than for OXC, the latter may pose fewer safety concerns. If any of these sodium-channel blockers is ineffective, referral for a surgical consultation would be a reasonable next step.

Limited evidence supports add-on therapy with lamotrigine or a switch to baclofen (pimozide being no longer in use).

Recommendations for trigeminal neuralgia

Although all the surgical procedures are inherently supported by low-level evidence, the results in thousands of patients indicates that the surgical treatments for trigeminal neuralgia are efficacious and acceptably safe. An evidence-based direct comparison between the different surgical procedures is so far impossible. To briefly differentiate them we may summarise that the percutaneous Gasserian lesions can be safely performed in the elderly but often engender facial numbness, microvascular decompression provides the longest-lasting pain relief but involves some risk of major neurological complications, gamma-knife is the least invasive and safest procedure but pain relief may take one month to develop.



EFNS Guidelines NP Treatment 2010

European Journal of Neurology 2010 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2009 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

[a]*EFNS Panel Neuropathic Pain;* [b]*INSERM U987, Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré, APHP, Boulogne-Billancourt, and Université Versailles-Saint-Quentin,Versailles, France;* [c]*Department of Neurological Sciences, La Sapienza University, Rome, Italy;* [d]*Division of Neurological Pain Research and Therapy, Department of Neurology, Universitatsklinikum Schleswig-Holstein, Kiel, Germany;* [e]*Rehabilitation ORTON and Department of Neurosurgery, Helsinki University Hospital, Helsinki, Finland;* [f]*Department of Molecular Medicine and Surgery, Clinical Pain Research and Pain Center, Department of Neurosurgery, Karolinska Institutet/University Hospital, Stockholm, Sweden;* [g]*Department of Neurology and Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark; and* [h]*Pain Research Institute, Neuroscience Research Unit, School of Clinical Sciences, University of Liverpool, Liverpool, UK*

EFNS=European Federation of Neurological Societies; NP=Neuropathic pain.

Classification of evidence for drug treatments in commonly studied NP conditions

NP condition	Level A rating for efficacy	Level B rating for efficacy	Level A/B rating for inefficacy or discrepant results
Diabetic NP	Duloxetine, Gabapentin-morphine, TCA, Gabapentin, Nicotine agonist*, Nitrate derivatives*, Oxycodone, Pregabalin, TCA_a, Tramadol alone or with Paracetamol, Venlafaxine ER	BTX-A** Dextromethorphan Gabapentin/ Venlafaxine** Levodopa**	Capsaicin cream, Lacosamide, Lamotrigine, Memantine, Mexiletine, Mianserin, NK1 antagonist*, Oxcarbazepine SSRI, Topical clonidine, Topiramate, Valproate, Zonisamide
Post-herpetic neuralgia	Capsaicin 8% patch*, Gabapentin Gabapentin ER, Lidocaine plasters Opioids, Pregabalin, TCA_a	Capsaicin cream Valproate**	Benzydamine topical, Dextromethorphan, Fluphenazine, Memantine, Lorazepam, Mexiletine, COX-2 inhibitor, Tramadol
Classic TN	Carbamazepine	Oxcarbazepine	
Central pain	Cannabinoids (oro-mucosal* oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)** Opioids	Carbamazepine, Gabapentin, Lamotrigine (SCI), Levetiracetam Mexiletine, Valproate, S-ketamine iont.

a=amitriptyline, clomipramine (diabetic neuropathy), nortriptyline, desipramine, imipramine. *Not yet available for use; **Effective in single class II/III studies, generally not recommended; BTX-A=*Botulinum* toxin A; CPSP=Central post-stroke pain; ER=Extended release; MS=Multiple sclerosis; NK=Neurokinin; SCI=Spinal cord injury; THC= Tetrahydrocannabinol; TN=Trigeminal neuralgia.

Attal N, et al. *Eur J Neurol.* 2010;17:1113–e88.

