

Management of Pain related to Spinal Cord Lesion

A Neurologist's Perspective

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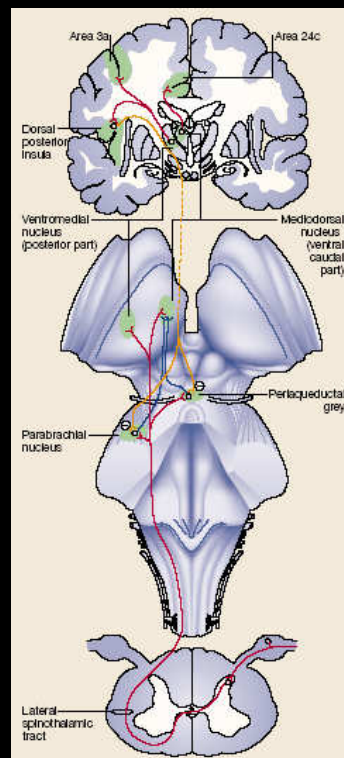
Division of Neurology

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The Chinese University of Hong Kong

Cortico-Spinothalamic Sensory Pathways

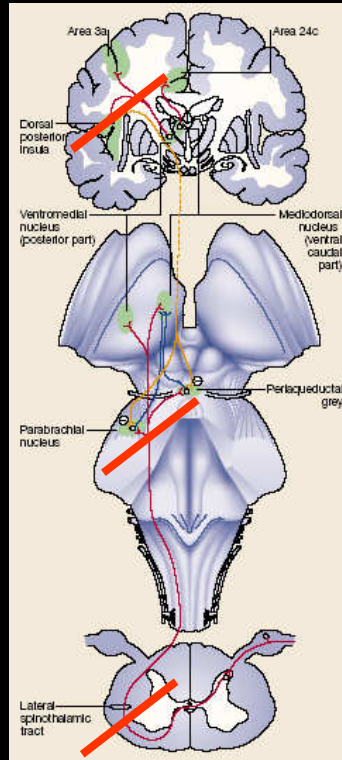
CNS



Nature Reviews 2002

Central Pain

e.g.
stroke
demyelination



e.g.
trauma
demyelination

Pathophysiology

Peripheral Mechanisms

*Peripheral neuron
hyperexcitability
(peripheral sensitization)*

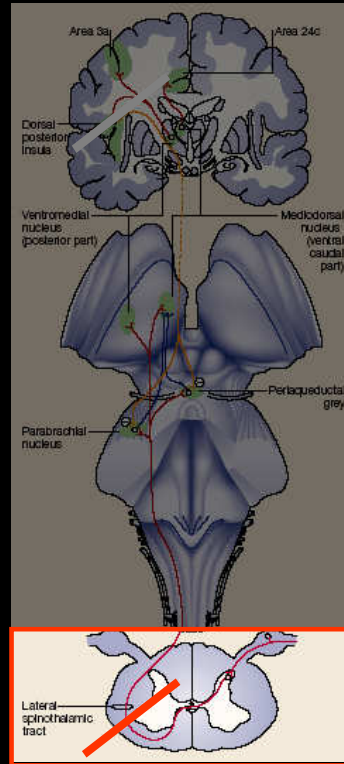
Central Mechanisms

*Loss of
inhibitory controls*

*Central neuron
hyperexcitability
(central sensitization)*

Central Pain

e.g.
stroke
demyelination



e.g.
trauma
demyelination

Spinal Cord

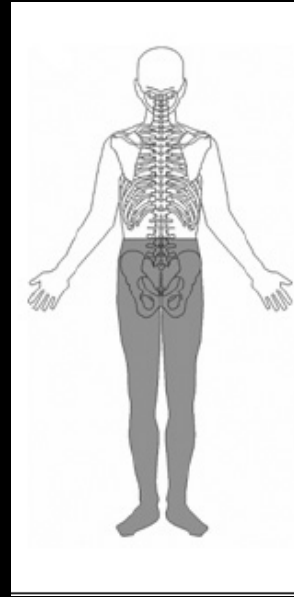
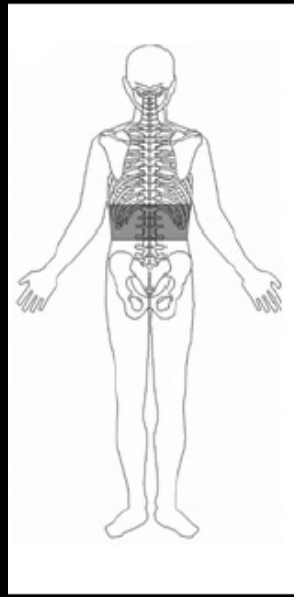
Physical Sequel of Spinal Cord Lesions

