Pharmacologic Management of Neuropathic Pain

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Disclosure Statement

- I have nothing to disclose

True or False

- Opioids are not effective analgesic agents for neuropathic pain

A. True
B. False

True or False

- Pregabalin doses do not need to be adjusted in a patient with chronic kidney disease stage IV

A. True
B. False

- All of the following agents may be considered first line medications for the treatment of neuropathic pain except:

A. Nortriptyline
B. Duloxetine
C. Desipramine
D. Oxycodone CR
E. Venlafaxine

NEUROPATHIC PAIN DEFINITION

Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy

- The IASP has defined neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system.”
- Controversy exists regarding the definition of neuropathic pain and what it entails. Max has argued for removal of the words “or *dysfunction”* from the IASP definition and proposed that the definition for neuropathic pain be “pain initiated or caused by a primary lesion of the nervous system.”
- Conversely, Jensen and coworkers have opined that on the other hand, going back to a pure neuroanatomic description of neuropathic pain overlooks the plasticity of the nervous system and its continuous modulation, which may change after activation or injury

Smith HS, et al . Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy. In, Current Therapy in Pain. Ed. **Smith HS**. Elsevier. Philadelphia, PA. 2009.

A New Definition of Neuropathic Pain

- IASP has recently published a new definition of neuropathic pain according to which neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory system" (www.iasp-pain.org/resources/painDefinition)
- This definition replaces the 17-year old definition that appeared in the *Classification of Chronic Pain* published by IASP in 1994, which defined neuropathic pain as "pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system"
- Two important changes in the new version:
  - The word "dysfunction" has been removed
  - A lesion or disease affecting the nervous system has been specified to be a lesion or disease of the somatosensory system.

Jensen TS. Pain. 2011; In Press.

Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy

- Treede and associates proposed that neuropathic pain (NP) be redefined/reworded as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”. Peripheral NP and central NP are proposed to refer to lesions/disease of the peripheral nervous system (PNS) and central nervous system (CNS), respectively.

Smith HS, et al . Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy. In, Current Therapy in Pain. Ed. **Smith HS**. Elsevier. Philadelphia, PA. 2009.

Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy

The NP grading system is used to decide on the level of certainty with which the presence or absence of neuropathic pain can be determined in an individual patient. The grading of certainty for the presence of NP consists of:

- Definite NP: all (1–4)
- Probable NP: 1 and 2, plus either 3 or 4
- Possible NP: 1 and 2, without confirmatory evidence from 3 or 4

Smith HS, et al . Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy. In, Current Therapy in Pain. Ed. **Smith HS**. Elsevier. Philadelphia, PA. 2009.

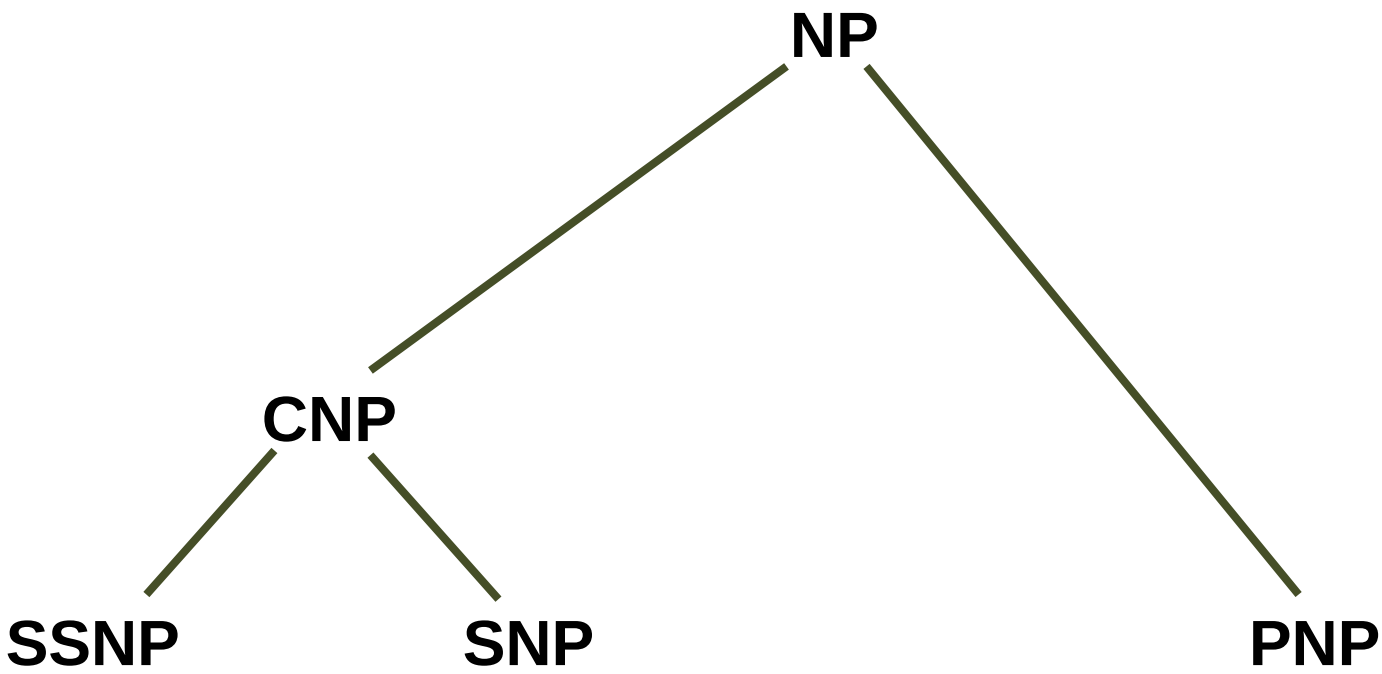
Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy

If a patient does not fulfill the criteria for any of these three levels, it is considered unlikely that this patient has NP.

The criteria to be evaluated for each patient are:

1) Pain with a distinct neuroanatomically plausible distribution
2) A history suggestive of a relevant lesion of disease affecting the peripheral or central somatosensory system
3) Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test
4) Demonstration of the relevant lesion or disease by at least one confirmatory test.

Smith HS, et al . Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy. In, Current Therapy in Pain. Ed. **Smith HS**. Elsevier. Philadelphia, PA. 2009.


NP
CNP
SSNP
SNP
PNP

Categories of peripheral and central neuropathic pain

Peripheral

- Osteoarthritis/disc disease with nerve root pain (usually C5 and C6, and L5 and S1)
- Postherpetic neuralgia (may have a central component)
- Painful neuropathies (diabetes, alcohol/nutritional, HIV, etc)
- Cancer-associated neuropathic pain
- Phantom limb pain
- Nerve trauma (causalgia)
- Incisional neuralgias (post-thoracotomy, postmastectomy, etc)
- Brachial plexus avulsion (likely a central component)
- Neuropathic facial pain exclusive of trigeminal neuralgia
- Trigeminal neuralgia*, glossopharyngeal neuralgia

Central

- Central poststroke pain
- Spinal cord injury pain
- Traumatic brain injury
- Multiple sclerosis
- Syringomyelia

**Trigeminal neuralgia is a unique and common form of neuropathic pain with a differing medical and surgical approach from other forms of neuropathic pain (except the rare condition of glossopharyngeal neuralgia)*

Watson CP, et al. Pain Res Manag. 2010; 15:147-57.