Classification of evidence for drug treatments in less studied NP conditions

Aetiology of NP	Level A rating for efficacy	Level B rating for efficacy	Level A/B rating for inefficacy/poor efficacy or discrepant results
HIV neuropathy	Capsaicin 8% patch Smoked cannabis	Lamotrigine	Amitriptyline, Capsaicin cream, Gabapentin, Lidocaine plasters, Memantine
Post-traumatic or post-surgical NP		Amitriptyline* Botulinum toxin-A* Pregabalin*	Cannabinoids, Capsaicin, Gabapentin, Levetiracetam, Propranolol, Venlafaxine ER
Chronic radiculopathy			Morphine* Nortriptyline* Nortriptyline-morphine Pregabalin (unpublished) Topiramate
Cancer NP	Gabapentin	Amitriptyline* Tramadol*	Valproate
Phantom pain	Morphine Tramadol		Amitriptyline, Gabapentin, Memantine, Mexiletine
Multi-aetiology NP	Bupropion Cannabinoids (oromucosal, synthetic analogue) Levorphanol	Methadone TCA (nortriptyline, clomipramine)	Amitriptyline/ketamine topical, CCK2 antagonists, Dextromethorphan, Dihydrocodeine, Gabapentin[a] Venlafaxine ER[a] , Lamotrigine, Lidocaine plasters, Mexiletine[a], Nabilone, Riluzole

*Effective in single class II studies; a=Effective in some spontaneous neuropathic symptoms (gabapentin) or only on brush-induced or static mechanical allodynia (mexiletine, venlafaxine) in single trials; CCK2=Cholecystokinin2.

Attal N, et al. Eur J Neurol. 2010;17:1113–e88.

Classification of evidence for drug treatments in commonly studied NP conditions

NP condition	Level A rating for efficacy	Level B rating for efficacy	Recommendations for first line	Recommendations for second line
Diabetic NP	Duloxetine, Gabapentin-morphine, TCA, Gabapentin, Nicotine agonist*, Nitrate derivatives*, Oxycodone, Pregabalin, TCA_a Tramadol alone or with Paracetamol, Venlafaxine ER	BTX-A** Dextro-methorphan Gabapentin/ Venlafaxine** Levodopa**	Duloxetine Gabapentin Pregabalin TCA Venlafaxine ER	Opioids Tramadol
Post-herpetic neuralgia	Capsaicin 8% patch*, Gabapentin, Gabapentin ER, Lidocaine plasters, Opioids, Pregabalin,TCA_a	Capsaicin cream Valproate**	Gabapentin Pregabalin TCA Lidocaine plasters	Capsaicin Opioids
Classic TN	Carbamazepine	Oxcarbazepine	Carbamazepine Oxcarbazepine	Surgery
Central pain	Cannabinoids (oro-mucosal* oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)** Opioids	Gabapentin Pregabalin TCA	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI)

a=amitriptyline, clomipramine (diabetic neuropathy), nortriptyline, desipramine, imipramine. *Not yet available for use; **Effective in single class II/III studies, generally not recommended.

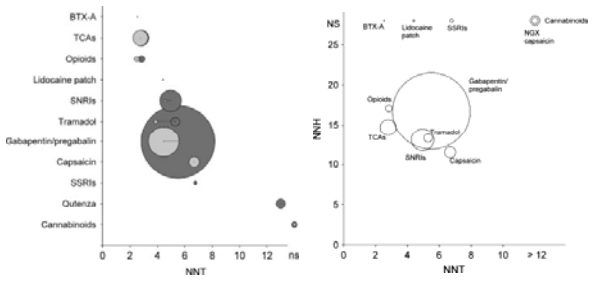
Attal N, et al. Eur J Neurol. 2010;17:1113–e88.

Why scoring level A evidence is not enough to ensure first-line recommendation

1. Effect Size
2. Quality of Life
3. Safety concerns

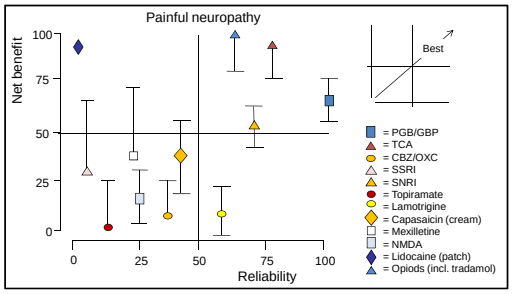
Attal N, et al. *Eur J Neurol.* 2010.
Cruccu G. *Curr Opin Neurol* 2007

