Treatment of Peripheral Nerve-Muscular Disorders

2015 대한신경과학회 전문의 평생교육
성균관의대 강북삼성병원
신경과 서범천

Treatment of

- OPD based NM disorders
  - Bell's palsy
  - Carpal tunnel syndrome
  - Diabetic polyneuropathy
- IPD based NM disorders
  - IVIg
- Guideline Review

Facial Expression…

The human being's facial expression fascinates me, because it serves the most basic and bestial pleasure and participates in the strongest and most gentle emotion of spirit

Charles Bell
in Essays on the anatomy of expression in painting, 1806

MEMO

Bell's Palsy

- First described in 1797
  - By Nicolaus Friedreich
  - Named after Sir Charles Bell
- Definition
  - "Acute unilateral facial nerve paresis or paralysis with onset in less than 72 hours and without an identifiable cause"

Bell's Palsy

- Idiopathic peripheral facial nerve palsy
- Incidence 15-30/100,000
  - 10% recurrent, mean latency of 10 years
  - Pregnant women: 43/100,000
- At any age (15-45), F≥M
- Complete recovery
  - 70% within 3 months
- Synkinesis
  - Begins 3-4 months. Continue for up to 2 years
  - 9-55% of patients with incomplete recovery

Bell's Palsy

- Diagnosis of exclusion
- Facial nerve inflammation & edema
  - Facial nerve travels in a narrow canal within the temporal bone
  - Swelling may lead to nerve compression and result in temporary or permanent nerve damage

MEMO

Bell's Palsy - Etiology

- Unknown
- Viral hypothesis
  - Neurotrophic viruses: HSV-1, HSV-2, VZV
  - 1972, Mc Cormick hypothesized HSV
  - 1992, detection of latent HSV in geniculate ganglia by PCR
  - 1996, HSV-1 DNA detection in endoneurial fluids of facial nerve during decompression
- Against viral hypothesis
  - Latent in sensory ganglia, not in motor neuron
  - In majority, Bell's palsy is not recurrent

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Evidence-based guideline update: Steroids and antivirals for Bell palsy

Report of the Guideline Development Subcommittee of the American Academy of Neurology

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ABSTRACT

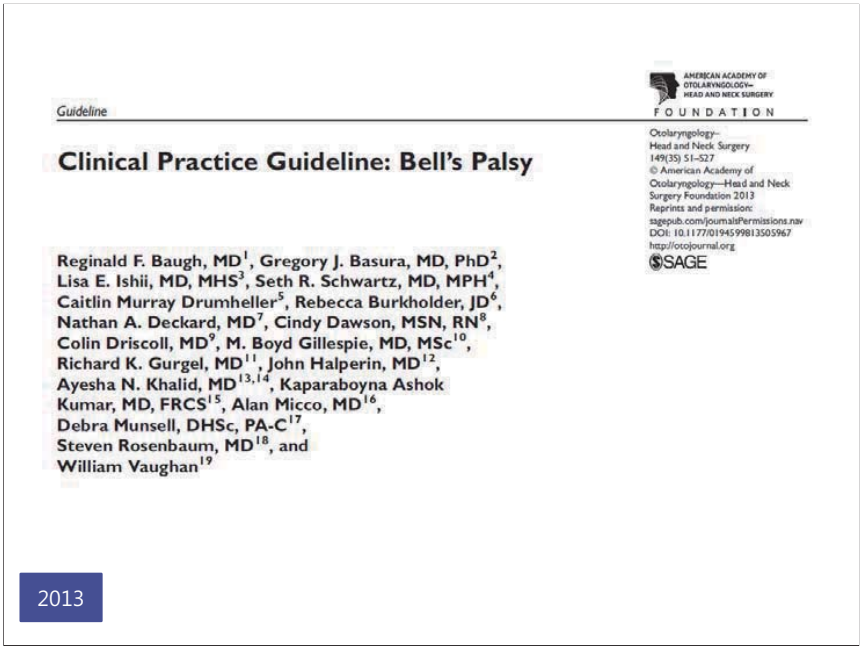
Objective: To review evidence published since the 2001 American Academy of Neurology (AAN) practice parameter regarding the effectiveness, safety, and tolerability of steroids and antiviral agents for Bell palsy.

Methods: We searched Medline and the Cochrane Database of Controlled Clinical Trials for studies published since January 2000 that compared facial functional outcomes in patients with Bell palsy receiving steroids/antivirals with patients not receiving these medications. We graded each study (Class I–IV) using the AAN therapeutic classification of evidence scheme. We compared the proportion of patients recovering facial function in the treated group with the proportion of patients recovering facial function in the control group.

Results: Nine studies published since June 2000 on patients with Bell palsy receiving steroids/antiviral agents were identified. Two of these studies were rated Class I because of high methodologic quality.

Conclusions and Recommendations: For patients with new-onset Bell palsy, steroids are highly likely to be effective and should be offered to increase the probability of recovery of facial nerve function (2 Class I studies, Level A) (risk difference 12.8%–15%). For patients with new-onset Bell palsy, antiviral agents in combination with steroids do not increase the probability of facial functional recovery by >7%. Because of the possibility of a modest increase in recovery, patients might be offered antivirals (in addition to steroids) (Level C). Patients offered antivirals should be counseled that a benefit from antivirals has not been established, and, if there is a benefit, it is likely that it is modest at best. *Neurology*® 2012;79:2209–2213

2012



Guideline

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Clinical Practice Guideline: Bell's Palsy

Otolaryngology–Head and Neck Surgery
149(3S) S1–S27
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2013

MEMO

VIEWS & REVIEWS

Reconciling the clinical practice guidelines on Bell palsy from the AAO-HNSF and the AAN

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Thomas S.D. Getchius
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ABSTRACT

Bell palsy, named after the Scottish anatomist Sir Charles Bell, is the most common acute mononeuropathy, or disorder affecting a single nerve, and is the most common diagnosis associated with facial nerve weakness/paralysis. In the past 2 years, both the American Academy of Neurology and the Academy of Otolaryngology–Head and Neck Surgery Foundation have published clinical practice guidelines aimed at improving the quality of care and outcomes for patients diagnosed with Bell palsy. This commentary aims to address the similarities and differences in the scope and final recommendations made by each guideline development group. *Neurology*® 2014;82:1927–1929

GLOSSARY

AAN = American Academy of Neurology; **AAO-HNSF** = American Academy of Otolaryngology–Head and Neck Surgery Foundation; **CPG** = clinical practice guideline; **KAS** = key action statements; **RCT** = randomized controlled trials.