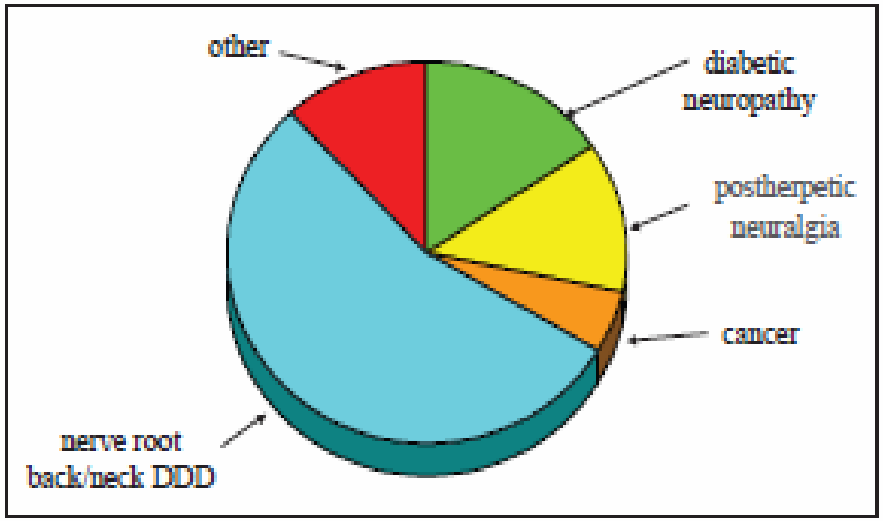
The prevalence of NP derived from the survey of Weingarten and coworkers (8.8%) is very close to that reported by Torrance and associates (7-8%).

Smith HS, et al . Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy. In, Current Therapy in Pain. Ed. **Smith HS**. Elsevier. Philadelphia, PA. 2009.

Epidemiology of Refractory Neuropathic Pain

- Two postal surveys, carried out in a large community samples from UK and France, using different NP pain questionnaires (S-LANSS in UK and DN4 in France), reported similar estimates of the prevalence of chronic pain with NP characteristics in the general population around 7-8%.

Argyra E. Abstract 834

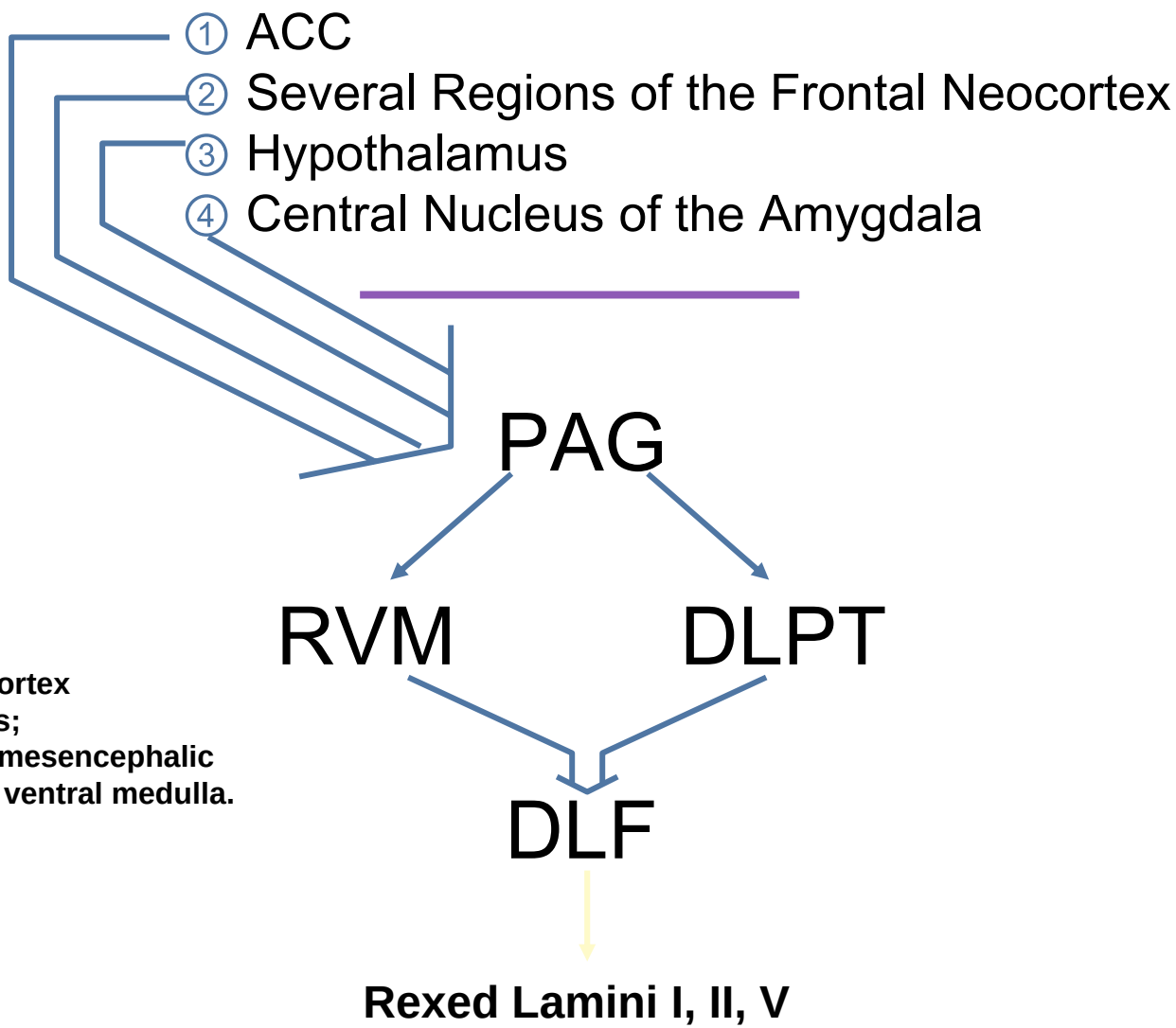


Prevalence of some forms of peripheral neuropathic pain.
***DDD** Degenerative disc disease.*

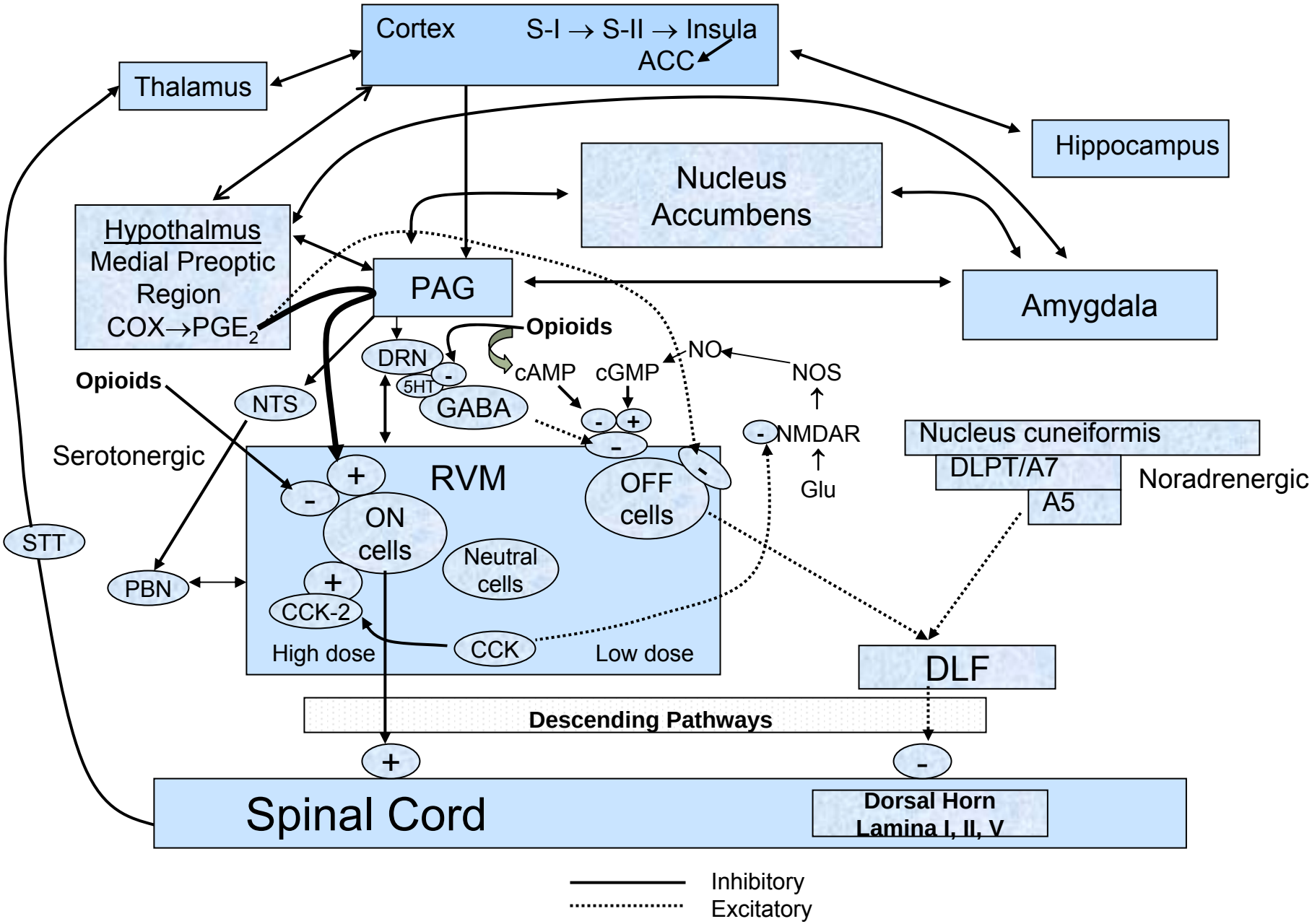
Watson CP, et al. Pain Res Manag. 2010; 15:147-57.

