

Neuropathic Pain

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Neuropathic Pain

- Definition of neuropathic pain
- Symptoms and signs
- Conditions producing neuropathic pain
- Treatments
- Cost of neuropathic pain

Types of Pain

Nociceptive Pain

An appropriate
Physiologic
response
to painful stimuli

Neuropathic Pain

An inappropriate
response caused
by a dysfunction
in the nervous
system

Definition of Neuropathic Pain

- Pain resulting from or thought to be resulting from a disturbance of the central or peripheral nervous system
- Acute vs Chronic (six months)
- Non Cancer vs Cancer

How common is it?

- UK 1% point prevalence - But likely more common than that
- Around 7–8% of adults have pain with neuropathic characteristics
- A quarter of people with diabetes and 35% of people with HIV have neuropathic pain

Symptoms and Signs

- Spontaneous vs stimulus evoked
- Burning, constant, throbbing vs jabbing, stabbing
- Mild, moderate, severe
- Distribution may not along classical neuroanatomical lines
- Associated with
 - analgesia
 - hyperalgesia
 - allodynia

Symptoms of Neuropathic Pain

Stimulus-Independent Pain (Symptoms Described by the Patient)

- Continuous burning pain
- Intermittent shooting, lancinating pain
- Electric-shock like pain
- Some paresthesias
- Some dysesthesias

Signs of Neuropathic Pain

**Stimulus-Evoked Pain
(Elicited by the Physician on Examination)**

Hyperalgesia

An increased
Response to a
stimulus that is
normally painful

Allodynia

Pain due to a
stimulus that is
*not normally
painful*

Nerve Pathways and Types of Pain

Afferent Fibers

C and A δ

A β

Spontaneous Symptoms

**Burning/
pricking pain**

**Dysesthesias/
paresthesias**

Stimulus- Evoked Signs

Hyperalgesia

Allodynia

Peripheral Nervous system

Central Nervous System

Normal A-Beta fibers



Normal C-fibers



**Normal
Sensory
Processing**



**Touch
Pain**

Sensitized A-Beta fibers



Sensitized C-fibers



**“Wind-up”
(Central
Sensitization)**



**Touch-evoked pain
Pain & hypersensitivity**

Conditions producing neuropathic pain

- Diabetic neuropathy
- Post herpetic neuralgia
- Cervical and lumbar radiculopathy
- Post thoracotomy, post mastectomy
- Multiple sclerosis
- Post-stroke
- Phantom limb

Neuropathic pain – subtypes (according a primary location of sustaining mechanism)

a) Predominating peripheral generator:

e.g. compression or entrapment neuropathies, plexopathies, radiculopathies, polyneuropathies