Upper Motor Neurons	Sensory	Autonomic	Indirect
<i>e.g.</i>			
<ul style="list-style-type: none"> • Weakness • Spasticity 	<ul style="list-style-type: none"> • NeP • Reduced sensation 	<ul style="list-style-type: none"> • Sphincter disturbances (e.g. visceral pain) 	<ul style="list-style-type: none"> • Musculo-skeletal pain

Pain related to Spinal Cord Lesions			
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Spinal Cord Lesions			
Upper Motor Neurons	Sensory	Autonomic	Indirect
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Sleep Disturbances, Anxiety, Depression, Reduced QoL			

At Level of Lesion



Below Level of Lesion

NeP and other Positive Sensory Dysfunctions

Spontaneous symptoms

Spontaneous pain	Persistent burning, intermittent shock-like or lancinating pain
Dysesthesias	Abnormal unpleasant sensations e.g. shooting, burning
Parasthesias	Abnormal, not unpleasant sensations e.g. tingling

Stimulus-evoked symptoms

Allodynia	Painful response to a <i>non-painful</i> stimulus e.g. warmth, pressure, stroking (with brush)
Hyperalgesia	Heightened response to <i>painful</i> stimulus e.g. pinprick, cold, heat
Hyperpathia	Delayed, explosive response to <u>any</u> painful stimulus

Positive Symptoms, e.g.	Negative Symptoms, e.g.
Spontaneous pain Allodynia Hyperalgesia Dysesthesia Paresthesia	Hypoesthesia / anesthesia Hypoalgesia / analgesia
Each patient may have a combination of symptoms that may change over time (even within a single etiology)	

Pain related to Spinal Cord Lesions			
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ID Pain Questionnaire

	Yes 是	No 否
1. Did the pain feel like pins and needles? 您出現的痛楚是否如被針刺般疼痛？	+1	0
2. Did the pain feel hot/burning? 您是否感到痛楚灼熱或如被火燒一樣？	+1	0
3. Did the pain feel numb? 您出現的痛楚是否帶有麻痺感？	+1	0
4. Did the pain feel like electrical shocks? 您出現的痛楚是否如觸電一樣？	+1	0
5. Is the pain made worse with the touch of clothing or bedsheets? 您的痛楚是否會因衣服或床單觸碰而加劇？	+1	0
6. Is the pain limited to your joints? 您的痛楚是否只出現於關節部位？	-1	0
Total 總分		

Minimum total score = -1 最低總分 = -1
Maximum total score = 5 最高總分 = 5

Interpretation 結果分析

Score 得分	-1	0	1	2	3	4	5
Interpretation 分析	NeP not likely 不大可能診斷為神經痛	NeP less likely 較少機會診斷為神經痛		Consider NeP 考慮診斷為神經痛			Strongly consider NeP 強烈考慮診斷為神經痛

NeP = Neuropathic Pain

Management

Multi-disciplinary e.g.	Multi-modality e.g.
Physicians / Surgeons (e.g. neurologists, rehabilitation specialists, neurosurgeons, orthopedics)	Drugs (mono / combination) for pain and other comorbidities (e.g. anxiety)
Anesthetists	Physical (e.g. TENS, acupuncture), Psychotherapy (e.g. cognitive behavioral therapy, life-style redesign) Patient group
Health Care Professionals (e.g. Nurses, PT, OT, Social worker, clinical psychologist)	Surgery / Stimulation – deep brain and motor cortex stimulation