NEUROPATHIC PAIN PATHOPHYSIOLOGY

Descending Pain Modulating Circuits



PAG: Periaqueductal Grey
ACC: Anterior Cingulate Cortex
DLF=dorsolateral funiculus;
DLPT = dorsolateral pontomesencephalic tegmentum; RVM = rostral ventral medulla.



Potential Supraspinal Mechanisms of Prostanoid Effects on Modulation of Nociception

Peripheral Nerve Injury

- Altered Channel Expression
  - ↑NaV1.8 – Eutopic Spontaneous Discharge
  - ↑$\alpha 2\delta 1$ auxilary subunit – Cav2.1
- Altered Spinal Receptors
  - NGF = TrkA
    - Recruitment of silent nociceptors
    - ↑Responsiveness to BK
    - Stimulation Mast Cells/SNS
    - ↑TRP1/ASICs (sensitzation of nociceptors)
- Activity Induced Facilitation
  - Glu → NMDA
  - ↑AMPA subunit expression
- Loss of Inhibition (Disinhibition)
  - ↑PG2 EP → Gly
- Increased Descending Spinobulbospinal Facilitatory Serotonergic Pathways
  - SP → NK 1
- Activation of non-neuronal (Glial) cells
  - ↑Fractalkine/↑IL 6→ p38MAPK → p p38MAPK → ↑CX3CR1
  - ↑ATP → ↑BDNF = TrkB → ↑KCC2 → ↑ Intracellular Cl^- →
    ↓ efficacy of GABAergic Inhibition (Disinhibtion)

Comprehensive H & P
Laboratory Studies
Imaging Studies
Ancillary Diagnostic Studies

Disease-Specific Treatment of Neuropathic Pain

- Painful Diabetic Polyneuropathy

Painful Neuropathy may be the presenting symptom and may antedate DM onset by up to FOUR years

Polydefkis M, et al. JAMA. 2003; 290

Classification of Diabetic Neuropathy

Generalized Neuropathies

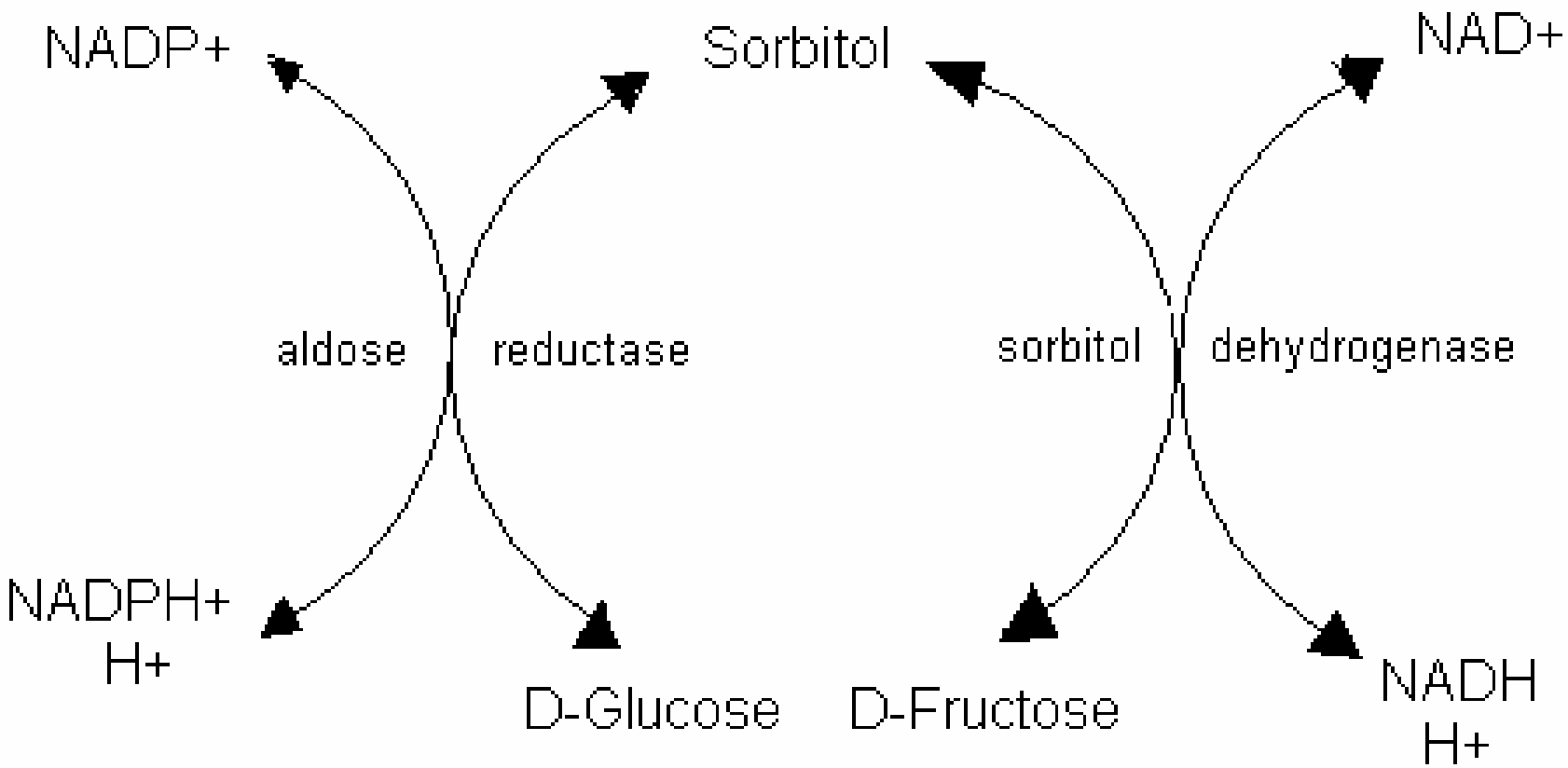
- Distal symmetric polyneuropathy
  - Large fiber sensory
  - Small fiber painful sensory
  - Subclinical neuropathy
- Acute Painful diabetic neuropathy
- Autonomic neuropathy