The clinical practice guideline (CPG) on Bell palsy, recently produced by the American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF),[1] follows closely on the heels of the guideline on Bell palsy published by the American Academy of Neurology (AAN).[2] In an effort to provide harmonization between these 2 guidelines for the end users, authors and staff from both CPGs have worked together to develop this commentary for publication in both *Neurology*® and *Otolaryngology—Head and Neck Surgery*. Both CPGs were developed to improve patient care and reduce variations in practice. This commentary compares and contrasts the 2 CPGs.

2014

Table 1 Oral steroid and antiviral therapy recommendations

Topic	AAN recommendation	AAO-HNSF recommendation
Oral steroids	For patients with new-onset Bell palsy, oral steroids should be offered to increase the probability of recovery of facial nerve function	Clinicians should prescribe oral steroids within 72 hours of symptom onset for patients with Bell palsy 16 years and older
Antiviral therapy	For patients with new-onset Bell palsy, antivirals (in addition to steroids) might be offered to increase the probability of recovery of facial function	Clinicians may offer oral antiviral therapy in addition to oral steroids within 72 hours of symptom onset for patients with Bell palsy

Abbreviations: AAN = American Academy of Neurology; AAO-HNSF = American Academy of Otolaryngology–Head and Neck Surgery Foundation.

Table 2 Comparison of AAO-HNSF and AAN Bell palsy guidelines

	AAO-HNSF	AAN
Content		
Recommends steroids	Yes	Yes
Recommends against antivirals alone	Yes	Yes
Option for combined therapy	Yes	Yes
Recommends history and physical examination to rule out other causes	Yes	NR
Recommends against routine laboratory testing and routine imaging	Yes	NR
Recommends eye care if impaired eye closure	Yes	NR
Recommends follow-up if incomplete resolution	Yes	NR
Methods		
Group composition	Multidisciplinary	Single specialty
Systematic review	Yes	Yes
Harm benefit assessment	Yes	Yes

Abbreviations: AAN = American Academy of Neurology; AAO-HNSF = American Academy of Otolaryngology–Head and Neck Surgery Foundation; NR = no recommendation for or against (beyond the scope of the clinical practice guideline); Yes = addressed in the clinical practice guideline.

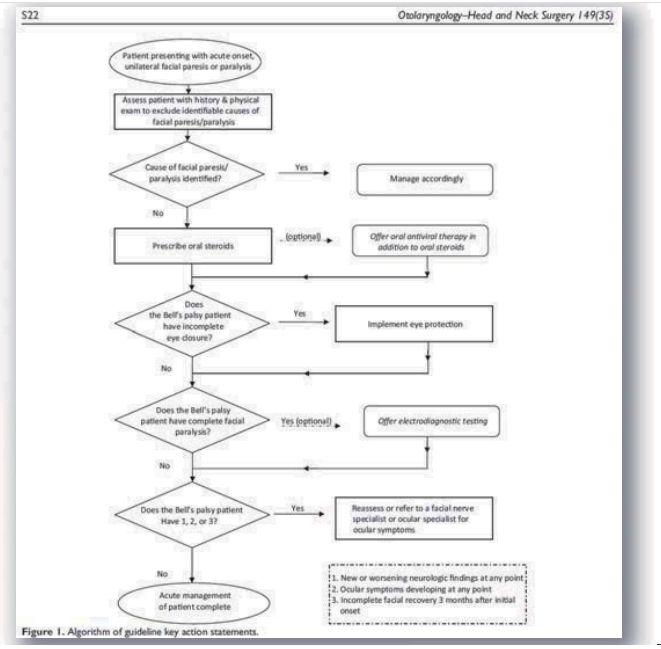
2014

Table 6. Summary of guideline action statements.

Statement	Action	Strength
1. Patient history and physical examination	Clinicians should assess the patient using history and physical examination to exclude identifiable causes of facial paresis or paralysis in patients presenting with acute-onset unilateral facial paresis or paralysis.	Strong recommendation
2. Laboratory testing	Clinicians should not obtain routine laboratory testing in patients with new-onset Bell's palsy.	Recommendation (against)
3. Diagnostic imaging	Clinicians should not routinely perform diagnostic imaging for patients with new-onset Bell's palsy.	Recommendation (against)
4. Oral steroids	Clinicians should prescribe oral steroids within 72 hours of symptom onset for Bell's palsy patients 16 years and older.	Strong recommendation
5A. Antiviral monotherapy	Clinicians should not prescribe oral antiviral therapy alone for patients with new-onset Bell's palsy.	Strong recommendation (against)
5B. Combination antiviral therapy	Clinicians may offer oral antiviral therapy in addition to oral steroids within 72 hours of symptom onset for patients with Bell's palsy.	Option
6. Eye care	Clinicians should implement eye protection for Bell's palsy patients with impaired eye closure.	Strong recommendation
7A. Electrodiagnostic testing with incomplete paralysis	Clinicians should not perform electrodiagnostic testing in Bell's palsy patients with incomplete facial paralysis.	Recommendation (against)
7B. Electrodiagnostic testing with complete paralysis	Clinicians may offer electrodiagnostic testing to Bell's palsy patients with complete facial paralysis.	Option
8. Surgical decompression	No recommendation can be made regarding surgical decompression for Bell's palsy patients.	No recommendation
9. Acupuncture	No recommendation can be made regarding the effect of acupuncture in Bell's palsy patients.	No recommendation
10. Physical therapy	No recommendation can be made regarding the effect of physical therapy in Bell's palsy patients.	No recommendation
11. Patient follow-up	Clinicians should reassess or refer to a facial nerve specialist those Bell's palsy patients with (1) new or worsening neurologic findings at any point, (2) ocular symptoms developing at any point, or (3) incomplete facial recovery 3 months after initial symptom onset.	Recommendation