Number needed to treat (NNT) and Number needed to harm (NNH)



Finnerup et al. *Pain* 2010

Reliability / effective gain



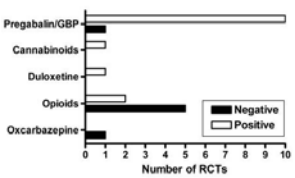
On the X-axis reliability provides a quantitative measure of the evidence, assessing both quality of the trials and their sample size. On the Y-axis net benefit calculates the advantage over the placebo both as efficacy and tolerability. Four classes of drugs in the upper-right quadrant: gabapentinoids, opioids, SNRI and TCA, provide the highest benefit.

CBX/OXC=Carbamazepine/oxcarbazepine; NMDA=N-methyl-D-aspartate; PGB/GBP=Pregablin/gabapentin; SSRI=Selective serotonin-reuptake inhibitor; SNRI=Serotonin-noradrenalin-reuptake inhibitor; TCA=Tricyclic antidepressants.

Cruccu G. *Curr Opin Neurol* 2007

Importance of QoL and comorbidities

- In the majority of pain trials, pain relief is the primary endpoint
- In clinical practice, our goal is to provide the patient with a good standard of living
- Hence, the evaluation of treatments for their effect on global change, sleep, mood, functional capacity, and QoL are recommended[1]



QoL=Quality of life.
1. Attal N, et al. Eur J Neurol. 2006.

Major discussions: safety concerns about opioids

- The lack of long-term studies of opioids in chronic non-cancer patients pain was one of the main objections raised in the guidelines[1]
- One study of slow-release oxycodone (average dose 52.5 mg) followed-up 233 patients for up to 36 months[2]
  - 10% of patients required an increase in their average daily dose from month 12[2]
  - 2.6% of patients were reported as possible drug misusers[2]
- However, these are only the first results. More controlled, long-term studies, and QoL assessments are needed[1]

1. Attal N, et al. *Eur J Neurol.* 2010; 2. Portenoy RK, et al. *Clin J Pain.* 2007.

Major discussions: safety concerns about TCAs

- An association between TCA treatment and sudden cardiac death has raised concerns
- A 2004 epidemiological study found an increase in sudden cardiac death with high-dose TCAs[1]
  - Caution is recommended for older patients, particularly those with cardiovascular risk factors[1]
- Older patients are currently being prescribed TCAs at daily dosages that are universally low (average 23 mg)[2]
  - This was demonstrated in 1,732 patients with painful neuropathy[2]

1. Ray WA, et al. *Clin Pharmacol Ther.* 2004;75:234–41; 2. Berger A, et al. *Eur J Clin Pharmacol.* 2006;62:757–64.

Final recommendations for first-line in commonly studied NP conditions

NP condition	Level A rating for efficacy	Level B rating for efficacy	Recommendations for first line	Recommendations for second line
Diabetic NP	Duloxetine Gabapentin-morphine TCA Gabapentin Nicotine agonist* Nitrate derivatives* Oxycodone Pregabalin TCA_s Tramadol alone or with Paracetamol Venlafaxine ER	BTX-A** Dextromethorphan Gabapentin/ Venlafaxine** Levodopa**	**Duloxetine Gabapentin Pregabalin TCA Venlafaxine ER**	Opioids Tramadol
PHN	Capsaicin 8% patch* Gabapentin Gabapentin ER Lidocaine plasters Opioids Pregabalin TCA_s	Capsaicin cream Valproate**	**Gabapentin Pregabalin TCA Lidocaine plasters**	Capsaicin Opioids
Classic TN	Carbamazepine	Oxcarbazepine	**Carbamazepine Oxcarbazepine**	Surgery
Central pain	Cannabinoids (oro-mucosal* oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)** Opioids	**Gabapentin Pregabalin TCA**	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI)

Attal N, et al. Eur J Neurol. 2010;17:1113–e88.