Focal or Multifocal Neuropathies

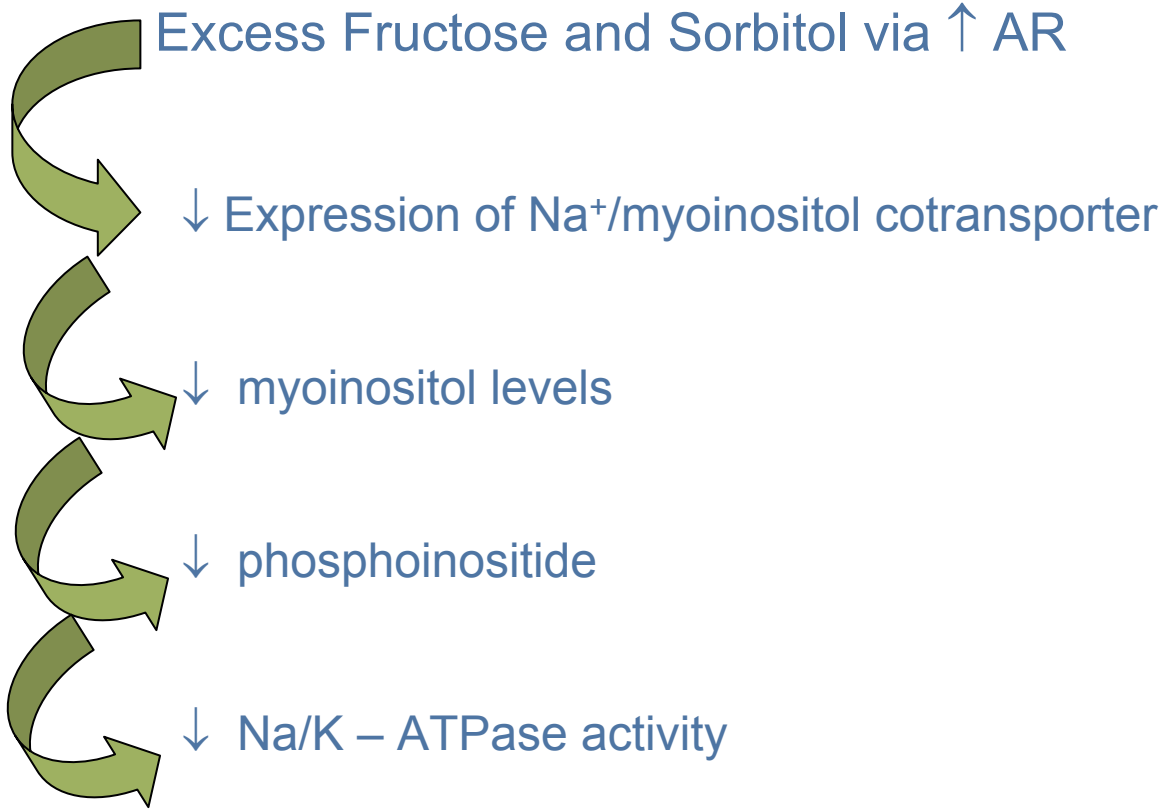
- Compressive focal neuropathies
  - Carpal tunnel syndrome, unlar neuropathy, peroneal neuropathy
- Noncompressive focal and multifocal neuropathies
  - Diabetic amyotrophy
  - Mononeuritis multiplex
  - Cranial neuropathies
  - Femoral, sciatic, ulnar, peroneal neuropathy
  - Trunal neuropathies

TREATMENT OF PAINFUL DIABETIC NEUROPATHY

- Tight Control


NADP+
NADPH+
H+
aldose
reductase
D-Glucose
Sorbitol
D-Fructose
sorbitol
dehydrogenase
NAD+
NADH
H+

POLYOL PATHWAY THEORY



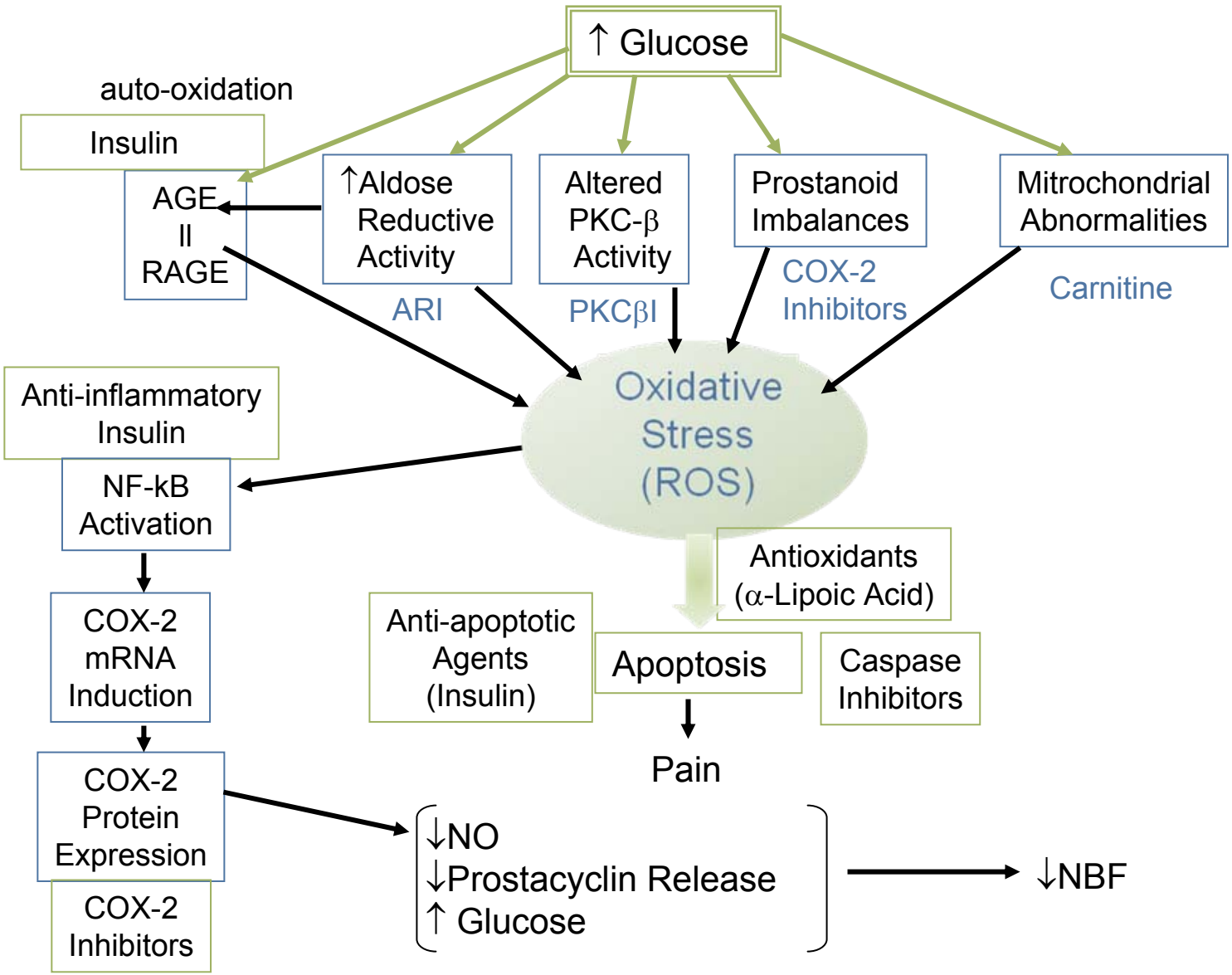
Therapies for PDPN Pathophysiology

Aldose Reductase Inhibitors

- Multiple ARIs including sorbinil, tolrestat,ponalrestat, zopolrestat, zenarestat, lidorestat, fidarestat, rainrestat (AS-3201) and epalrestat have been studied.

Smith HS, et al. Drugs. 2011; 71:557-589.

OXIDATIVE STRESS



Therapies for PDPN Pathophysiology

α-Lipoic Acid

- α-Lipoic acid, also termed thioctic acid, is an antioxidant that is available for treatment of DPN.