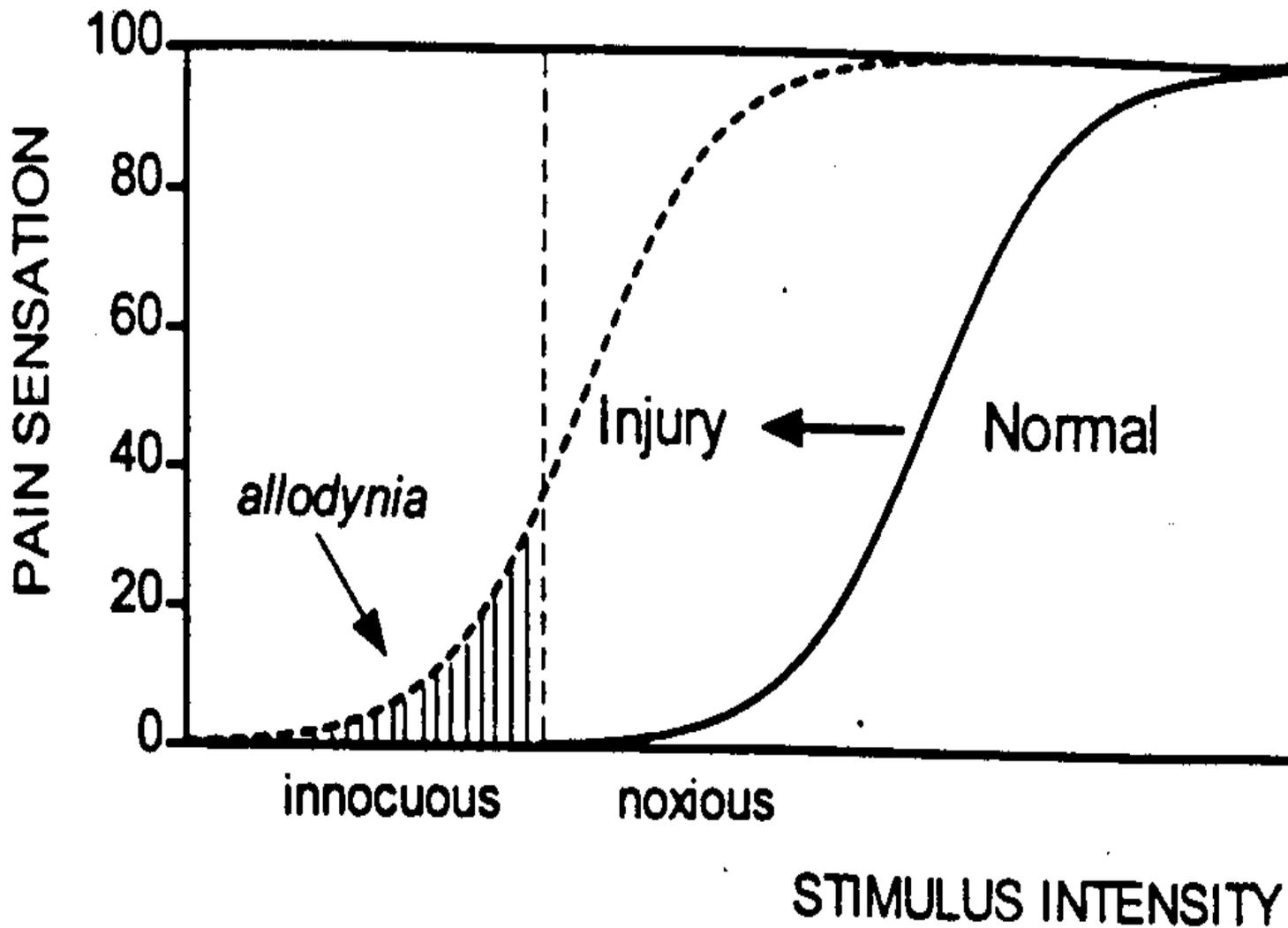
b) Predominating central generator:

e.g. spinal cord injury, post-stroke pain

- **Deafferentation pain - form of neuropathic pain: a term implying that sensory deficit in the painful area is a prominent feature (anesthesia dolorosa)**

- **Phantom pain- pain localized into non-existing organ (tissue)**

HYPERALGESIA



Neurotransmitters Involved in Pain Pathways

- Serotonin
- GABA
- Glutamate
- Substance P
- Opioid peptides

Common etiology of neuropathic pain

- Alcohol
- Diabetes mellitus type 1 and 2
- Eosinophilia-myalgia syndrome
- Guillain-Barre syndrome
- Heavy metals
 - Arsenic
 - Lead
 - Mercury
 - Thallium

Common etiology of neuropathic pain

- Medication

hydralazine

isoniazid

metronidazole

nitrofurantoin

paclitaxel

phenytoin

vincristine

Monoclonal gammopathies

Multiple sclerosis

Common etiology of neuropathic pain

- Post-stroke central pain
- Postherpetic neuralgia
- Traumatic
 - Carpal tunnel syndrome
 - Cervical or lumbar radiculopathy
 - Complex regional pain syndrome
 - Spinal cord injury
 - Stump pain
- Trigeminal neuralgia
- Vasculitis
- Vitamin B6 megadosing
- Vitamin deficiencies (B12, B1, B6, E)