2013

MEMO



2013

Carpal Tunnel Syndrome (CTS)

ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation
Journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2014;95:2253-63

ORIGINAL ARTICLE

Carpal Tunnel Syndrome: Hand Surgeons, Hand Therapists, and Physical Medicine and Rehabilitation Physicians Agree on a Multidisciplinary Treatment Guideline—Results From the European HANDGUIDE Study

Bionka M. Huisstede, PhD,[a,b] Jan Fridén, MD, PhD,[c,d] J. Henk Coert, MD, PhD,[e] Peter Hoogvliet, MD, PhD,[a,f] the European HANDGUIDE Group

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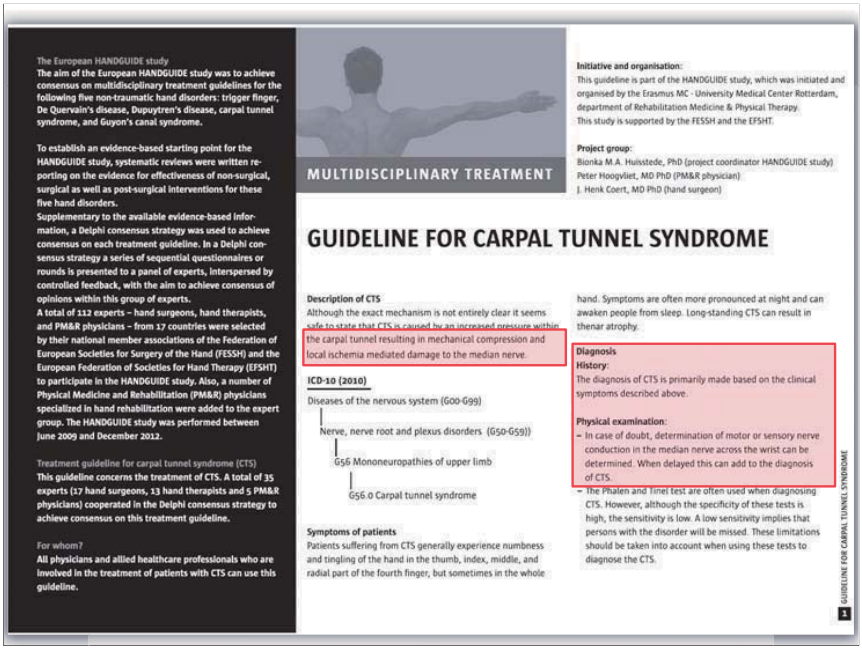


The European HANDGUIDE study
The aim of the European HANDGUIDE study was to achieve consensus on multidisciplinary treatment guidelines for the following five non-traumatic hand disorders: trigger finger, De Quervain's disease, Dupuytren's disease, carpal tunnel syndrome, and Guyon's canal syndrome.

To establish an evidence-based starting point for the HANDGUIDE study, systematic reviews were written reporting on the evidence for effectiveness of non-surgical, surgical as well as post-surgical interventions for these five hand disorders.
Supplementary to the available evidence-based information, a Delphi consensus strategy was used to achieve consensus on each treatment guideline. In a Delphi consensus strategy a series of sequential questionnaires or rounds is presented to a panel of experts, interspersed by controlled feedback, with the aim to achieve consensus of opinions within this group of experts.
A total of 112 experts – hand surgeons, hand therapists, and PM&R physicians – from 17 countries were selected by their national member associations of the Federation of European Societies for Surgery of the Hand (FESSH) and the European Federation of Societies for Hand Therapy (EFSHT) to participate in the HANDGUIDE study. Also, a number of Physical Medicine and Rehabilitation (PM&R) physicians specialized in hand rehabilitation were added to the expert group. The HANDGUIDE study was performed between June 2009 and December 2012.

Treatment guideline for carpal tunnel syndrome (CTS)
This guideline concerns the treatment of CTS. A total of 35 experts (17 hand surgeons, 13 hand therapists and 5 PM&R physicians) cooperated in the Delphi consensus strategy to achieve consensus on this treatment guideline.

For whom?
All physicians and allied healthcare professionals who are involved in the treatment of patients with CTS can use this guideline.

MULTIDISCIPLINARY TREATMENT

Initiative and organisation:
This guideline is part of the HANDGUIDE study, which was initiated and organised by the Erasmus MC - University Medical Center Rotterdam, department of Rehabilitation Medicine & Physical Therapy.
This study is supported by the FESSH and the EFSHT.

Project group:
Bionka M.A. Huisstede, PhD (project coordinator HANDGUIDE study)
Peter Hoogvliet, MD PhD (PM&R physician)
J. Henk Coert, MD PhD (hand surgeon)

GUIDELINE FOR CARPAL TUNNEL SYNDROME

Description of CTS
Although the exact mechanism is not entirely clear it seems safe to state that CTS is caused by an increased pressure within the carpal tunnel resulting in mechanical compression and local ischemia mediated damage to the median nerve.

ICD-10 (2010)
Diseases of the nervous system (G00-G99)
Nerve, nerve root and plexus disorders (G50-G59))
G56 Mononeuropathies of upper limb
G56.0 Carpal tunnel syndrome

Symptoms of patients
Patients suffering from CTS generally experience numbness and tingling of the hand in the thumb, index, middle, and radial part of the fourth finger, but sometimes in the whole hand. Symptoms are often more pronounced at night and can awaken people from sleep. Long-standing CTS can result in thenar atrophy.

Diagnosis
History:
The diagnosis of CTS is primarily made based on the clinical symptoms described above.