Pathophysiology	Pharmacology
Peripheral Mechanisms	Na^+ <ul style="list-style-type: none"> Carbamazepine Lamotrigine Lidocaine / mexilitine Oxcarbazepine Topiramate TCA's
<i>Peripheral neuron hyperexcitability (peripheral sensitization)</i>	
Central Mechanisms	NE/5HT opioid receptors <ul style="list-style-type: none"> Alpha adrenergic agents Opioids SNRIs SSRIs Tramadol TCA's
<i>Loss of inhibitory controls</i>	
<i>Central neuron hyperexcitability (central sensitization)</i>	Ca^{2+} <ul style="list-style-type: none"> Gabapentin (GBA) Lamotrigine Levetiracetam Oxcarbazepine Pregabalin (PGA)
	NMDA <ul style="list-style-type: none"> Dextromethorphan Ketamine Methadone Memantine

General Recommendations for NeP
1st Line TCA / SNRI, PGB, GBA, topical lidocaine for local Peripheral NeP
2nd Line Opioids, Tramadol
3rd Line AEDs (e.g. CBZ, LMG), mexiletine
4th Line Refer to Pain Specialist / Multidisciplinary pain center
Current guidelines for NeP are based mostly on trials for peripheral NeP, may not be applicable to NeP / SCI

RCT for SCI NeP

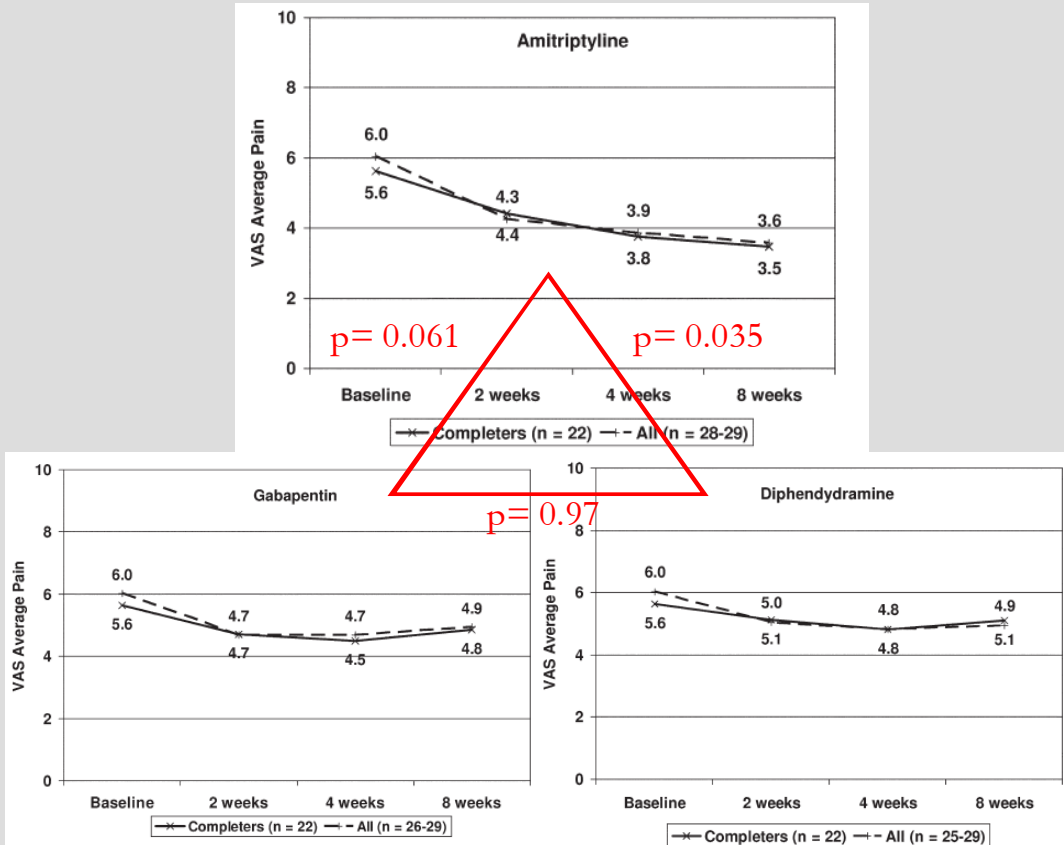
Drugs	n, Duration	Design	Results
1. Amitriptyline (≤150mg)	22, 8 wks	Crossover	+
2. Trazodone (50-150mg)	19, 6 wks	Parallel	-
3. Sodium Valproate (600-2400mg)	20, 3 wks	Crossover	-
4. Gabapentine			
a. ≤3600mg	20, 8 wks	Crossover	+
b. ≤3600mg	22, 8 wks	Crossover	-
c. ≤1800mg	7, 4 wks	Crossover	-
5. Lamotrigine (200-400mg)	22, 9 wks	Crossover	- /+***?
6. Pregabalin			
a. 150-600mg	137, 12 wks	Parallel	+
b. ≤600mg*	21, 4 wks	Parallel	+
7. Mexelitine (450mg)	11, 4 wks	Crossover	-
8. IV Lidocaine (5mg/kg over 30min)*	10, 6 hrs	Crossover	+