The National Institute for Health and Clinical Excellence (NICE)

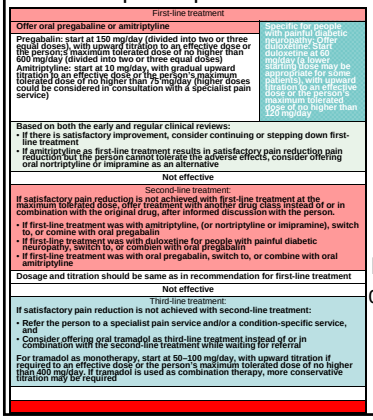
Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings

Full guideline

Draft for consultation, October 2009

- **Non-specialist settings** Primary and secondary care services that do not provide specialist pain services. Non-specialist settings include general practice, general community care and hospital care.

Neuropathic pain: NICE clinical guideline (2010)



First-line treatment

Offer oral pregabaline or amitriptyline

Pregabalin: start at 150 mg/day (divided into two or three equal doses), with upward titration to an effective dose or the person's maximum tolerated dose of no higher than 600 mg/day (divided into two or three equal doses)

Amitriptyline: start at 10 mg/day, with gradual upward titration to an effective dose or the person's maximum tolerated dose of no higher than 75 mg/day (higher doses could be considered in consultation with a specialist pain service)

specific for people with painful diabetic neuropathy: Offer duloxetine: Start duloxetine at 60 mg/day (a lower starting dose may be appropriate for some patients), with upward titration to the effective dose or the person's maximum tolerated dose of no higher than 120 mg/day

Based on both the early and regular clinical reviews:

- If there is satisfactory improvement, consider continuing or stepping down first-line treatment
- If amitriptyline as first-line treatment results in satisfactory pain reduction pain reduction but the person cannot tolerate the adverse effects, consider offering oral nortriptyline or imipramine as an alternative

Not effective

Second-line treatment:

If satisfactory pain reduction is not achieved with first-line treatment at the maximum tolerated dose, offer treatment with another drug class instead of or in combination with the original drug, after informed discussion with the person.

- If first-line treatment was with amitriptyline, (or nortriptyline or imipramine), switch to, or comine with oral pregabalin
- If first-line treatment was with duloxetine for people with painful diabetic neuropathy, switch to, or combien with oral pregabalin
- If first-line treatment was with oral pregabalin, switch to, or combine with oral amitriptyline

Dosage and titration should be same as in recommendation for first-line treatment

Not effective

Third-line treatment:

If satisfactory pain reduction is not achieved with second-line treatment:

- Refer the person to a specialist pain service and/or a condition-specific service, and
- Consider offering oral tramadol as third-line treatment instead of or in combination with the second-line treatment while waiting for referral

For tramadol as monotherapy, start at 50–100 mg/day, with upward titration if required to an effective dose or the person's maximum tolerated dose of no higher than 400 mg/day. If tramadol is used as combination therapy, more conservative titration may be required

Pregabalin or Amitriptyline

Diabetic PN: Duloxetine

Switch or combine

Refer to pain specialist and offer Tramadol while waiting

No opioids without pain specialist

Currently available drugs are not enough

Despite the advances in the area, still there is a gap in our ability to treat neuropathic pain. With respect to old drugs such as carbamazepine and amitriptyline, the new drugs seem to be conceived for being more tolerable than for being more efficacious.

A considerable number of patients do not get a sufficient pain relief. In real life a sufficient pain relief should probably be the one that allows the patient to have a decent quality of life. In evidence-based studies on pain it is customary to consider "responders" to treatment those patients that report a pain relief greater than 50%.

On that basis, the evidence tells us that in painful neuropathies, regardless of type of pharmacological treatment, we are only able to succeed in 30-40% of the patients. Hence it is natural to try combination therapy and we all do it in clinical practice.

Combination Therapy

Unfortunately there are too few controlled studies. Three class I studies found a superiority of gabapentin-opioids (morphine, oxycodone) and gabapentin-nortriptyline compared to each drug alone in patients with diabetic PN or PHN, while a small study suggested superiority of gabapentin-venlafaxine compared with gabapentin and placebo.

Hence we must rely on good sense. Combination therapy should preferably use drugs with complementary mechanisms. The synergistic actions of opioids with antidepressants, and these with gabapentin/pregabalin, and these with opioids are not only logical but also encouraged by results from pre-clinical studies.