Physical examination:
- In case of doubt, determination of motor or sensory nerve conduction in the median nerve across the wrist can be determined. When delayed this can add to the diagnosis of CTS.
- The Phalen and Tinel test are often used when diagnosing CTS. However, although the specificity of these tests is high, the sensitivity is low. A low sensitivity implies that persons with the disorder will be missed. These limitations should be taken into account when using these tests to diagnose the CTS.

GUIDELINE FOR CARPAL TUNNEL SYNDROME 1

MEMO

I NON-SURGICAL TREATMENT [1]

1 Instructions for the patient

Aim of instructions: To restrict certain activities, or perform them in an alternative way, and to limit extreme flexion and extension positions of the wrist to decrease mechanical loading of the affected nerve and thereby decrease the symptoms of CTS.

Patients with CTS should **always** be instructed. Instructions should be combined with another form of treatment.

Advice to the patient should include: Information on the nature of CTS as well as advice to limit full extension and flexion of the wrist, to reduce heavy work activities, and to avoid repetitive movements.

2 Splinting

Aim of splinting: To decrease the amount of mechanical load on the affected nerve by immobilizing the tendons and the median nerve in the carpal tunnel, to decrease the symptoms of CTS.

Type of splint: Long-based splint (i.e. incorporating the wrist) with the wrist in neutral position (thereby maximally lowering the pressure in the carpal tunnel), and the fingers free.

Duration of wearing the splint: For 4 to 12 weeks. The splint should be used at night only, or both at night and during the day in case of aggravating activities.

When should a splint be adjusted or stopped? When the patient is free of symptoms, or splinting has insufficient or no effect.

3 Corticosteroid injection

Aim of a corticosteroid injection: To decrease the symptoms of CTS; however, the mechanism behind this reduction has not yet been fully elucidated.[2]

Kind of corticosteroid injections: Intermediate-acting corticosteroid injections such as methylprednisolone or triamcinolone, with or without a local anaesthetic.

Maximum number of injections: 3; an interval of 2-3 months should be considered when more than one corticosteroid injection is used.

Advice after treatment with a corticosteroid injections should concentrate on 2 levels:
1 Post-treatment
- Resting the hand, i.e. no stressful use for 24-48 hours.

2 Possible adverse effects due to the corticosteroid injection
- Pain: the patients may have increased pain for 2-3 days,
- In case of diabetes: there might be an increase in blood sugar level.

When should treatment with corticosteroid injections be stopped? When the patient is free of symptoms, when there is insufficient or no effect, and in case of complications. Complications can be local (e.g. infections and tendon ruptures) or systemic (e.g. hyperglycemia in patients with diabetes mellitus, an allergic reaction, or hypertension).

II SURGICAL TREATMENT

Surgical decompression

Aim of surgery: To reduce the pressure on the median nerve in the carpal tunnel by surgically opening the roof of the carpal tunnel, thereby reducing the symptoms of CTS.

Preferable technique:
- Anaesthesia technique: Local anaesthesia,
- Incision: Longitudinal, not extended,
- Open surgery,
- Sutures: Non-resorbable.

What to do if the effect of carpal tunnel release is insufficient?
1 The diagnosis should be reconsidered,
2 Consider whether the release of the flexor retinaculum was incomplete.

Primary post-operative advice: During this primary post-operative period – i.e. up to 10-15 days after surgery, when the sutures are removed - advice for the patient consists of:
1 Elevation of the hand,
2 Rest the hand, but with gradual movement of the fingers/wrist as tolerated,
3 Avoid heavy loading of the fingers and hand.

Post-surgical interventions

Interventions after surgery can include instructions to the patient, splinting, and exercise therapy.

Post-operative instructions should concentrate on:
1 Scar care,
2 Edema control,
3 Exercise therapy such as tendon and nerve gliding exercises.

Post-surgical splinting can be indicated after surgery to treat CTS, but should not be used routinely. It can, for example, be applied in case of severe post-operative symptoms.

Post-surgical exercise therapy is indicated for those who are afraid to use the hand, for scar care, in case of stiffness and/or edema of the hand, and to promote tendon and nerve gliding.

Treatment combinations for CTS

The following combinations of treatments are applicable in the treatment of CTS:
- Instructions plus splinting (IS),
- Instructions plus corticosteroid injection (IC),
- Instructions plus corticosteroid injection plus splinting (ICS),
- Instructions plus operative treatment/surgery (IO).

[1] Treatment with NSAIDs was considered **not** useful for treating CTS.
[2] Originally, the aim of corticosteroid use was to decrease the amount of inflammation. Although inflammatory changes of the synovial sheath of flexor tendons are present in CTS, this is not the most important cause, and the effects of corticosteroids in CTS are generally temporary. Therefore, the exact mode of action of corticosteroids in CTS remains unclear.

Table Severity and duration of CTS and suitable treatment options

Severity and duration of CTS are the main factors when deciding on the type of treatment. Both severity and duration were divided into five subgroups. For each subgroup of patients the suitable treatment options are indicated below:

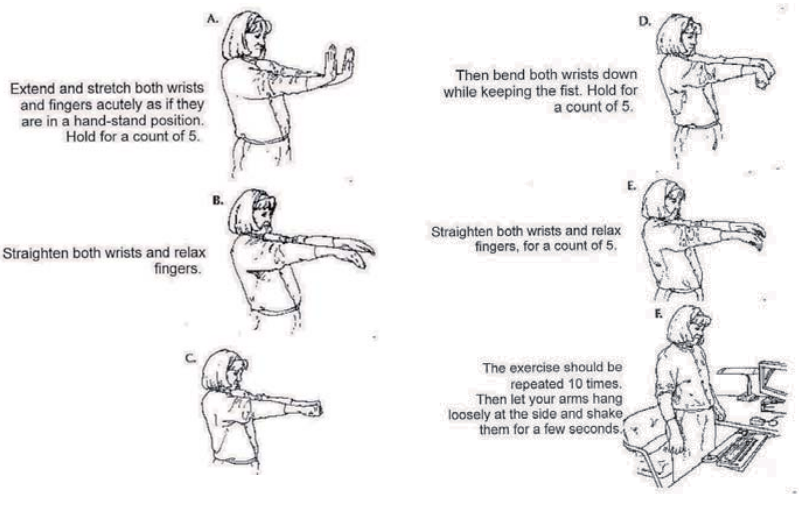
DURATION	1 Very mild symptoms	2 Mild symptoms	3 Moderate symptoms	4 Severe symptoms	5 Very severe symptoms
5 Chronic stage ≥ 6 months	IS	Note 1 and 2	IO	IO	IO
4 Chronic stage 3 ≤ 6 months	IS	IC, ICS	ICS, IO	ICS, IO	IO
3 Subacute stage 2 ≤ 3 months	IS	IS, IC, ICS	IS, IC, ICS, IO	IC, ICS, IO	IO
2 Subacute stage (1 ≤ 2 months)	IS	IS, IC, ICS	IS, IC, ICS	IC, ICS	Note 1 and 3
1 Acute stage (≤ 1 month)	IS	IS	IS	IS	Note 1 and 4
	Very mild symptoms [A]				Continuous very severe symptoms [B]
	SEVERITY				

