Treatment of Peripheral Nerve-Muscular Disorders

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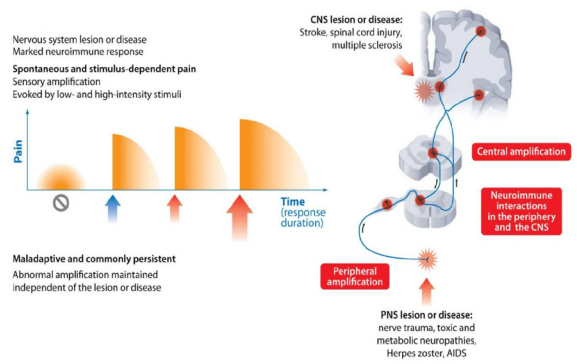
Today's Talks

1. Pharmacological management of neuropathic pain
2. Management of Bell's palsy and Carpal tunnel syndrome
3. Practical use of corticosteroids

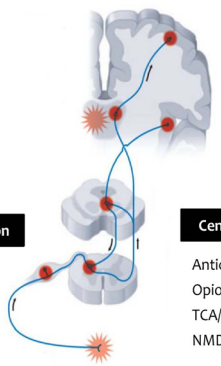
Neuropathic Pain



Symptoms of NeuP

Loss of sensory function		Paradoxical sensory symptom
먹먹하다	plus	저리다
둔하다		찌릿하다
뻣뻣하다		서물거린다
남의 살 같다		화끈거린다
시멘트가 붙은 것 같다		시리다
나무 토막같다		얼얼하다
		칼로 스치게 아프다
		손만 닿아도 아프다

Mechanism of NeuP



Descending modulation

Opioids
TCA/SNRI
Anticonvulsants

Peripheral sensitization

Anticonvulsants
Topical analgesics
Local anesthetics
TCA

Central sensitization

Anticonvulsants
Opioids
TCA/SNRI
NMDA antagonists

IASP Guideline for NeuP

First line medication
- TCAs
- Gabapentin / Pregabalin
- SNRIs
- Lidocaine patch**

** in PHN

Second line medication
- Tramadol
- Opioids

Third line medication
- Other AEDs
- SSRIs
- Capsaicin cream**

EFNS Guideline for NeuP

Etiology	Level A rating	Level C rating	Recommendation for first line
Diabetic NP	Duloxetine Gabapentin/Pregabalin TCA Oxycodone/Tramadol	Carbamazepine Phenytoin	Duloxetine Gabapentin/Pregabalin TCA Venlafaxine ER
PHN	Capsaicin 8% patch Gabapentin/Pregabalin Lidocain plaster TCA		Gabapentin/Pregabalin TCA Lidocaine plaster
TG	Carbamazepine	Baclofen Lamotrigine	Carbamazepine Oxcarbazepine
Central pain	Cannabinnoid (MS) Pregabalin (SCI)		Gabapentin/Pregabalin TCA

AAN Recommendation for DPNP

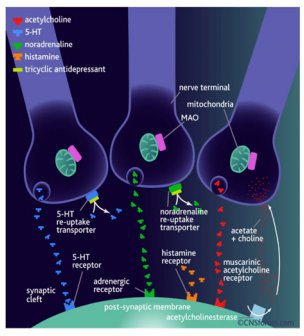
	Recommended drug and dose	Not recommended
Level A	Pregabalin, 300-600 mg/d	
Level B	Gabapentin, 900-3,600 mg/d	Oxcarbazepine
	Sodium valproate, 500-1,200 mg/d	Lamotrigine
	Venlafaxine, 75-225 mg/d	Lacosamide
	Duloxetine, 60-120 mg/d	Clonidine
	Amitriptyline, 25-100 mg/d	Pentoxifylline
	Dextromethorphan, 400 mg/d	Mexiletine
	Morphine sulphate, titrated to 120 mg/d	Magnetic field treatment
	Tramadol, 210 mg/d	Low-intensity laser therapy
	Oxycodone, mean 37 mg/d, max 120 mg/d	Reiki therapy
	Capsaicin, 0.075% QID	
	Isosorbide dinitrate spray	
	Electrical stimulation, percutaneous nerve stimulation ×3-4 weeks	

Mayo Clinic Recommendation for DPNP

Agent type	Reason for recommendation	Agent name
First tier	≥ 2 RCTs in DPN	Duloxetine, Pregabalin, TCAs, Oxycodone CR
Second tier	1 RCT in DPN	Carbamazepine, Gabapentin, Lamotrigine, Tramadol, Venlafaxine ER
Topical	Mechanism of action	Capsaicin, Lidocaine
Others	≥ 1 RCTs in other painful neuropathies	Bupropion, Citalopram, Paroxetine, Topiramate