* Study consisting of CP of different etiologies ** posthoc analysis with + results on incomplete SCI with allodynia

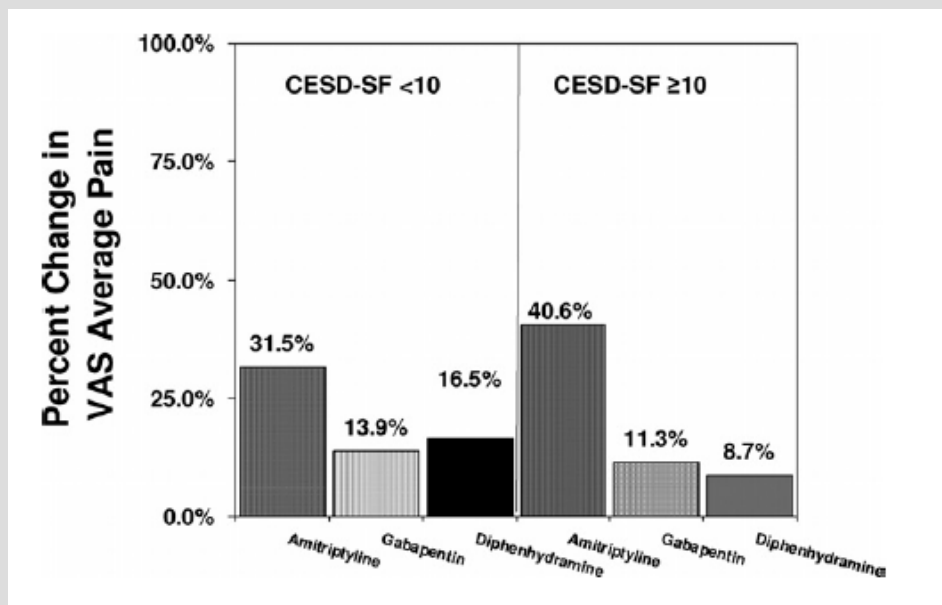
Amitriptyline vs GBA in Chronic NeP with Spinal Cord Injury N=38 (RCT, double blind, cross over)

Amitriptyline (max:50mg tds)	GBA (max: 1200mg tds)	Placebo (Diphenhydramine)
Week 1-4 (titration up)		
Week 5-8 (maintenance)		
Week 9 (titration down)		
Week 10 (wash out)		
Primary Outcome: Visual Analogue Scale		