- At least seven randomized controlled clinical trials of thioctic acid in patients with DPN have been completed (ALADIN I–III [Alpha-Lipoic Acid in Diabetic Neuropathy], DEKAN[Deutsche Kardiale Autonome Neuropathie], ORPIL [Oral Pilot], SYDNEY [Symptomatic Diabetic Neuropathy] and NATHAN [Neurological Assessment of Thioctic Acid in Neuropathy] II) using different study designs, durations of treatment, doses, sample sizes and patient populations.

Smith HS, et al. Drugs. 2011; 71:557-589.

Therapies for PDPN Pathophysiology

α-Lipoic Acid

- Ziegler et al. performed a meta-analysis on four trials (ALADIN I, ALADIN III, SYDNEY and NATHAN II); 1258 patients (α-lipoic acid, n = 716; placebo, n = 542).

- This meta-analysis demonstrates that treatment with intravenous α-lipoic acid 600 mg/day for 3 weeks improves the chief symptoms of PDPN to a clinically meaningful degree.

- A statistically significant difference in the TSS between α-lipoic acid and placebo was observed from the second week of treatment onward and continuously increased until the end of treatment.

Smith HS, et al. Drugs. 2011; 71:557-589.

Rational Polypharmacy for Diabetic Peripheral Neuropathic Pain*

First-tier agent	Add-on therapy	Avoid
SNRIs	α2δ ligands, opioids, topical agents	Other SNRIs, TCAs, tramadol
α2δ	ligands SNRIs, TCAs, opioids, tramadol, topicals	Other α2δ ligands
TCAs	α2δ ligands, opioids, topicals	SNRIs, tramadol
Opioids	SNRIs, α2δ ligands, TCAs, topicals	Other opioids
Tramadol	α2δ ligands, opioids, topicals	SNRIs, TCAs
Topical agents	SNRIs, α2δ ligands, TCAs, opioids, tramadol, topicals	None

*Rationale for polypharmacy includes the ability to decrease toxicity, address treatment failures, take advantage of complementary mechanisms of action, and decrease drug-drug interactions. SNRI = serotonin-norepinephrine reuptake inhibitor; TCAs = tricyclic antidepressants.

Smith HS, et al. Drugs. 2011; 71:557-589.

Painful Diabetic Peripheral Neuropathy: Consensus Recommendations on Diagnosis, Assessment and Management

Tesfaye S, et al. Diabetes Metab Res Rev. 2011; In Press.

Mechanisms of Neuropathic Pain

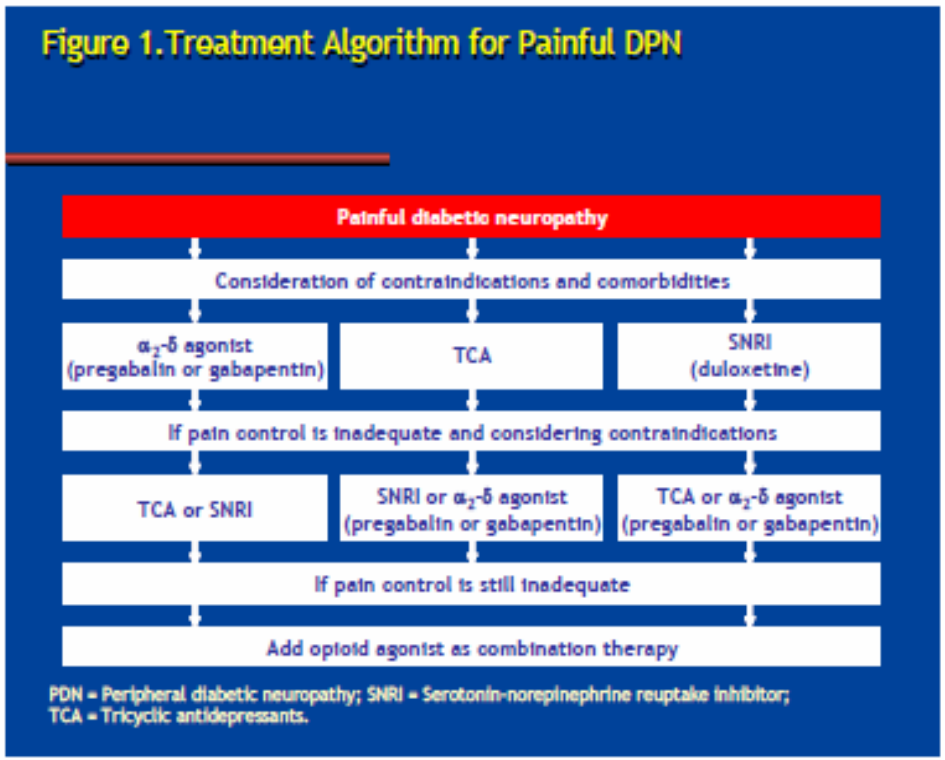
Peripheral Mechanisms	Central Mechanisms
• Changes in sodium channel distribution and expression • Changes in Calcium Distribution and Expression • Altered neuro-peptide expression • Sympathetic sprouting • Peripheral sensitization • Altered peripheral blood flow • Axonal atrophy, degeneration or regeneration • Damage to small fibres • Glycaemic flux	• Central sensitization • Aβ fibre sprouting into Channel lamina II of the dorsal horn • Reduced inhibition via descending pathways

- Tesfaye S, et al. Diabetes Metab Res Rev. 2011; In Press.

Evidence-based guideline: treatment of painful diabetic neuropathy--report of the American Association of Neuromuscular and Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine & Rehabilitation

Recommendations were linked to the strength of the evidence. The results indicate that pregabalin is established as effective and should be offered for relief of PDN (Level A). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of PDN (Level B). Other treatments have less robust evidence, or the evidence is negative.

Bril V, et al. Muscle Nerve. 2011; 43:910-917.



Toronto Expert Panel on Diabetic Neuropathy

Tailoring treatment to the patient		
	Factor	Contraindication
Comorbidities	Glaucoma	TCAs
	Orthostatic hypotension	TCAs
	Cardiovascular disease	TCAs
	Hepatic disease	Duloxetine
	Oedema	Pregabalin, gabapentin
	Unsteadiness & falls	TCAs
	Weight gain	TCAs, pregabalin, gabapentin

Toronto Expert Panel on Diabetic Neuropathy

TREATMENT OF NEUROPATHIC PAIN

Multiple Dimensions of Neuropathic Pain

- Currently, optimal therapeutic approaches to NP involve interdisciplinary treatment teams working closely together with the
- appropriate use of behavioral medicine, physical medicine, interventional,
- and neuromodulation techniques in conjunction with pharmacologic regimes.

Smith HS, et al . Neuropathic Pain – Definition, Identification, and Implications for Research and Therapy. In, Current Therapy in Pain. Ed. **Smith HS**. Elsevier. Philadelphia, PA. 2009.

PHARMACOLOGIC

Update on pharmacotherapy guidelines for the treatment of neuropathic pain

There currently are five medications approved by the US Food and Drug Administration (FDA) for the treatment of neuropathic pain, which include:

	Approval Year
pregabalin	2004
duloxetine	2004
gabapentin	2002
5% lidocaine patch	1999
carbamazepine	1968

Dobecki DA, et al. Curr Pain Headache Rep. 2006; 10: 185-90.

ANTIDEPRESSANTS

Antidepressant medications may be classified as follows:

1. Cyclic antidepressants, including the tricyclic antidepressants (TCAs) and tetracyclic antidepressants (e.g. maprotiline)
2. Selective serotonin reuptake inhibitors (SSRIs)
3. Serotonin norepinephrine reuptake inhibitors (SNRIs)
4. Dopamine norepinephrine reuptake inhibitors (DNRIs)
5. Norepinephrine reuptake inhibitors (NRIs)
6. Monoamine oxidase inhibitors (MAOIs)
7. The miscellaneous category of “atypical antidepressants”

TCAs

»

- The tertiary amine TCAs include the following:
  - amitriptyline
  - imipramine
  - trimipramine
  - clomipramine
  - doxepin

- The secondary amine TCAs include the following:
  - nortriptyline
  - desipramine
  - protriptyline
  - amoxapine

TCAs
Mechanisms of Analgesia

- Inhibition of Monoamine Reuptake
- Na^+ Channel Blockade
  - Amitriptyline 8x as potent as Lidocaine
- NMDA Receptor Antagonism
- Stimulation of beta (2)-adrenoceptor
- α-Adrenergic Receptor blockade
- Interactions with Other Receptors
  - Opioid
  - Adenosine
  - TRPV1
  - Nicotinic
  - Muscarinic
  - Histaminergic

Beta2-adrenoceptors are essential for desipramine, venlafaxine or reboxetine action in neuropathic pain

- Yalcin et al. shoed that the anticonvulsant gabapentin was still effective in beta(2)-AR deficient mice. Their results demonstrate that beta(2)-ARs are essential for the antiallodynic action of antidepressant drugs.