Common etiology of neuropathic pain

- HIV/AIDS
- Malignant tumor-related
- Medications
 - amiodarone
 - aurothioglucose
 - cisplatinum
 - dapsons
 - d4T (stavudine)
 - ddC (zalcitabine)
 - ddI (didanosine)
 - disulfiram

When to refer

- Consider refer if:
 - severe pain
 - pain significantly limits their lifestyle, daily activities (including sleep disturbance)
 - underlying health condition has deteriorated

Informed drug choices? Neuropathic pain.

Estimation *publication bias*:

Searched trial data available on line but not in peer reviewed journals (almost 10% studies).

Finnerup estimated:

publication bias leads **10% overstatement** treatment effect.

NNT (50% relief) **high** – (4-10 in +ve trials)

Efficacy across range neuropathic pain conditions.

Studies looking at combination therapy haven't been done.

Management

- Pharmacotherapy

Oral: Tricyclic antidepressant

Antiepileptic

Opiate Methadone

Topical: Lidocaine

Capsaicin

Intrathecal: Opiate Clonidine

Other

First line medication

- Gabapentin
- 5% Lidocaine patch
- Opioid analgesics: Controlled-release and short-acting

Oxycodone hydrochloride monotherapy or in combination with hydrocodone bitartrate and acetaminophen, aspirin, or ibuprofen

Morphine sulfate

Levorphanol tartrate

Transdermal fentanyl

Methadone hydrochloride

First line medication

- Tramadol hydrochloride
- Tricyclic antidepressants, such as:
 - Amitriptyline
 - Nortriptyline
 - Desipramine hydrochloride

Second line medication

- Other anti-convulsant medications
 - Lamotrigine
 - Carbamazepine
- Other antidepressant medications
 - Bupropion hydrochloride
 - Citalopram
 - Paroxetine
 - Venlafaxine hydrochloride
 - Imipramine hydrochloride

Second line medication

- Beyond second-line medications include capsaicin, clonidine, dextromethorphan, mexiletine

Drug treatment for neuropathic pain – updated recommendations from the International Association for the Study of Pain (2018)

Recommendation	Drugs
First-line	SNRI – duloxetine, venlafaxine
	Tricyclic antidepressants
	Gabapentin, pregabalin
Second-line	Capsaicin 8% patches
	Lidocaine (lignocaine) patches
	Tramadol
Third-line	Strong opioids

	NNT (50% relief)	NNH (One patient w/d)
TCA'S	3.6	13.4
SNRI'S	6.4	11.8
SSRI'S	7.0	
GABAPENTIN	6.3 (8.3)	26.1
PREGABLIN	7.7	13.9
TOPIRAMATE	7.4	6.3
OPIOIDS	4.3	11.7
CODEINE	12	
TRAMADOL	4.7	9.0
CAPSAICIN 8%	10.6	

Table 3
Benefit-Risk Analysis of Agents Used to Treat Neuropathic Pain

Medication	Number of Patients Needed to Treat (NNT) for Efficacy/Adverse Effects			
	Painful/Diabetic Neuropathy	Postherpetic Neuralgia	Peripheral Nerve Injury	Trigeminal Neuralgia
Tricyclic antidepressants	2.4/4.9	2.3/6		—
Amitriptyline	2.0/9.7	2.3/6.2	2.5/ND	—
Desipramine	3.4/20	1.9/4.8	2.5/ND	—
SSRIs	6.7/ND	—	—	—
Paroxetine	2.9/ND	—	—	—
Citalopram	7.7/ND	—	—	—
Phenytoin	2.1/9.5	—	—	—
Carbamazepine	3.3/1.9	—	—	2.6/3.4
Gabapentin	3.7/1.8	3.2/3.4	—	—
Lamotrigine	—	—	—	2.1/ND
Mexiletine	10.0/6.3	—	—	—
Baclofen	—	—	—	1.4/ND
Tramadol	3.4/ND	—	—	—
Oxycodone	—	2.5/ND	—	—