TCA – Mechanism of Action

- Inhibition 5-HT and NA reuptake
- Block NMDA receptor
- Block sodium channel
- Block α-adrenergic receptors
- Activate opioid receptors



Adverse Effect of TCA

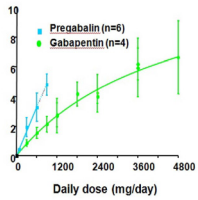
- Blurred vision
- Cognitive changes
- Constipation
- Dry mouth
- Orthostatic hypotension
- Sedation
- Sexual dysfunction
- Tachycardia
- QTc prolongation
- Urinary retention
- Glaucoma

Severe → fewer

- Amitriptyline
- Doxepine
- Imipramine
- Nortriptyline
- Desipramine

Pregabalin vs. Gabapentin

Parameter	Pregabalin	Gabapentin
Bioabailability	>90%, dose independent	60%/300mg, 40%/600mg
Time max	1hr	2~3hr
Titration	A few days	Several weeks
Starting dose	75~150mg/day	100~900mg/day
Maximal dose	600mg/day	3600mg/day



Some Precaution for PGB Use

- Adjustment based on renal function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a]				Dose Regimen
≥60	150	300	450	600	BID or TID
30–60	75	150	225	300	BID or TID
15–30	25–50	75	100–150	150	QD or BID
<15	25	25–50	50–75	75	QD
Supplementary dosage following hemodialysis (mg)[b]					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg					
Patients on the 25–50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg					
Patients on the 50–75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg					
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

- Caution to problematic edema

  Thiazolidinedione antidiabetic agent (Actos®, Avandia ®)

  New York Heart Association (NYHA) Class III or IV cardiac status

Opioids

- **Tramadol**

  induces serotonin release and inhibits NE uptake

  μ-opioid agonist

  Tramadol 50 mg = 60 mg codeine

  = 12.5 mg oral morphine

- **Tapentadol**

  inhibits NE uptake

  μ-opioid agonist

- **Oxycodone + naloxone**

  opioid agonist

  naloxone acts locally on opioid receptors in the gut wall

Topical Agents

Lidocaine patch

Blocking sodium channel

Effective in postherpetic neuralgia

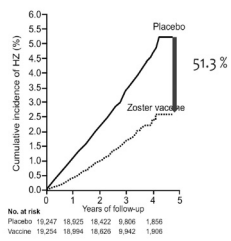
Mechanical barrier decreasing allodynia

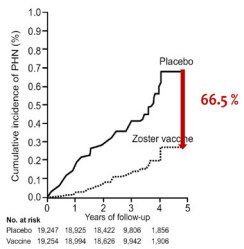
No adjustment for renal or hepatic dysfunction

12 hours on, 12 hours off

Prevention of NeuP?

- Randomized, double-blind, placebo-controlled trial of live-attenuated VZV vaccine (38,546 adults, aged 60 years old or more)





Pharmacotherapeutic Considerations

- **Efficacy**
- **Safety / tolerability**
- **Patient's co-morbidity**
- **Patient's current medications**
- **Ease of use**

  dosing / titration / patient's acceptability

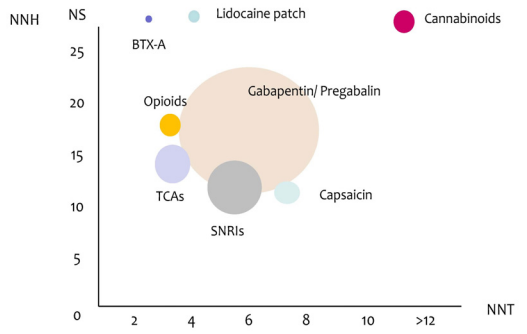
- **Cost**

Efficacy with NNT and NNH

	PPN	PHN	HIV	Central pain	NNH
TCA	11 + (2.1)	4 + (2.8)	2 -	2 + (2.7)	15.9
SNRIs	5 + (5.0)				13.1
Gabapentin	3+/1- (6.4)	2+ (4.3)	1-	1+/1-	32.5
Pregabalin	5 + (4.5)	4+ (4.2)	1-	1+ (3.8)	10.6
Carbamazepine	3 +/2- (3.7)			1-	6.6
Opioid	2 + (2.6)	2 + (2.6)			17.1
Lidocaine		2+ (NA)	1-		NS
Capsaicin	3+/2- (11)	2+ (3.2)	1-		11.5