Yalcin I, et al. Neurobiol Dis 2009; 33:386-394.

Anticholinergic adverse affects are common and include dry mouth, orthostatic hypotension, constipation and urinary retention. These affects can be reduced by starting with low dosages administered at bedtime and with slow titration to higher dosage as well as by using a secondary amine TCAs (e.g., nortriptyline or desipramine).

Limiting the dosages to less than 100 mg per day when possible and obtaining a screening electrocardiogram for patients older than 40 years

Antidepressants

- First-line agents for neuropathic across the board in 3 guidelines (IASP NeuroSig, Canadian, EFNS)

- European Federation of Neurological Societies (EFNS) guidelines – revised 2010
  - Antidepressants remained first-line agents “across the board” in all commonly studied neuropathic pain conditions except trigeminal neuralgia

Antidepressants for neuropathic pain: a Cochrane review

- Sixty-one randomized controlled trials (66 reports) of 31 antidepressants (3293 participants) were considered eligible for inclusion.
- Antidepressants are effective for a variety of neuropathic pains. Both TCAs and venlafaxine have a NNT of approximately 3. This means that for approximately every three patients with neuropathic pain who are treated with either of these antidepressants, one will have at least moderate pain relief who would not have done so with placebo.

Saarto T, et al.J Neurol Neurosurg Psychiatry. 2010 ;81(12):1372-3

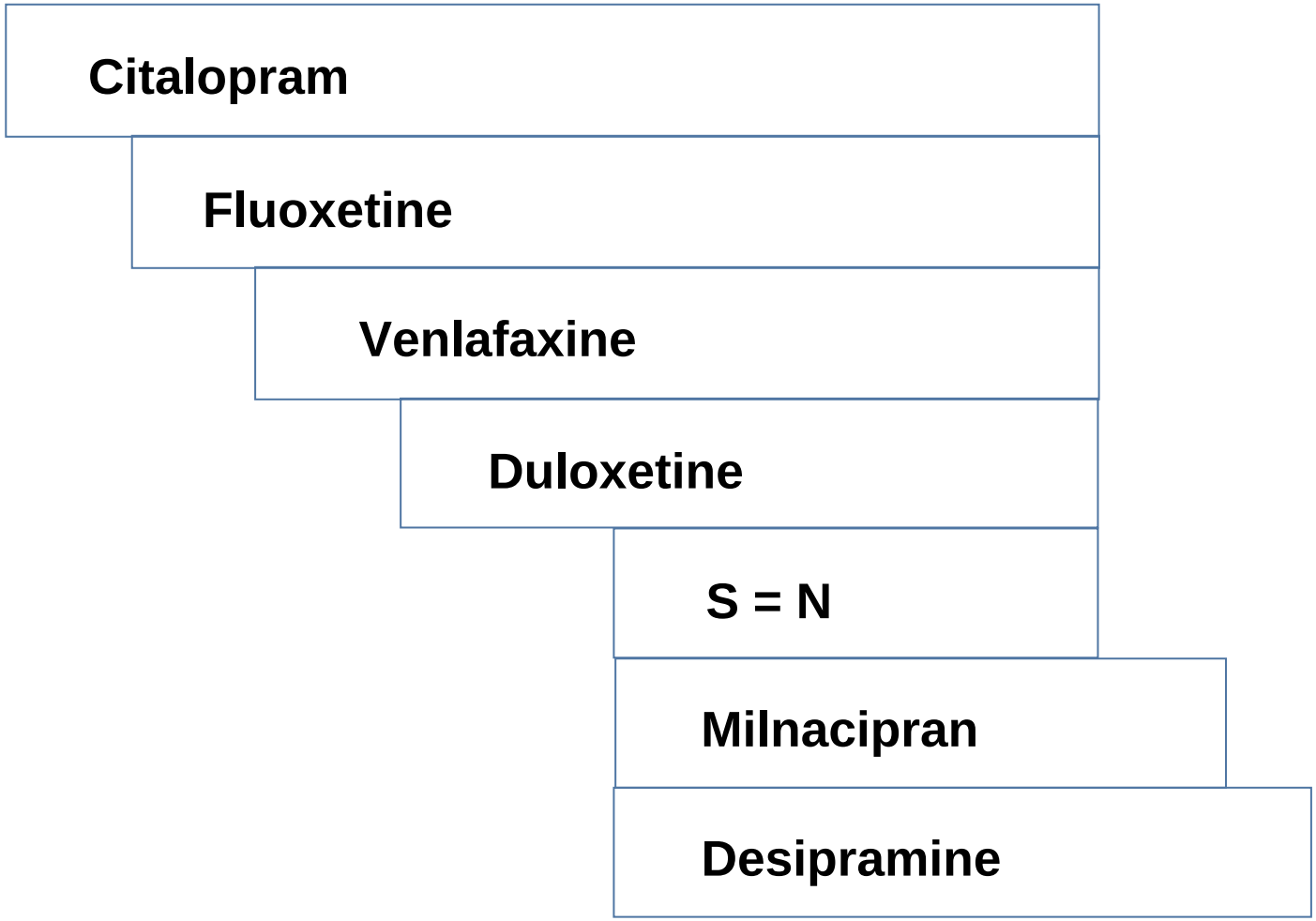
Serotonin Selective Reuptake Inhibitors (SSRIs)– Pharmacokinetic Selective Overview

SSRI-Pharmacotherpy	T12β	Css	CYP450 substrate	CYP450 Inhibitor	PG category
Citalopram	35 hrs	7d	2C19, 3A4	2D6	C
Escitalopram	30 hrs	7d	2C19, 3A4	2D6	C
Fluoxetine (and active metabolite S-nor Fluoxetine	1-16 days	2-4 wks	2C19, 2D6	2C19, 2D6, 3A4	C
Fluvoxamine	16 wks	7d	1A2, 2D6	1A2, 2D6, 2C9, 3A4	C
Paroxetine	21 wks	10d	2D6	2D6	C
Sertraline (includes active desmethyl metabolite)	1-4 days	7d	2C19, 2D6. 3A4	2D6, 3A4	

SNRIs

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)–Pharmacokinetic Selective Overview

SNRI-Pharmacotherpy	T12β	Css	CYP450 substrate	CYP450 Inhibitor	PG category
Duloxetine	8-17 hrs	3d	1A2, 2D6	1A2 (mild), 2D6(moderate)	C
Venlafaxine	5 hr parent 11 hr metabolite	3d	2D6		C
Desvenlafaxine (active metabolite of venlafaxine)	11-15 hr	3-5d	2D6		C
Milnacipran (includes active enantiomer; d-milnacipran)	8-10 hr	1 ½-2d	No CYP450 events	No CYP450 events	C



Relative Activity on Serotonin and Norepinephrine Reuptake Among Antidepressants

S=Serotonin, N=Norepinephrine

Pharmacologic Overview of Duloxetine

- Duloxetine is classified pharmacologically as a serotonin-norepinephrine reuptake inhibitor (SNRI) which possesses high k_i values for monoamine transporters (e.g. serotonin and norepinephrine transporters).
- Duloxetine inhibits serotonin reuptake significantly ore than norepinephrine reuptake (in an approximate 10:1 ratio).