Source: References 15,21,22,26,27,30-32,37



PAIN

www.elsevier.com/locate/pain

Algorithm for Neuropathic pain treatment: An Evidence based Proposal

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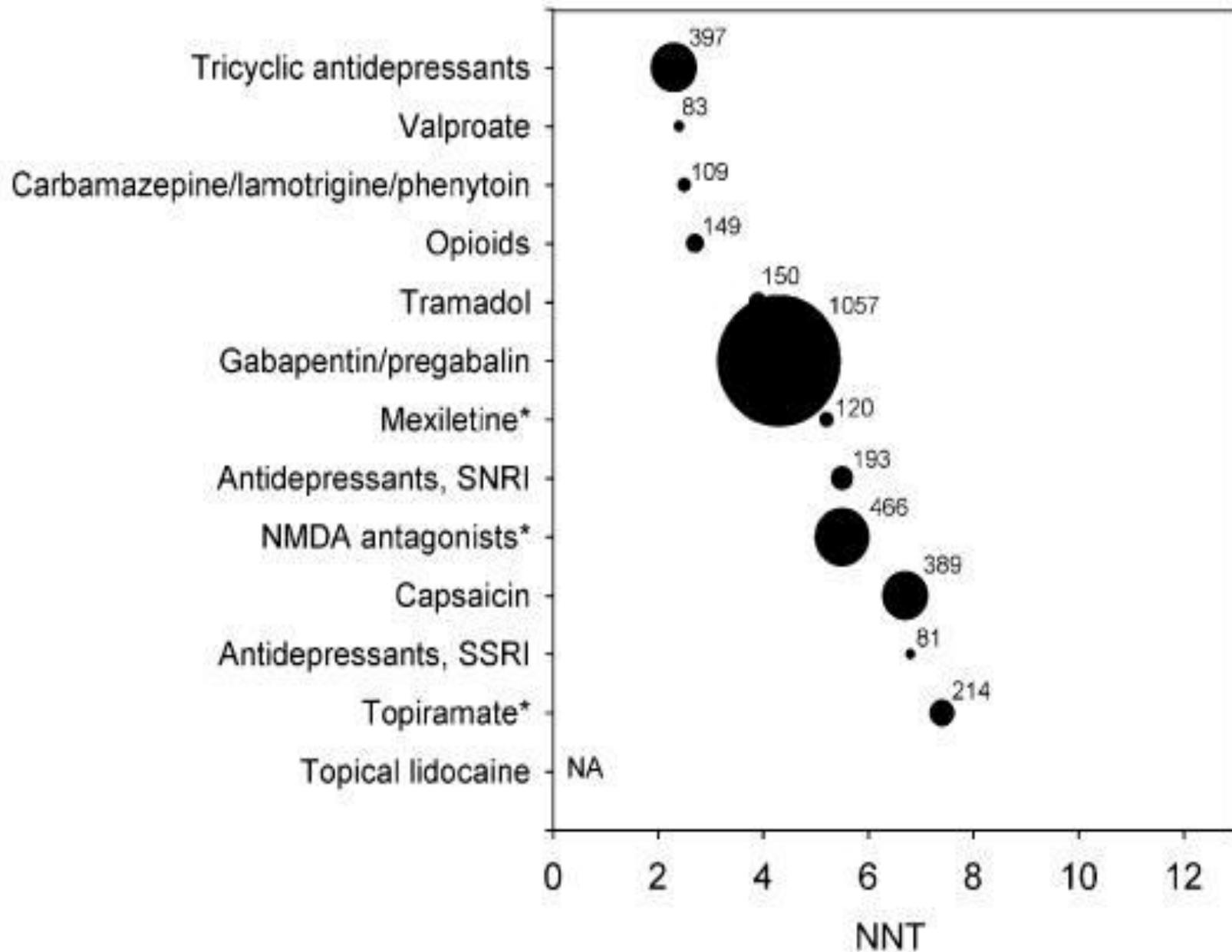
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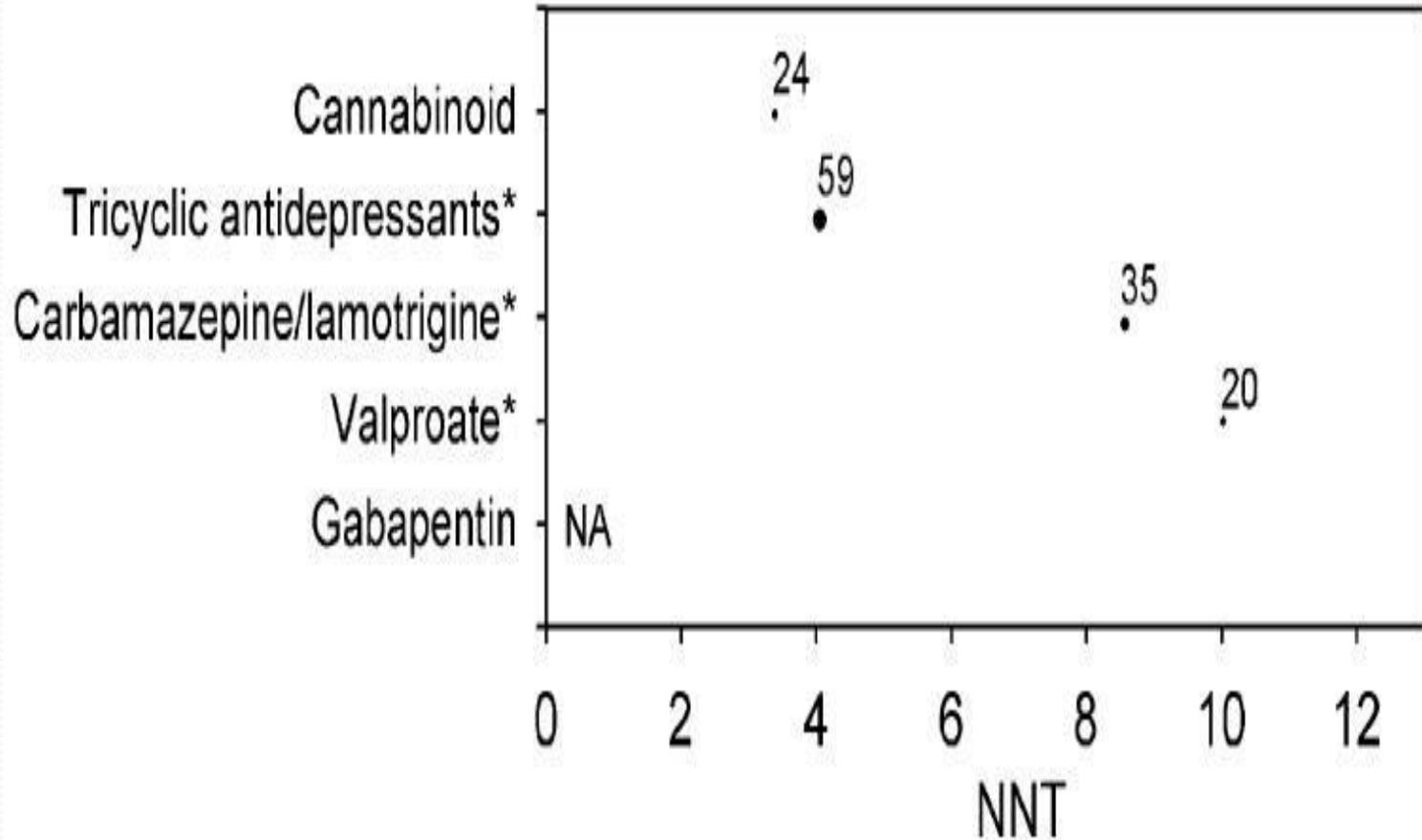
(a)