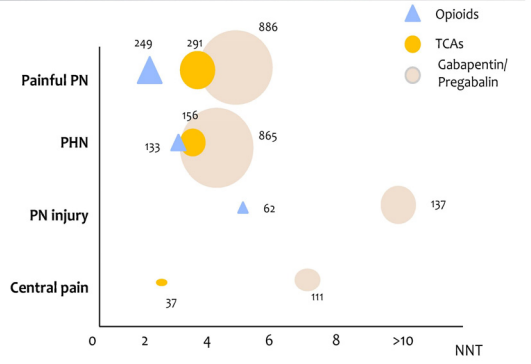
Finenrup NB, et al. Pain (2010)

Overall NNT and NNH



Finenrup NB, et al. Pain (2010)

NNT for Specific Etiology



Finenrup NB, et al. Pain (2010)

Safety

Medication	Major side effect	Precautions
Secondary TCA	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma
Duloxetine	Nausea	Hepatic dysfunction, renal insufficiency
Gabapentin	Sedation, dizziness, peripheral edema	Renal insufficiency
Pregabalin	Sedation, dizziness, peripheral edema	Renal insufficiency
Topical lidocaine	Local erythema, rash	None
Oxycodone	Nausea, vomiting, constipation, dizziness, drowsiness	History of substance abuse
Tramadol	Nausea, vomiting, constipation, dizziness, drowsiness, seizure	History of substance abuse, seizure disorders, with TCA or SNRI

Additional Benefit for Comorbidity

Medication	Index	Benefit	Maximum dose	Duration
Secondary TCA	+	Depression, insomnia	150 mg/d	6-8 wk
Duloxetine	++	Depression	60 mg bid	4 wk
Gabapentin	++	Sleep disturbance, little drug interaction	3600 mg/d	3-8 wk
Pregabalin	++	Sleep disturbance, anxiety, little drug interaction	600 mg/d	4 wk
Topical lidocaine	++	No systemic side effect	3 patches/d	2 wk
Oxycodone	+	Rapid onset	180 mg/d	4-6 wk
Tramadol	+	Rapid onset	400 mg/d	4 wk

Drug-Drug Interactions

Medications	Potential Drug-Drug Interactions with common medications
Pregabalin/ Gabapentin	No known CYP450 based interactions
TCAs	• **Glimepiride** (CYP2C9 substrate) • **Atenolol, metoprolol** (CYP2D6 substrate) • **Atorvastatin, simvastatin** (CYP3A4 substrate, >90% protein bound) • **Furosemide** (>90% protein bound) • **Levothryroxine sodium** (>90% protein bound)
SNRIs	• **Atenolol, metoprolol** (CYP2D6 substrate) • **Atorvastatin, simvastatin** (CYP3A4 substrate, >90% protein bound) • **Furosemide** (>90% protein bound) • **Levothryroxine sodium** (>90% protein bound)

Combination Treatment

Combination therapy or single drug with multiple mechanism?

Combination therapy

- Avoid drugs with no effect
- Can combine two route of administration
- Complicated assessment of efficacy and identification of optimal dose-ratio
- Non-compliance

Single drug with MM

- Easy administration
- Better compliance
- May have unnecessary side effects

Combination Therapy in DPN

Combination	Study type	No. of patients	Periods	Results	Adverse effects
GBP vs NT vs CT	CT vs mono	56	6 weeks	Better with CT	Less with CT
GBP+VX vs GBP+PC	Add-on	60	8 weeks	Better with GBP+VX	Similar
GBP+OX vs GBP+PC	Add-on	338	12 weeks	Better with GBP+OX	Similar
PGB vs PGB+OX	CT vs mono	62	4 week	No better with CT	Similar
PGB vs 5% LP vs CT	Add-on	229	8 week	Better with CT	Fewer with 5% LP

GBP=gabapentin, NT=nortriptyline, CT=combined therapy, VX=venlafaxine, PC=placebo, OX=oxycodone, PGB=pregabalin, LP=lidocaine