IS: Instructions plus splinting;
IC: Instructions plus corticosteroid injection;
ICS: Instructions plus corticosteroid injection plus splinting;
IO: Instructions plus operative treatment/surgery.

A Very mild symptoms (mostly only during night-time) of pins and needles, pain, no thenar atrophy and/or sensibility loss in the fingers and/or the hand
B Continuous very severe symptoms of pins and needles, pain, significant thenar atrophy and/or significant sensibility loss in the fingers and/or the hand

Notes
1 No consensus was achieved by the experts on the treatment option(s) for this cell.
2 ≥50% of the experts (i.e. 50%) indicated that 'ICS' should be included in this cell.
3 ≥50% of the experts (i.e. 50%) indicated that 'IO' should be included in this cell.
4 ≥50% of the experts indicated (i.e. 55%) that 'IS' should be included in this cell.

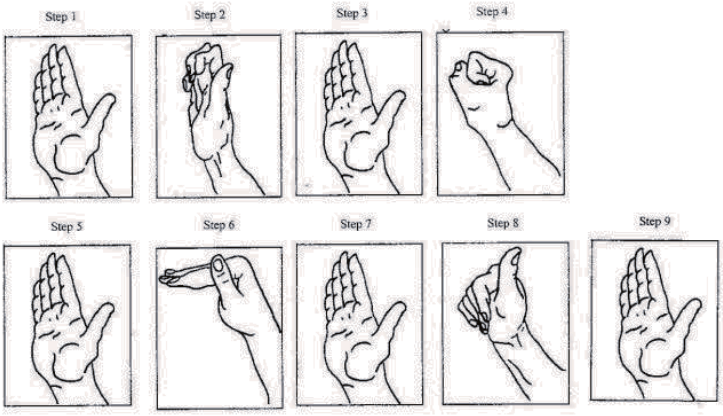
CTS Exercise: Preventive/Mild CTS



MEMO

CTS – Tendon Glide Exercise

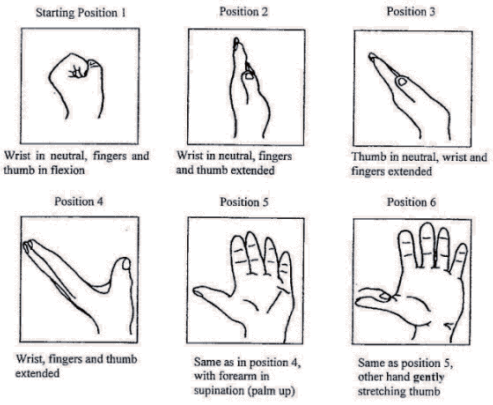
It is very important to follow the sequence outlined below.Do 5 "cycles" 3 or 4 times each day



CTS – Nerve Glide Exercise

When doing these nerve gliding exercises, move directly through the positions 1-6, performing 5 "cycles" 3-4 times each day.

DO NOT PUT TOO MUCH PRESSURE OR STRESS ON YOUR THUMB IN STEP 6!



Recurrent CTS

- Complication & Failure of CTS Op
  - 3-25%
    - 48/2357 (2%) required 2nd surgery
  - Revision surgery: disappointing (up to 40%)
  - Persistent symptoms
  - Recurrent CTS
    - Initial relief
    - About 6 months interval
  - New symptoms

MEMO

Recurrent CTS

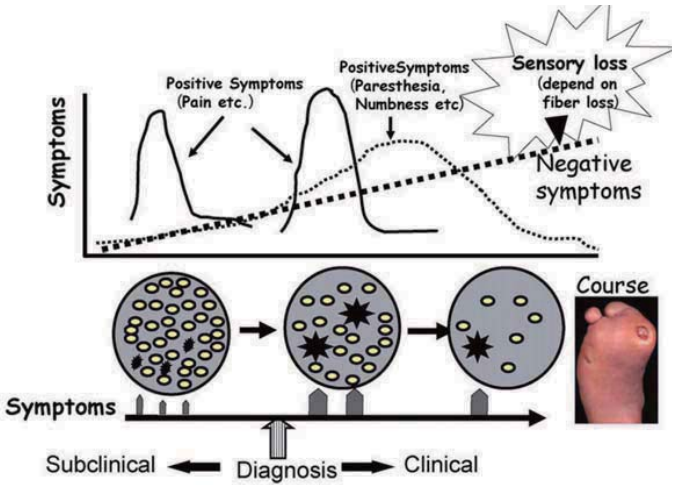
Table 1
Recurrent carpal tunnel syndrome causes and treatments

Symptoms	Potential Causes	Treatment Options
Persistent	Incomplete release of the TLC	• Revision CTR
Recurrent	Circumferential fibrosis Reconstitution of the TLC	• Revision CTR • Neurolysis • Interposition graft ◦ Synovial flap ◦ Muscle flap ◦ Hypothenar fat pad flap ◦ Vein wrap
New	Nerve injury	• Neurolysis • Nerve repair • Interposition graft

Abbreviations: CTR, carpal tunnel release; TLC, transverse carpal ligament.