Smith HS, et al. J Central Nervous Syst Disease. 2010: 2:57-72.

Pharmacologic Overview of Duloxetine

- Duloxetine exhibits a peak effect on platelet serotonin reuptake at 4-6 hours. Its inhibition persists for a duration of action of 7 days.
- The maximum plasma concentration (C_{max}) is achieved 6 hours after a post-prandial dose.
- The pharmacokinetics of duloxetine exhibits linearity and the steady-state concentration (C_{ss}) is reached in approximately 3-5 days.

Smith HS, et al. J Central Nervous Syst Disease. 2010: 2:57-72.

Pharmacologic Overview of Duloxetine

- Its absorption and bioavailability are demonstrated to be 30%-80%.
- Duloxetine exhibits a high degree of protein binding (90%) and binds primarily to albumin and alpha-1 acid glycoprotein.
- Duloxetine has a usual half-life of 8-17 hours. Its metabolic pathways include cytochrome P450 1A2 and 2D6.

Smith HS, et al. J Central Nervous Syst Disease. 2010: 2:57-72.

Pharmacologic Overview of Duloxetine – *Adverse Effects*

- Adverse effects that may occur commonly (> 10%) in patients include somnolence, dizziness, headaches, and insomnia. Possible cardiovascular effects include increase in blood pressure, orthostatic hypotension, syncope, and palpitations. Possible gastrointestinal effects include nausea, xerostomia, diarrhea, and constipation. Other adverse effects reported in patients include hyperhidrosis, sexual dysfunction, diminished appetite, and urinary hesitancy.

Smith HS, et al. J Central Nervous Syst Disease. 2010: 2:57-72.

Duloxetine for the management of diabetic peripheral neuropathic pain: evaluation of functional outcomes

- To assess the effectiveness of duloxetine, compared with placebo, on patient-reported health outcomes over a 12-week period, in the management of diabetic peripheral neuropathic pain (DPNP) Armstrong and colleagues pooled results from three 12-week multicenter, double-blind studies (N=1,139).
- In the SF-36 health survey and the BPI interference, duloxetine 60 mg QD and 60 mg BID were significantly superior to placebo in all the domains (P <or= 0.03).
- In the analysis of the EQ-5D, duloxetine 60 mg QD (P = 0.004) and 60 mg BID (P < 0.001) were significantly better than placebo on all items.
- Acute treatment with duloxetine was associated with significant improvement in functional outcomes in persons with DPNP.

Armstrong DG, et al. Pain Med. 2007; 8:410-418.

Safety and tolerability of duloxetine in the acute management of diabetic peripheral neuropathic pain: analysis of pooled data from three placebo-controlled clinical trials

Duloxetine was generally safe and well tolerated, with the three most commonly reported TEAEs being nausea, somnolence and constipation. Modest changes in glycemia were associated with duloxetine. Aspartate transaminase/alanine transaminase increases were transient and not considered predictive of more severe outcomes

Hall JA, et al. Expert Opin Drug Saf. 2010; 9:525-537.

Duloxetine for treating painful neuropathy or chronic pain

- Lunn and colleagues published a Cochrane Systematic Review, selecting all randomized or quasi-randomized trials of any formulation of duloxetine, used for the treatment of painful peripheral neuropathy or fibromyalgia in adult participants.
- Six trials were identified including 2220 participants.
- Three studies included participants with painful diabetic neuropathy and three treated participants with fibromyalgia.
- Duloxetine at 60 mg daily is effective in treating painful diabetic peripheral neuropathy in the short-term to 12 weeks with a risk ratio (RR) for 50% pain reduction at 12 weeks of 1.65 (95% confidence interval (CI) 1.34 to 2.03), number needed to treat (NNT) 6 (95% CI 5 to 10).
- There is moderately strong evidence that duloxetine 60 mg and 120 mg daily are efficacious for treating pain in diabetic peripheral neuropathy and fibromyalgia but 20 mg daily is not.

Lunn MP, et al. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007115.

The effect of venlafaxine HCl on painful peripheral dibetic neuropathy in patients with type 2 diabetes mellitus.

- Venlafaxine HCl is a safe and well-tolerated analgesic drug in the symptomatic treatment of PPDN.

Kadiroglu AK, et al. J Diabetes Complications. 2008; 22:241-245.

CALCIUM CHANNEL ALPHA 2-DELTA LIGANDS

- Gabapentin
- Pregabalin)

- Gabapentin is absorbed slowly after oral administration, with maximum plasma concentrations attained within 3–4 hours.
- Orally administered gabapentin exhibits saturable absorption--a nonlinear (zero-order) process--making its pharmacokinetics less predictable.
- Plasma concentrations of gabapentin do not increase proportionally with increasing dose.
- Orally administered pregabalin is absorbed more rapidly, with maximum plasma concentrations attained within 1 hour.
- Absorption is linear (first order), with plasma concentrations increasing proportionately with increasing dose.
- The absolute bioavailability of gabapentin drops from 60% to 33% as the dosage increases from 900 to 3600 mg/day, while the absolute bioavailability of pregabalin remains at > or = 90% irrespective of the dosage.

Gabapentin adjunctive therapy in neuropathic pain states

- Rosner H, et al. Clin J Pain. 1996; 12:56-58.

- A 2005 systematic review of 15 trials (1468 participants) evaluating gabapentin included 1 acute pain trial and 14 trials in neuropathic (7 in diabetic neuropathy, 2 in postherpetic neuralgia and 1 each in cancer related neuropathy, phantom limb pain, spinal cord injury, Guillain-Barré syndrome and miscellaneous neuropathies). In the 14 chronic neuropathic pain trials, 42% of the participants had pain relief of 50% or greater on gabapentin versus 19% on placebo, and the NNT for improvement in all trials with evaluable data was 4.3 (95% CI, 3.5-5.7).

Wiffen PJ, et al (2005) Cochrane Database Syst Rev Jul 20;(3):CD005452

- In an updated 2011 Cochrane Review evaluating gabapentin for chronic neuropathic pain and fibromyalgia in adults, Moore and colleagues found that gabapentin provides pain relief of a high level in about a third of people who take if for painful neuropathic pain. Using the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) definition of at least moderate benefit, gabapentin was superior to placebo in 14 studies with 2831 participants, 43% improving with gabapentin and 26% with placebo; the NNT was 5.8 (4.8 to 7.2). Using the IMMPACT definition of substantial benefit, gabapentin was superior to placebo in 13 studies with 2627 participants, 31% improving with gabapentin and 17% with placebo; the NNT was 6.8 (5.6 to 8.7).

Moore RA, et al (2011) Cochrane Database Syst Rev Mar 16;3:CD007938

Gabapentin extended release for the treatment of painful diabetic peripheral neuropathy: efficacy and tolerability in a double-blind, randomized, controlled clinical trial

Sandercock D, et al. Diabetes Care. 2009; 32(2):e20.

Efficacy of gabapentin enacarbil vs placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral gabapentin.

- The improvement in mean weekly pain scores from baseline to the end of treatment (primary endpoint) was significantly greater for GEn (−2.1) vs. placebo (−1.2), $P = 0.0321$. Significant improvements from GEn vs. placebo were also seen in sleep, mood, and patient global assessment ($P < 0.05$). With a 31% lower daily dose of gabapentin equivalents, GEn tablets provided a significant increase in average steady state gabapentin concentrations vs. gabapentin capsules in the same patients ($n = 42$; $P = 0.0050$).