Corticosteroid with or without Antiviral in Bell's palsy

Author and year	Cohort size	Age, y	Steroid dose duration Rx	Severity, %[a]	Duration, d[b]	Follow-up, mo	Completion rate, %[c]	Blind	Class	NH %[d]	RD good recovery (CI)	RD complete recovery (CI)
Engström[9] 2008	422	Median 39 (IQR 23-54)	Prednisolone[e] 60 mg daily × 5, taper	Med HB 4 IQR 3-5	3	12	99	Yes	I	56	—	15% (9%-21%)
Sullivan[11] 2007	551	Mean 44 (16.4 SD)	Prednisolone 25 mg BID	Mean HB 3.6 ± 1.3	3	9	90	Yes	I	82	—	12.8% (7.2%-18.6%)
Lagalla[13] 2002	58	Range 15-84	Prednisone 1 g IV × 3 d then 0.5 g IV × 3 d	24	3	12	100	Yes	II	75	7% (−14% to 27%)	—
May[14] 1976	51	53% >30	Prednisone 410 mg 10 d	47	2	6	100	Yes	II[f]	81	−0.75% (−18% to 22.5%)	—
Taverner[17] 1954	26	Mean 40 (range 12-76)	Hydrocortisone 1 g 8 d	23	9	NS	100	Yes	II[f]	67	5.25% (−27% to 55%)	—

Author and year	Cohort size	Age, y (range)	Dose duration Rx	Severity, %[a]	Duration, d[b]	Follow-up, mo	Completion rate, %[c]	Blind	Class	NH %[d]	RD complete recovery (CI)
Engström[9] 2008	829	Median 39 (IQR 23-54)	VC 3000 mg/day 7 days	Med HB 4 IQR 3-5	3	12	99	Yes	I	76	3.4% (−4.6-11.3%)
Sullivan[11] 2007	551	Mean 44 (16.4 SD)	AC 2000 mg/day 10 days	Mean HB 3.6 ± 1.3	3	9	90	Yes	I	93	−3.3% (−9.7-2.7%)
Yeo[12] 2008	91	Mean 41 (17 SD)	AC 1000 mg/d 5 days	23	53% ≤ 3 d	6	100	Yes	II	85	8.1% (−5.6-21.6%)
Adour[16] 1996	99	Mean 43	AC 400 mg × 5 qd 10 days	20	3	12	83	Yes	II	72	15% (−0.9-30.8%)

Current Guideline of management of Bell's palsy

For new-onset (72-hrs of symptoms) patients,

- Steroids are highly likely to be effective and should be offered to increase the possibility of recovery of facial nerve function.
- Antiviral agents in combination with steroids do not increase the probability of facial function recovery by > 7%. Patients might be offered antivirals in addition to steroid, and should be counseled that the benefit has not been established and its benefit id modest at best.

AAN. Neurology (2012)

Other management of Bell's palsy

Eye care

- Frequent use of lubricating ophthalmic drops
- Use of a moisture chamber using a polyethylene cover
- Eye patching or taping

Surgical decompression

- No recommendation

Acupunture

- No recommendation

Physical Tx

- No recommendation

Reginald E, et al. Otolaryngol Head Surg (2013)

Focal compression neuropathies

Acute compression	Entrapment neuropathy
• Often abrupt onset	• Slowly progressive
• Severe weakness	• Late feature of weakness
• Less pain and sensory	• Prominent pain and sensory
• Saturday night palsy	• Carpal tunnel syndrome

Carpal Tunnel Syndrome

- Compression of median nerve in carpal tunnel
- Prevalence of 2% in men and 3% in women
- Mostly idiopathic, diabetes, pregnancy, hypothyroidism, CKD, obesity
- Early subjective weakness (dropping objects), atrophy in severe case

	Specificity	Sensitivity
Phalen test	47 %	75 %
EDX	95 %	85 %

Management of Carpal tunnel syndrome

- Spontaneous improvement : 20 %
- Mild to moderate CTS : trial of conservative treatment
  - ✓ avoid aggravating activities
  - ✓ wrist splint (usually for 6 weeks)
  - ✓ oral or injected corticosteroid
- Severe or persistent CTS : consider surgical release

Nonsurgical management of Carpal tunnel syndrome

Proven benefit

- Oral steroids
- Splinting/hand braces
- Ultrasound
- Yoga
- Carpal bone mobilisation
- Insulin and steroid injection for diabetes

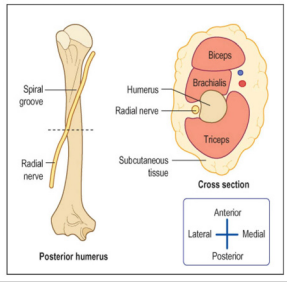
Uncertain

- vitamin B_6
- nonsteroidal anti-inflammatory drugs
- Magnets
- Laser acupunture
- Exercise or chiropractic

Reginald E, et al. Otolaryngol Head Surg (2013)