Hand Clin 29 (2013) 427–434

Diabetic Polyneuropathy (DPN)



Yagihashi S, et al. Diab Res Clin Pract (2007)

Diagnosis of DPN

- Toronto (Canada) joint meeting at 2009
  - Diabetic Neuropathy Study Group of EURODIAB (European Association for the Study of Diabetes)
  - International Symposium

Table 1. Defining criteria for diabetic polyneuropathy according to The Toronto Expert Panel on Diabetic Neuropathy [5••]

Classification	Characteristics
Possible clinical DN	Symptoms or signs of DN. Symptoms can be positive (pain) or negative (loss of sensation) in the feet. Signs can include symmetrical decreased sensory loss in the feet or decreased or absent ankle reflexes.
Probable clinical DN	A combination of symptoms and signs of DN, as described above, with any two or more of the following: neuropathic symptoms, decreased sensation, or decreased or absent ankle reflexes.
Confirmed clinical DN	An abnormal nerve conduction study and a symptom or sign of DN, as described above.
Subclinical DN (stage 1a)	An abnormal nerve conduction study with no signs or symptoms of DN.

DN, diabetic polyneuropathy.

MEMO

Prediabetes
– IFG, IGT, high-risk HbA1C

- IGT
  - 40~50% of otherwise idiopathic neuropathy
- MONICA/KORA study
  - 195 diabetics, 198 control (IGT 23.2%, IFG 36%)
  - Neuropathic pain:
    - 13.3% in DM, 8.7% in IGT, 4.2% in IFG, 1.2% in normal subject

Table 1. Diagnostic criteria for diabetes and pre-diabetes.

Diagnosis	Fasting plasma glucose	2-hour OGTT	Hemoglobin A1C
Normal	<100 mg/dl (5.6 mmol/l)	<140 mg/dl (7.8 mmol/l)	<5.7%
Pre-diabetes	100–125 mg/dl (5.6–6.9 mmol/l)	140–199 mg/dl (7.8–11.0 mmol/l)	5.7–6.4%
Diabetes	≥126 mg/dl (7.0 mmol/l)	≥200 mg/dl (11.1 mmol/l)	≥6.5%

Prediabetes Associated Neuropathy
- Neuropathic Pain

- Similar to small fiber neuropathy
- Burning or tingling foot pain
- Potentially reversible
  - *Lifestyle intervention* improves metabolic parameters
  - Resulting in recovery of small fiber function

DPN - Guiedelines

Table 1
International guidelines: treatment of painful diabetic peripheral neuropathy.

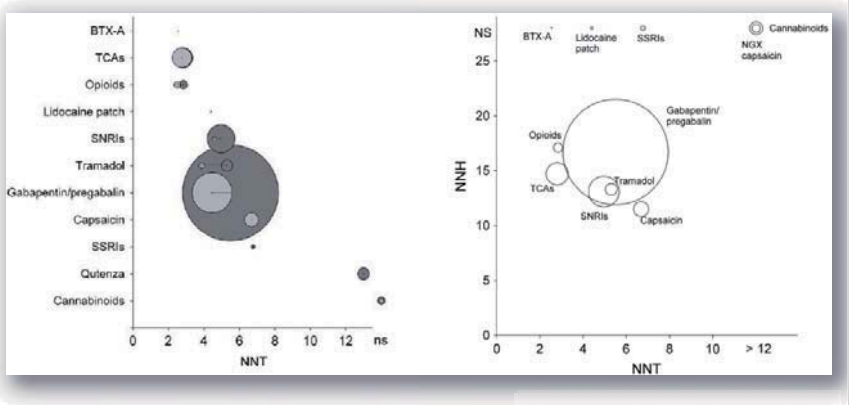
Recommendation: 1 = first choice, 2 = second choice, 3 = third choice
NR = not recommended; – = not mentioned

	AACE (Handelsman et al., 2011) 2011	AAN (Bril et al., 2011) 2011	EFNS (Attal et al., 2010) 2010	NICE (National Institute for Health & Clinical Excellence) 2013	Toronto Consensus 2010 (Tesfaye et al., 2011)
Tricyclic antidepressants	1	2	1	1–2	1
Duloxetine	1	2	1	1–2	1
Venlafaxine	–	2	1	–	–
Valproate	–	2	NR	–	–
Gabapentin	1	2	1	1–2	1
Pregabalin	1	1	1	1–2	1
Carbamazepine	–	–	NR	–	–
Tramadol	2	2	2–3	3	2
Opioids	2	2	2–3	–	2
Caps-aicin ≤0.1%	2	2	NR	3	–
Lidocaine 5%	2	3	–	–	–

AACE, American Association of Clinical Endocrinologists; AAN, American Academy of Neurology; EFNS, European Federation of Neurological Societies; NICE, National Institute for Health and Clinical Excellence (UK).

The best treatment is
Only slightly better than the worst!

MEMO



Finnerup NB et al(Pain, 2010)

Diabetic Polyneuropathy (DPN)

Characterization of effect of treatment on patient characteristics.

	Duloxetine	Pregabalin	TCAs	Opioids
Depression	⇧		⇧	⇔
Obesity	⇔	⇩	⇩	⇔
Generalized anxiety disorder	⇧	⇧		
Sleep disturbances	⇧	⇧	⇧	⇧
Coronary heart disease	⇔	⇔	⇩	⇔
Autonomic neuropathy		*	⇩	⇩
Fasting glucose	⇩	⇔	⇩	⇔
Hepatic failure	⇩	⇔	◊	◊
Renal failure	⇩	Adapt dose	◊	◊
Drug interactions	⇩	⇧	⇩	⇔
Elderly	⇔	⇔	⇩	⇩

Effect: ⇧, favorable; ⇩, unfavorable; ⇔◊, depends on specific agent.
Table adapted from Ziegler D. *Curr Diabet Rev.* 2011;7:208-220.
* Improvement in heart rate variability in one study.