We are aware of in-progress studies assessing pregabalin-oxycodone and pregabalin-duloxetine.

Conclusions

Four drug classes have strong evidence of being effective in painful neuropathy: opioids, TCA, gabapentin/pregabalin, and SNRI (in order of efficacy on pain). In choosing the individual treatment, however, many other considerations should be taken into account, including the cardiac risk with TCA in the older patients and the risk of tolerance/addiction in the long-term treatment with strong opioids.

Only 30-40% of patients are satisfactorily treated with monotherapy, but we lack controlled trials with polytherapy. The great majority of the available literature is dedicated to diabetic neuropathy and postherpetic neuralgia.

Because treatment choice depends more on pain pathophysiology than etiology, it is probably better to rely on well-established compounds rather than on sparse reports in specific neuropathies.

European Journal of Neurology 2007, 14: 952-970 doi:10.1111/j.1468-1331.2007.01916.x

CME ARTICLE

EFNS guidelines on neurostimulation therapy for neuropathic pain

G. Cruccu[a,b], T. Z. Aziz[c], L. Garcia-Larrea[a,d], P. Hansson[a,e], T. S. Jensen[a,f], J.-P. Lefaucheur[g], B. A. Simpson[h] and R. S. Taylor[i]

[a]EFNS Panel on Neuropathic Pain, Vienna, Austria; [b]Department of Neurological Sciences, La Sapienza University, Roma, Italy; [c]Oxford Functional Neurosurgery, Department of Neurosurgery, Radcliffe Infirmary, Oxford, UK; [d]INSERM 'Central integration of pain' (U879) Bron, University Lyon 1, France; [e]Department of Neurosurgery, Pain Center, Karolinska University Hospital and Pain Section, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [f]Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark; [g]Department of Physiology, Henri Mondor Hospital, AP-HP, Créteil, France; [h]Department of Neurosurgery, University Hospital of Wales, Heath Park, Cardiff, UK; and [i]Peninsula Medical School, Universities of Exeter & Plymouth, UK

rTMS: repetitive Transcranial Magnetic Stimulation

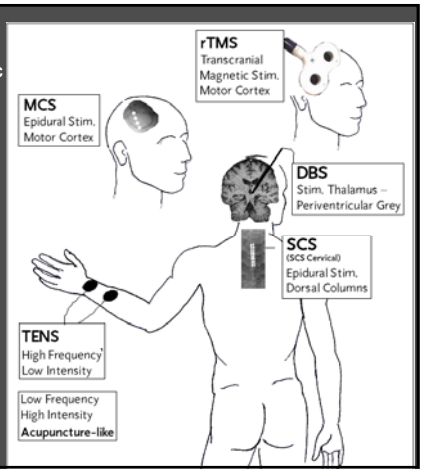
MCS: Motor Cortex Stimulation

DBS: Deep Brain Stimulation

SCS: Spinal Cord Stimulation

TENS: Transcutaneous Electrical Nerve Stimulation

Acupuncture-like (or Electro-acupuncture)

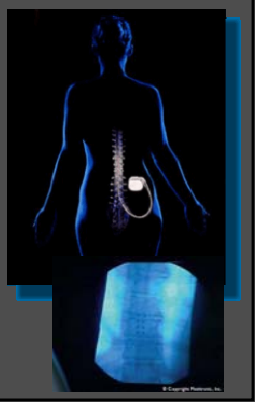


Peripheral Stimulations
(TENS/E-Acupuncture/PNS/NRS)

Recommendations. We cannot draw any conclusion for PNS and NRS. Even for TENS it is difficult to come to conclusive recommendations. The total number of patients with ascertained neuropathic pain was only some 200, with diseases, comparators, and results varying considerably from study to study. Stimulation parameters also vary considerably between the studies, using different pulse waveforms and a wide range of frequencies, not to mention number and duration of the sessions. In conclusion, standard high-frequency TENS is possibly better than placebo (Level C) though probably worse than acupuncture-like or any other kind of electrical stimulation (Level B).