Peripheral neuropathic pain



(b)

Central pain



Drug-related Adverse Effects

elderly

patients with a history of substance abuse

patients with depression

cardiovascular disease, hepatic insufficiency,
or renal insufficiency

patients taking medications that have the
potential for interaction with neuropathic-
medications

NEURONTIN[®]
(gabapentin)

Product availability

Strength and Pack:

Capsule 100mg (white)

Capsule 300mg (yellow)

Capsule 400mg (Orange)

Tablet 600mg (white)

Therapeutic class : Anti-epileptic drug

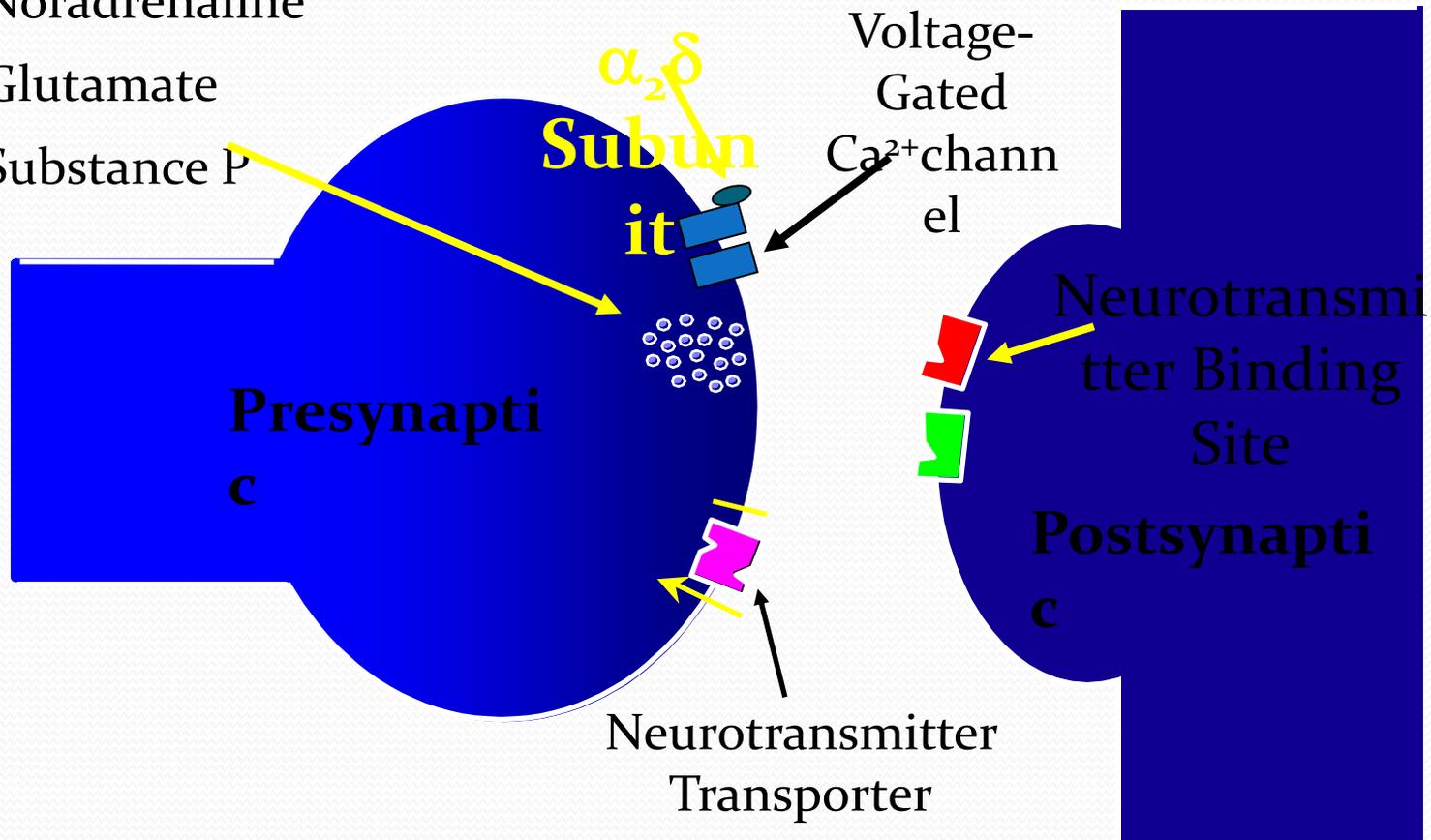
Pharmacologic Properties of gabapentin

- Increases GABA in brain, possibly by enhancing rate of synthesis from glutamate
- Binds to specific site localized to brain regions associated with major excitatory inputs
- Inhibits sodium currents by mechanism distinct from phenytoin and carbamazepine
- Inhibits branched-chain amino acid transferase, possibly reducing glutamate concentration
- No effect on GABA_A or GABA_B receptors

GBP & PGB Binds to the $\alpha_2\delta$ Subunit of Voltage-gated Ca^{2+} Channels in the Brain

Modulates neurotransmitter release

- ↓ Noradrenaline
- ↓ Glutamate
- ↓ Substance P



Dose regimen

Method of administration:

Initial Titration

Dose	Day1	Day2	Day3
900mg	300mgQD	300mgBID	
300mgTID			

- Increase if necessary, based on response, up to a maximum dose of 3600mg/day (given as three equally divided doses)

Adverse Events

Somnolence, dizziness, ataxia, fatigue, nystagmus which were generally mild to moderate with a median duration of 2 weeks