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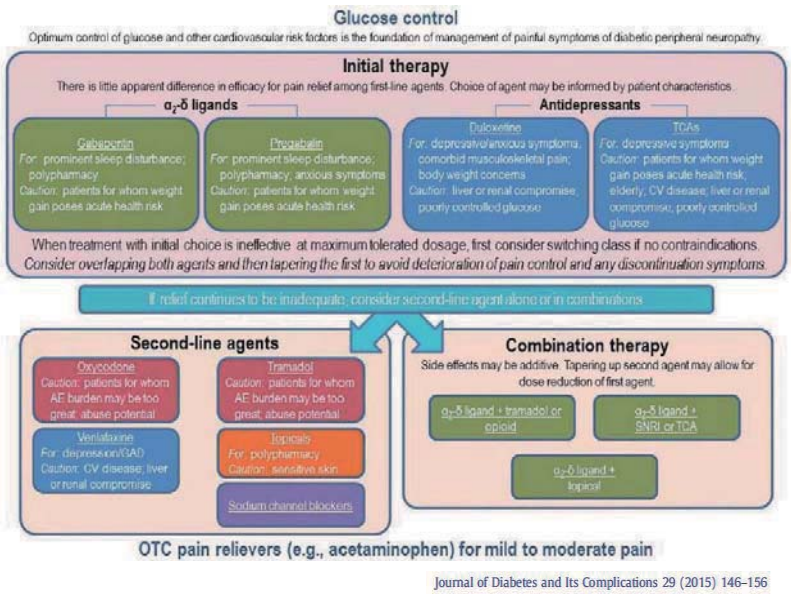

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MEMO

Intravenous Immunoglobulin (IVIg)

- Immuno-modulation rather than Immuno-suppression
- Not selective immunotherapy
  - Rapid onset
  - Therapeutic effect is not maintained
  - Not newly developed emerging treatment modalities
    - But still evolving treatment
    - And still expensive

IVIg

- Blood products administered intravenously
- Pooled, polyvalent IgG
- First used in 1952 to treat immunoglobulin deficiencies (like IgG deficiency)
- Since 1960s, some reports of IVIG
- 1981. ITP: Immediate increase of platelets
- For
  - Immune deficiencies: hypogammaglobulinemia
  - Autoimmune disease
  - Acute infection

IVIg

- IgG from 3,000~60,000 blood donors
- Mainly IgG
  - IgG1, IgG2 > IgG3, IgG4
- Half life : 21~33 days
- Purity : 97~100%
- Products differ in pH, IgA content, half life, osmolality, type of sugar, sodium content, viral reduction inactivation

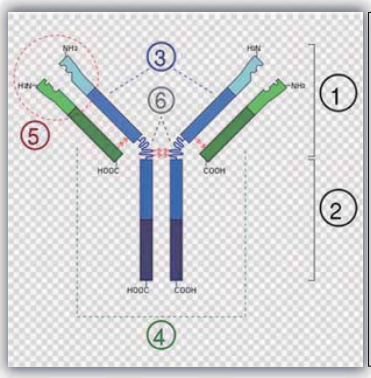
MEMO

IVIg

- Effective & Relatively Safe
  - Pregnancy
- Less side effect (<10%)
  - Headache. Aseptic meningitis
  - Thromboembolic event
  - Skin reaction
  - Renal tubular necrosis
  - Severe anaphylactic reaction (IgA def. 1/3000)
    - But testing for IgA Ab in impractical/unnecessary
- Intravenous, No oral preparation
- Expensive : $10,000 USD per 2g/kg

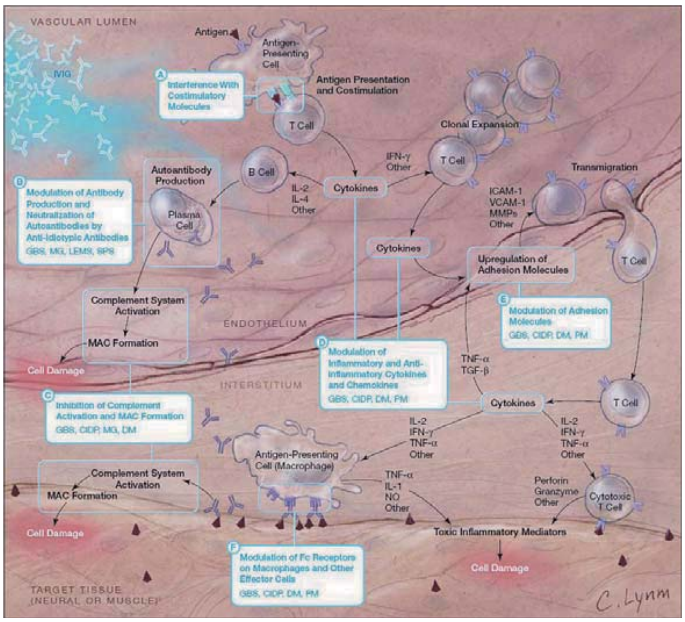
IVIg – Mode of Action

Remains Unclear



1. Fab (Ag binding fragment)
2. Fc (Crystallizable fragment)
3. heavy chain (consist of VH, CH1, hinge, CH2 and CH3 regions: from N-term)
4. light chain (consist of VL and CL regions: from N-term)
5. antigen binding site
6. hinge regions

(*) -S-S- mean disulfide bonds.