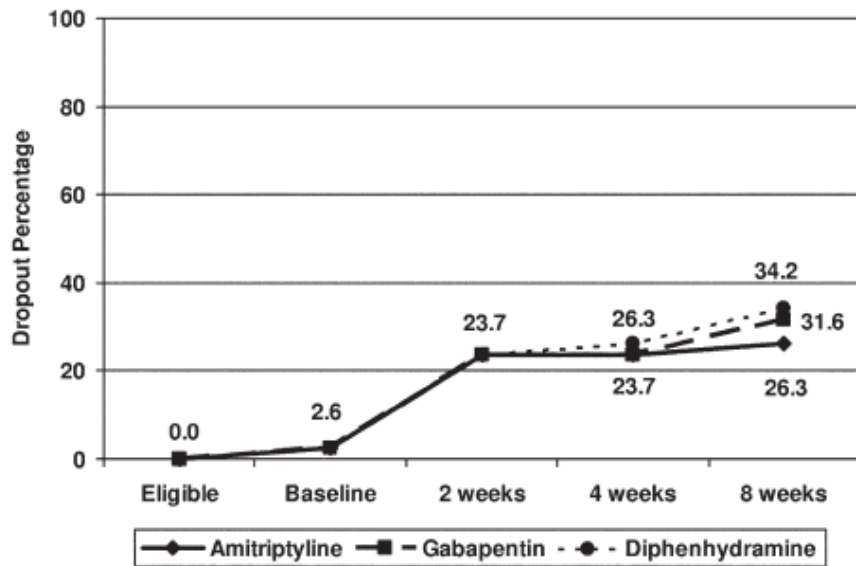
Results



Results



Dropout Rates



Results

Table 4: Reported Side Effects for Each 8-Week Medication Phase for Completers

Side Effects	Amitriptyline Percentage of Side-Effect Reports (n=210)	Gabapentin Percentage of Side-Effect Reports (n=201)	Diphenhydramine Percentage of Side-Effect Reports (n=205)	χ^2
Dry mouth	63.8	38.8	42.4	30.28*
Drowsiness	27.1	22.9	23.9	1.10
Fatigue	20.5	22.4	14.6	4.30
Constipation	29.2	10.9	12.7	28.74*
Increased spasticity	11.0	6.0	15.1	8.91 [†]
Dizziness	8.1	11.5	7.3	2.46
Difficulty emptying bowel	11.4	5.0	5.9	7.35 [†]
Nausea	9.0	6.5	2.9	6.76 [†]
Edema	5.7	5.5	5.4	0.25
Itching	5.7	3.5	6.8	2.32
Difficulty emptying bladder	5.2	1.0	1.5	8.87 [†]
Low blood pressure	2.4	3.0	1.5	1.08
Uncoordinated muscles	2.9	3.0	0.5	3.92
Vomiting	2.9	1.5	0.5	3.69
Abnormal heart rhythms	1.4	0.5	2.4	2.66
Skin rash	0.0	1.5	1.0	2.94
Weight gain	0.5	0.5	0.0	1.00
Seizure	0.0	0.0	0.0	NA

Abbreviation: NA, not applicable.
* $P < .001$; [†] $P < .05$.

Title	PGB in Central Pain associated with Spinal Cord Injury
Author / Country	PJ Siddal et al. Neurology 06; 67:1792-1800. Australia
Sample size / Drugs	N= 137; 70 PGB 150-600mg/d vs 67 placebo
Design	RCT, 12 weeks
Outcome	<p>Primary: Mean Pain Score on Visual Analogue Scale on last 7 days (Pain diary)</p> <p>Secondary: Responder rate, MPQ-SF, Sleep Scale, Anxiety and Depression Scale, Global measure of Change</p>

Baseline Characteristics

	Placebo, n = 67	Pregabalin, n = 70
Men, n (%)	54 (81)	60 (86)
Age, y, mean (range)	49.8 (21–80)	50.3 (23–78)
Aged 18 to 64 y, n (%)	58 (86.6)	59 (84.3)
White, n (%)	66 (98.5)	67 (95.7)
Weight, kg, mean	77.2	79.4
Paraplegic, n (%)	38 (56.7)	41 (58.6)
Tetraplegic, n (%)	29 (43.3)	29 (41.4)
Outpatient, n (%)	64 (95.5)	69 (98.6)
Mean duration of central pain, y (SD)	10.4 (9.8)	9.9 (7.7)
Persistent central pain in the last 3 mo, n (%)	59 (88.1)	62 (88.6)
Relapsing remitting central pain in the last 6 mo, n (%)	8 (11.9)	8 (11.4)
Central pain likely to be present*, n (%)	64 (95.5)	67 (95.7)
Any concomitant medication, n (%)	63 (94.0)	68 (97.1)
Concomitant pain medications, n (%)	46 (68.7)	53 (75.7)
Opioids	32 (47.8)	21 (30.0)
Tricyclic antidepressants	12 (17.9)	23 (32.9)
AEDs†	6 (9.0)	8 (11.4)
NSAIDs/COX-2	19 (28.3)	13 (18.6)
Other concomitant medications, n (%)		
Muscle relaxants‡	25 (37.3)	38 (54.3)
Benzodiazepines	26 (38.8)	28 (40.0)
SSRI/SNRI	7 (10.4)	5 (7.1)