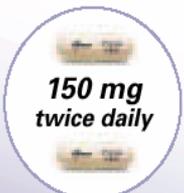


- Pregabalin

Pregabalin: Recently Defined Mechanism

- *Binds to neurons at the α_2 - δ subunit of voltage-gated calcium channels (brain and spinal cord)*
- *Attenuates calcium influx into depolarized nerve terminals*
 - *Reduces excitatory neurotransmitter release from hyperexcited neurons (e.g. glutamate, Substance P, noradrenaline)*
 - *No GABA activity*

Simple pregabalin dosing in neuropathic pain

150 mg/day	
 <p>75 mg twice daily</p>	Starting dose¹
300 mg/day	
 <p>150 mg twice daily</p>	May increase to 300 mg/day after 3-7 days, based on individual response¹
600 mg/day	
 <p>300 mg twice daily</p>	If needed, increase to maximum dose after an additional 7 days¹

Capsules not actual size.

- bd (twice daily) dosing
- The dose most often used in open-label studies was approximately 300 mg/day
- Clear dose-response relationship
- May be taken with or without food
- Dosage reduction is necessary in patients with renal impairment

Pregabalin

- post-herpetic neuralgia and painful diabetic neuropathy
- has a combined *NNT* for doses ranging from 150 to 600 mg of 4.2 (3.4-5.4) comparable to the effect of gabapentin.
- ✓ *NNH* = 11.7 (8.3-5.4)

Onset and resolution of dizziness and somnolence in neuropathic pain trials

	<i>Dizziness</i>	<i>Somnolence</i>
<i>Incidence*</i>	21.7%	13.8%
<i>Discontinuation*</i>	3.1%	2.6%
<i>Median time to onset †</i>	1-2 days	1-2 days
<i>Median time to resolution (completers) †</i>	6-17 days	26-31 days