2004 JAMA

MEMO

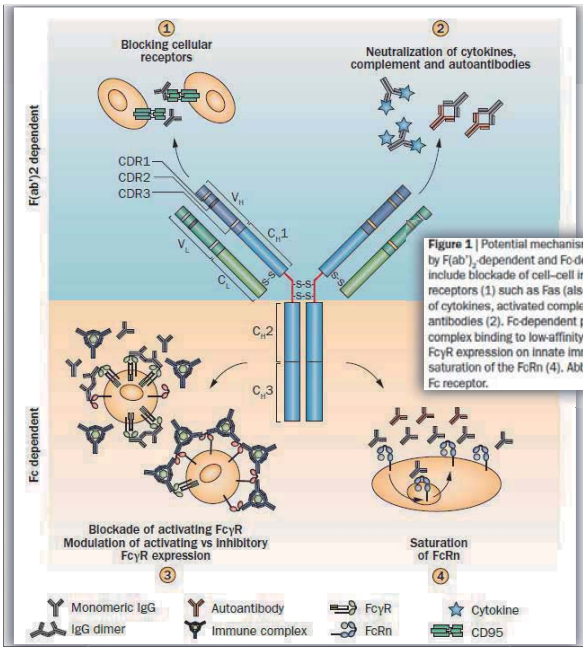


Figure 1 | Potential mechanisms of intravenous immunoglobulin activity mediated by $F(ab')_2$-dependent and Fc-dependent pathways. $F(ab')_2$-dependent mechanisms include blockade of cell–cell interactions that are mediated by cell-surface receptors (1) such as Fas (also called CD95) and Fas ligand, and neutralization of cytokines, activated complement proteins and autoantibodies by anti-idiotypic antibodies (2). Fc-dependent pathways include competitive blockade of immune complex binding to low-affinity FcγRs, and modulation of activating and inhibitory FcγR expression on innate immune effector cells and B cells (3), as well as saturation of the FcRn (4). Abbreviations: FcγR, Fcγ receptor; FcRn, neonatal Fc receptor.

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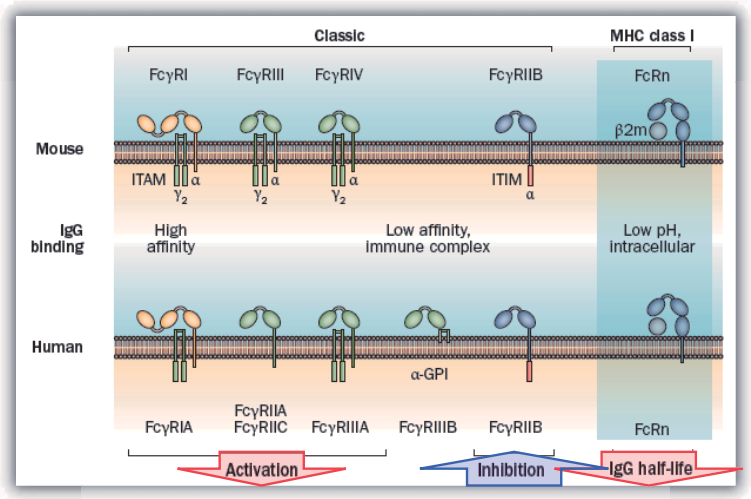

Family of Fc Receptors for IgG

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IVIg
- Evidence from Controlled Trials

- GBS
  - Comparable with plasmapheresis
  - Combining IVIg + plasmapheresis or steroid
    - No incremental response
  - MFS, acute dysautonomia
    - IVIg seems to be helpful (no controlled study)
  - Childhood
    - Treatment of choice (but no controlled study)
    - Mechanical ventilation: Plasmapheresis more helpful
  - Second IVIg when inadequate or absent effect
    - Unclear
    - 3 weeks after first infusion
    - Controlled study in progress

MEMO

IVIg
- Evidence from Controlled Trials

- CIDP
  - Steroids, plasmapheresis, IVIg
    - Short term: equally effective
    - ICE trial: long term effect proved
  - At least 2 infusion required
    - Effectiveness decision
    - Only became effective after 6 weeks
  - Maintenance IVIg therapy
    - 1g/kg every 4-6 weeks
    - Up to 20%, became chronically stable or inactive
      - Should be periodically challenged by skipping

IVIg
- Evidence from Controlled Trials

- Multifocal Motor Neuropathy
  - Respond only to IVIg
  - Reinfusion required at predictable interval
    - Improvement lasts from 3-6 weeks
    - Starts 2g/kg, maintenance 1g/kg monthly
- Other Neuropathies
  - Anti-MAG: unsuccessful
  - Anecdotal favorable evidence to
    - Diabetic amyotrophy, vasculitic neuropathy, paraneoplastic neuropathies, paraproteinemic neuropathy, painful sensory neuropathies with Sjögren sydnrome

IVIg
- Evidence from Controlled Trials

- Myasthenia Gravis
  - Exacerbation, worsening weakness
    - As effective as plasmapheresis
  - At present
    - Justified as an alternative to plasmapheresis
    - Acute exacerbation
    - Prevent or minimize bulbar or respiratory failure
    - Prepare a weak patient for thymectomy
    - May be effective in LEMS
  - Not tested
    - Seronegative MG
    - MuSK MG

MEMO

IVIg
- Evidence from Controlled Trials

- Inflammatory Myopathies
  - Dermatomyositis
    - Effective: weakness, active rash
  - Polymyositis
    - Seems to be effective
    - No controlled trial
- Stiff-person syndrome
  - Decreased stiffness score
  - Increased walking, daily activities

		Steroid	IVIg	TPE (Plasma Exchange)
Muscle	DM	Yes	2nd line. Add on	No
	PM	Yes	(2nd line. Add on)	No
	sIBM	No	No (Only rapid worsening /severe dysphagia)	No
MG	Crisis	Yes	Yes	Yes
	Worsening	Yes	Yes	Yes
	Chronic Tx	Yes	No	NA (not assessed)
	Pregnancy	Yes	Yes (Prefer than steroid)	NA
	MuSK	Yes	NA	Prefer than IVIg
PN	GBS	No (Only add on)	Yes	Yes
	CIDP	Yes	Yes	Yes
MS	Acute	Yes	No Severe gestational relapse	Yes
	Relapse prevention	Add on to Rebif	2nd or 3rd line Pregnancy	NA
Other	MMN	No	Yes	No
	Stiffperson	No	As supplementary Tx	No
	DLRPN	No	Not yet (Some reports)	No
	Post-polio	No	Not yet (Rapid progress)	No

MEMO