Results

	Placebo			Pregabalin			Endpoint comparison placebo–pregabalin*		
	N	Baseline	Endpoint	N	Baseline	Endpoint	Adjusted difference	95% CI	p Value
Pain†	67	6.73 (1.4)	6.27 (2.1)	69	6.54 (1.3)	4.62 (2.1)	1.53	0.92; 2.15	<0.001
Sleep interference‡	66	4.98 (2.6)	4.71 (2.7)	69	4.22 (2.6)	2.79 (2.5)	1.37	0.77; 1.97	<0.001
SF-MPQ	67			69					
Total		18.4 (9.0)	17.5 (10.3)		17.4 (9.2)	11.7 (9.9)	4.9	2.1; 7.7	<0.001
Affective		4.46 (3.2)	4.20 (3.4)		4.06 (3.2)	2.43 (3.0)	1.54	0.62; 2.47	0.001
Sensory		14.0 (6.7)	13.3 (7.5)		13.4 (6.5)	9.3 (7.3)	3.4	1.3; 5.4	0.002
VAS		73.1 (14.5)	68.5 (22.2)		69.1 (13.6)	49.2 (24.1)	17.6	10.0; 25.2	<0.001
PPI		2.63 (1.0)	2.55 (1.0)		2.46 (0.9)	1.85 (1.1)	0.66	0.32; 0.99	<0.001
MOS-sleep scale problems index‡	67	50.6 (19.1)	45.2 (21.3)	69	43.3 (19.8)	34.5 (18.3)	6.4	1.0; 11.8	0.021
HADS anxiety score§	67	8.67 (4.1)	7.49 (4.3)	69	6.74 (3.6)	5.16 (3.4)	1.1	0.03; 2.09	0.043
HADS depression score§	67	6.61 (3.7)	6.29 (4.2)	69	5.86 (3.7)	5.44 (4.1)	0.36	-0.65; 1.37	0.482

Pain, Sleep, Anxiety

Side Effects

	Placebo, n = 67		Pregabalin, n = 70	
	Incidence	Discontinuation	Incidence	Discontinuation
Somnolence	6 (9.0)	0	29 (41.4)	4 (5.7)
Dizziness	6 (9.0)	0	17 (24.3)	0
Edema†	4 (6.0)	2 (3.0)	14 (20.0)	4 (5.7)
Asthenia	4 (6.0)	0	11 (15.7)	3 (4.3)
Dry mouth	2 (3.0)	0	11 (15.7)	0
Constipation	4 (6.0)	0	9 (12.9)	0
Amnesia	2 (3.0)	0	7 (10.0)	1 (1.4)
Amblyopia‡	2 (3.0)	1 (1.5)	6 (8.6)	1 (1.4)
Infection	4 (6.0)	0	6 (8.6)	0
Myasthenia	3 (4.5)	1 (1.5)	6 (8.6)	0
Thinking abnormal	1 (1.5)	1 (1.5)	6 (8.6)	0
Paresthesia	1 (1.5)	1 (1.5)	4 (5.7)	0
Urinary incontinence	2 (3.0)	0	4 (5.7)	1 (1.4)
		6 (9%)		14 (20%)

General Recommendations for NeP in Spinal Cord Injury

1st Line

TCA or PGB

2nd Line

Combinations: TCA + PGB

Consider GBA

Opioids / Tramadol for strong nociceptive component

3rd Line

LMG for incomplete injury with mechanical allodynia

4th Line

Refer to Pain Specialist / Multidisciplinary pain center

Consider IV Lidocaine as rescue therapy

Attal N et al. *Annals of Phy & Rehab* 2009;52:124-141

THANK YOU