Radial neuropathy

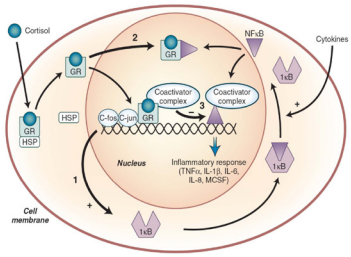
- External compression at the spiral groove (Saturday night palsy)
- DDx with central lesion
- Supportive wrist and finger extension brace



Lateral femoral cutaneous nerve

- Pure sensory nerve (L2-3)
- "meralgia paresthetica"
- Compression under the lateral portion of inguinal ligament
- Large abdomen, tight clothing or belt, lithotomy positioning, cycling
- High improvement rate following local steroid injection or surgical intervention

Anti-inflammatory Actions of Steroid



- Induction of the inhibitory protein IκB (binds and inactivates NFκB)
- Binding of GR-cortisol complex to NFκB
- Competition for the limited availability of coactivators against NFκB

Comparison of Steroids

Corticosteroids	Glucocorticoid potency	Equivalent dose (mg)	Minelarocorticoid potency
Short			
Cortisol (hydrocortisone)	1	20	Yes (1)
Prednisone	4	5	No
Prednisolone	**4**	**5**	**No (0.8)**
Methylprednisolone	**5**	**4**	**No (0.5)**
Intermediate			
Triamcinolone	5	4	No
Long			
Betamethasone	25	0.6	No
Dexamethasone	30	0.75	No (<0.2)

Methylprednisolone 1g = Prednisolone 800 mg, Dexamethasone 16 mg = Prednisolone 120 mg

Recommend General Guideline

Time of Administration

- 8 AM : No significant HPA suppression
- 4 PM : total suppression of HPA at midnight and partial at next 8 AM
- Midnight : Suppression of HPA for 24 hours

Dosing Interval

- Divided dose during 24 hours increase HPA suppression (5mg qid >>> 80 mg qod)
- Total 48 hr amount as a single dose (QOD) decrease HPA suppression
- More than 72 hr interval : therapeutically ineffective

Recommend General Guideline

Preparations

- Longer half-life cause more HPA suppression

Dose administered

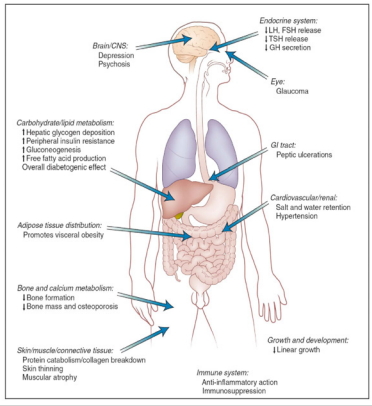
- Higher than physiological replacement dose are more suppressive
- Physiological dose

  Hydrocortisone 30 mg/d

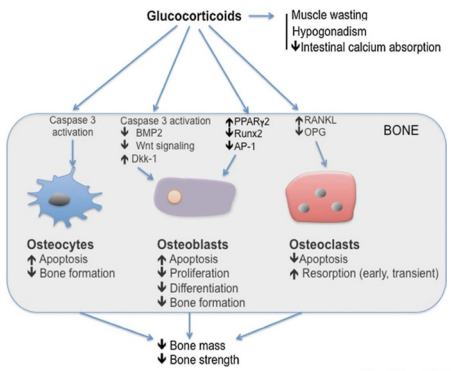
  Prednisolone 7.5 mg/d

  Dexamethasone 0.5-0.75 mg/d

Systemic Effects of Steroid



Mechanism of steroid induced osteoporosis



Rizzoli R, et al. Calcif Tissue Int (2012)

Recommendation for GIOP

- Glucocorticoid-sparing therapy: reduce glucocorticoid dose whenever possible
- Advise good nutrition, especially with calcium and vitamin D
- Recommend regular weight-bearing exercise
- Avoid tobacco use and alcohol abuse
- Assess falls risk and advise accordingly
- Assess adherence to therapy, including calcium and vitamin D
- If suspect vertebral fracture, assess by X-ray or DXA-based vertebral fracture assessment
- Measure height annually and BMD at appropriate intervals

Steroid Withdrawal Syndrome

- Sudden removal of prolonged or intensive steroid therapy
- Serious symptoms and morbidity

  Fatigue, weakness, anorexia, nausea, orthostatic dizziness, fainting, dyspnea
- Long term therapy

  Longer than 3 weeks

  2.5 mg every month down to 7.5 mg daily; then reduce more slowly

  1 mg every month