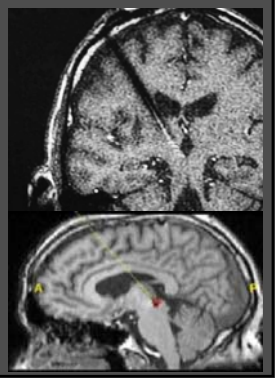
Spinal Cord Stimulation (SCS)

Recommendations. We found Level B evidence for the effectiveness of SCS in FBSS and CRPS I. After completion of a recent Class-I study the level would be A for FBSS. The available evidence is also positive for CRPS II, peripheral nerve injury, diabetic neuropathy, PHN, brachial plexus lesion, amputation (stump and phantom pains), and partial spinal cord injury, but still requires confirmatory comparative trials before the use of SCS can be unreservedly recommended in these conditions.



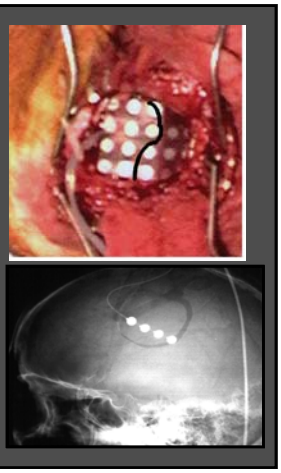
Deep Brain Stimulation (DBS)

Recommendations. For the use of DBS there is weak positive evidence in peripheral neuropathic pain including pain after amputation and facial pain (expert opinion requiring confirmatory trials). In Post-stroke pain, DBS results are equivocal and require further comparative trials.



Motor Cortex Stimulation (MCS)

Recommendations. There is Level C evidence (two convincing Class III studies, 15-20 convergent Class IV series) that MCS is useful in 50-60% of patients with Post-stroke pain and central or peripheral facial neuropathic pain, with small risk of medical complications. The evidence about any other condition remains insufficient.



repetitive Transcranial Magnetic Stimulation (rTMS)

Recommendations. There is moderate evidence that rTMS of the motor cortex, using a figure-of-eight coil and high frequency (5-20 Hz) induces significant pain relief in Post-stroke pain and several other neuropathic pain conditions (Level B). Because the effect, however, is modest and short-lasting, rTMS should not be used as the sole treatment in chronic neuropathic pain. It may be proposed for short-lasting pains or to identify suitable candidates for an epidural implant (MCS). In contrast, in the same pain conditions, low-frequency rTMS is probably ineffective (Level B).

Summary Results

Level A evidence	FBSS	SCS
Level B evidence	Painful neuropathy	Acupuncture-like and rTMS
	CRPS type I	SCS
	Post-Stroke Pain	rTMS
Level C evidence	Post-Stroke Pain	MCS
	Facial Pain	MCS
Expert Opinion on possible efficacy of SCS	CRPS II, peripheral nerve injury, diabetic neuropathy, PHN, brachial plexus lesion, stump and phantom pains, partial spinal cord injury	

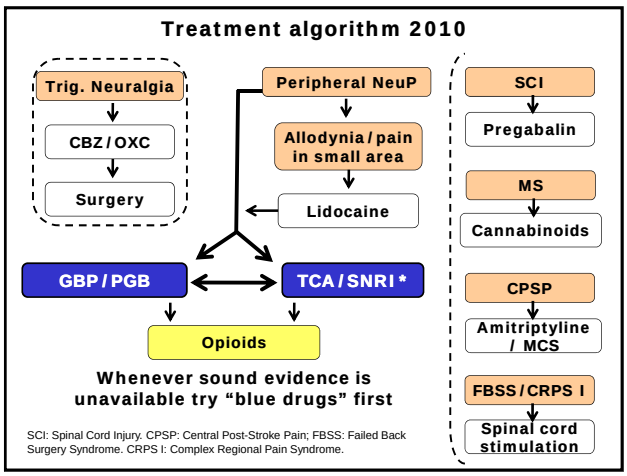
Conclusions

TENS and r-TMS are non-invasive and can be used as preliminary or add-on therapy.

Further controlled trials are warranted for SCS in conditions other than FBSS and CRPS, and for MCS and DBS in general.

In contrast with what one may be afraid of, neurostimulation procedures are quite safe.

Using these chronically implanted techniques, pain is satisfactorily relieved in many patients, including those who were impossible to treat effectively with drugs or by other means.



Main References

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