*All pregabalin dose groups pooled; n=1556

† Median time to onset and resolution across 150, 300 and 600 mg/day dose groups

Tricyclic Antidepressants

- analgesic effect that has been demonstrated to be independent of their antidepressant effect
- TCAs should be initiated at low dosages
10 to 25 mg hs
titrated every 3 to 7 days by 10 to 25 mg/d as tolerated

Tricyclic Antidepressants

- lower dosages than the antidepressant effect, there is no systematic evidence
- However, some data are consistent with a dose-response relationship; TCAs should be titrated to dosages of 75 to 150 mg/d as tolerated
- blood level of approximately 100 ng/mL
- Toxicity: Blood levels of > 500 ng/mL

Tricyclic Antidepressants

- **Contraindications**
 - especially in patients with cardiovascular disease
 - risks of conduction defects, arrhythmias, tachycardia, acute myocardial infarction.

Antidepressants

- Seven of nine studies with duloxetine 20–120 mg were positive
- Two of four studies identified efficacy with venlafaxine 150–225 mg daily
- The negative venlafaxine studies were at lower doses

Opioid Analgesics

- *Opioid Analgesics*: Numerous short- and long-acting opioid analgesics are available.
- One recommended approach is to begin treatment with opioid analgesics using a short-acting medication at dosages equianalgesic to the oral administration of **morphine sulfate at 5 to 15 mg every 4 hours as needed.**

Opioid Analgesics

- Commonly used short-acting opioid analgesics include oxycodone alone and hydrocodone bitartrate and oxycodone in combination with acetaminophen, aspirin, or ibuprofen
(a morphine elixir can be used with patients who have difficulty swallowing)

Tramadol

- *Tramadol* is a norepinephrine and serotonin re-uptake inhibitor with a major metabolite that is a mu-opioid agonist
- To decrease adverse effects and increase patient adherence to treatment :
initiated at low dosages—50 mg once or twice daily— and then titrated doses as tolerated.

Tramadol

- The maximum dosage of tramadol hydrochloride is 100 mg 4 times daily (in patients older than 75 years, 300 mg/d in divided doses), and an adequate trial requires 4 weeks

Other therapies

- Rehabilitation therapy
- Behavioural therapy
- Psychotherapy
- CBT; Meditation; Hypnotherapy
- Alternative: Acupuncture
- Neurostimulation
- Neuroblock
- Injections including Botox
- Surgery

Cost of neuropathic pain

- Mild pain: \$2619
- Moderate pain: \$3972
- Severe pain: \$8360

- Average \$4614

Cost of neuropathic pain

- Average cost \$4614/3 months
- Direct costs \$1068
- Indirect costs \$3546

Conclusions

- Neuropathic pain is being more commonly recognized
- Pain can be mild to severe
- Characteristic symptoms
- Seen in many common conditions
- Multimodal treatment
- Expensive in human and economic terms

Conclusion

- If only one set of criteria: pain relief is
- $TCA > \textit{opioids} \geq \textit{tramadol} \geq \textit{gabapentin/pregabalin}$
- If the criteria for efficacy are based on both pain relief and quality of life is
- $\textit{gabapentin/pregabalin} > \textit{tramadol} > \textit{opioids} > TCA$
- Occasionally dangerous side effects of TCA and strong opioids need to be considered.

Conclusion

- TCAs have lower NNT values than gabapentin/pregabalin but may be due to differences in study design.
- ✓ Gabapentin/pregabalin have higher NNH values and lack serious adverse effects
- ✓ TCA and Gabapentin/Pregabalin, these two drug classes as first line treatment of peripheral neuropathic pain.

Conclusion

- Tramadol and oxycodone may be considered second or third line drugs
- In trigeminal neuralgia, carbamazepine is first choice (consistent outcome with a low NNT), but studies of varying quality. Oxcarbazepine may be an alternative.

Conclusion

In the elderly

- Gabapentin/pregabalin seems to be first choice.
- TCAs, lamotrigine, cannabinoids, tramadol, and opioids may be second choice.

● Thank You
For Your
Attention