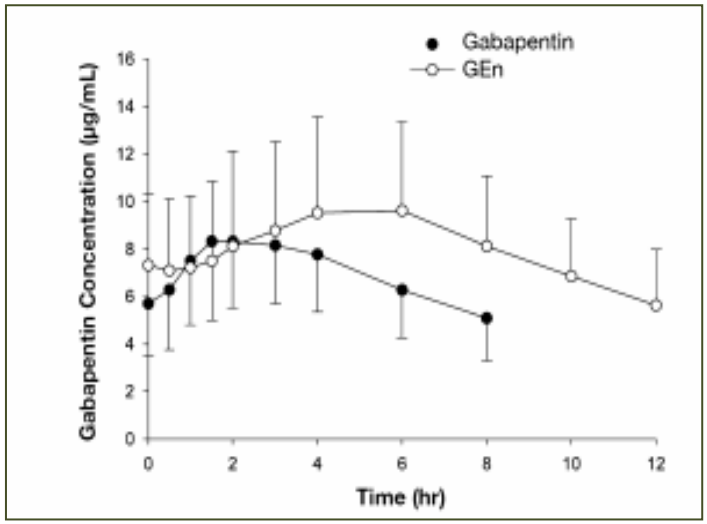
Backonja MM, et al. Pain Med. 2011; 12:1098-1108.

Pharmacokinetic results for patients who received both gabapentin and GEn†

Pharmacokinetic Parameters	Treatment	
	Gabapentin (*n = 42*)	GEn (*n = 42*)
Gabapentin equivalent Dose	1,800 mg	1,248 mg
$C_{ss,ave,}$ μg/mL	6.93 (2.25)	8.10 (2.91)
F, %	43.3 (19.8)‡	76.8 (26.4)‡
$AUC_{(0-24),}$ μg · h/mL	166 (54.1)	194 (69.9
$C_{ss,max,}$ μg/mL	9.07 (3.00)	11.00 (3.99)
$T_{max,}$ hours	2.31 (1.13)	4.63 (2.45)
$T_{1/2,}$ hours	7.23 (3.22)	7.37 (2.97)

† All values are means (standard deviation).
‡ *n = 38.*
$AUC_{(0-24)}$ = daily area under the concentration–vs–time curve at steady state; $C_{ss,ave}$ = steady-state average plasma concentration; $C_{ss,max}$ = steady-state maximum plasma concentration; F = bioavailability; GEn = gabapentin enacarbil; $T_{1/2}$ = apparent elimination half-life; T_{max} = time to maximum steady-state plasma concentration.

Backonja M, et al. Pain Med. 2011; 12:1098-1108.



Comparison of mean SD steady-state concentrations of gabapentin in plasma of 42 patients with postherpetic neuralgia after repeated dosing of either gabapentin (600 mg three times daily) or gabapentin enacarbil (1,200 mg twice daily). GEn = gabapentin enacarbil.

Backonja M, et al. Pain Med. 2011; 12:1098-1108.

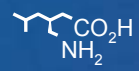
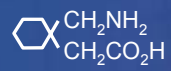
Pregabalin FDA Approved

- Pain Indications
  - Diabetic Peripheral Neuropathy (300 mg/d)
  - Postherptic Neuralgia (150-600 mg/d)
  - Fibromyalgia (300)
- Dosing Strengths
  - 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg
- Initial Dose
  - 150 mg/d in 2-3 divided doses
- Half-life
  - 5-7 hours

Selected Pharmacokinetic/Pharmacodynamic Parameters of Pregabalin

Absorption: well absorbed, ≥ 90% dose independent	**Metabolite: N-methylated derivative (0.9% of dose in urine)**
Metabolism: negligible, not by CYP450 or phase II metabolism	**Tmax:** 1.5 hour (fasting), 3 hour (postprandial) time to peak/maximum concentration
Bioavailability: (F) = 90%, linear, not saturable	**Css:** 24 to 48 hours (multiple dosing)
T½ ß: 6.3 hour (mean) 5.5–6.7 hour range, in presence of normal Clcr (67–80.9 ml/min)	**P-kin:** Cmax (plasma concentration) AUC (plasma concentration time curve), Cmax decreased by 20% to 30% post prandial
Plasma Protein Binding (PPB): none reported	**Vd:** 0.5L/kg
Elimination: renal mechanism, a function of Clcr, renal tubular reabsorption	**Chiral Compound:** S-enantiomer without racemization to R-enantiomer
Excretion: renally (≥ 98% as unchanged parent compound)	**PG category:** C
Note. Clcr = creatinine clearance; ml/min = milliliters per minute.	

Pregabalin and Gabapentin Pharmacology Facts

	Pregabalin 	Gabapentin 
FDA-approved pain indication	Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia	Postherpetic neuralgia
Mechanism of action	α_2-δ ligand • Selectively binds to the α_2-δ site in CNS tissues	α_2-δ ligand • Selectively binds to the α_2-δ site in CNS tissues
Pharmacokinetic profile	Linear • Plasma concentration is dose proportionate	Nonlinear • Plasma concentration increases disproportionately to dose
Oral bioavailability	≥90% all doses	60% 900 mg 47% 1200 mg 34% 2400 mg 33% 3600 mg
Dose potency for PHN	Effective at 150 mg/d • Dose range from 150 mg/d to 600 mg/d*	Effective at 1800 mg/d • No additional benefit at higher doses
Dosing (PHN)	BID or TID	TID
Time to effective dose (PHN)	1 day • Effective starting dose of 150 mg/d	9 or more days • Titrate to effective dose of 1800 mg/d

*Some patients with PHN may benefit from up to 600 mg/d given after 2 to 4 weeks of treatment with 300 mg/d. Adverse events may increase with dose. CNS = central nervous system.

Lyrica® (pregabalin) Capsules CV [package insert]. New York, NY: Pfizer Inc; 2005; Neurontin® (gabapentin) [package insert]. New York, NY: Pfizer Inc; 2004.

PREGABALIN

CC (ml/min)	Dose (mg)			
≥60 BID/TID	150	300	450	600
30–59 BID/TID	78	150	225	300
15–29 PD/BID	25–50	75	100–150	150
< 15 QD	25	25–50	50–75	75

- Moore et al. performed a 2009 Cochrane Review of pregabalin for acute and chronic pain. For chronic pain, pregabalin at 150 mg daily was generally ineffective. Efficacy was demonstrated for dichotomous outcomes equating to moderate or substantial pain relief, alongside lower rates for lack of efficacy discontinuations with increasing dose. The best (lowest) NNT for each condition for at least 50% pain relief over baseline (substantial benefit) for 600 mg pregabalin daily compared with placebo were 3.9 (95% confidence interval 3.1 to 5.1) for postherpetic neuralgia, 5.0 (4.0 to 6.6) for painful diabetic neuropathy, 5.6 (3.5 to 14) for central neuropathic pain, and 11 (7.1 to 21) for fibromyalgia. The FDA has improved pregabalin for treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia and for treatment of fibromyalgia; evidence from these trials is discussed under specific disorders.

Moore RA, et al (2009) Cochrane Database Syst Rev Jul 8;(3):CD007076

Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial

- One hundred sixty-five (65%) had a $\geq$30% pain improvement and 157 were randomized and treated, double blind, to either continue pregabalin (n=80) or to receive placebo (n=77) for 5 weeks.
- Gilron et al. concluded that their results support previous evidence of pregabalin efficacy but further demonstrate efficacy and tolerability in a broader range of peripheral neuropathic pain conditions beyond DPN and PHN.

Gilron I, et al. Clin J Pain. 2011; 27:185-193..

OPIOIDS

Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain

Arnér S, et al. Pain. 1988; 33:11-23.

Are opioids effective to provide analgesia for patients with neuropathic pain?

YES

Circumstances in which opioid analgesics and tramadol can be considered for first-line treatment of neuropathic pain

- During titration of a first-line medication to an efficacious dosage for prompt pain relief
- Episodic exacerbations of severe pain
- Acute neuropathic pain
- Neuropathic cancer pain

Dworkin RH, et al. Pain. 2007; 132: 237-251.

Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials

- Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain.
- Intermediate-term studies demonstrate significant efficacy of opioids over placebo for neuropathic pain, which is likely to be clinically important.
- Reported adverse events of opioids are common but not life-threatening.
- Further RCTs are needed to establish their long-term efficacy, safety (including addiction potential), and effects on quality of life.

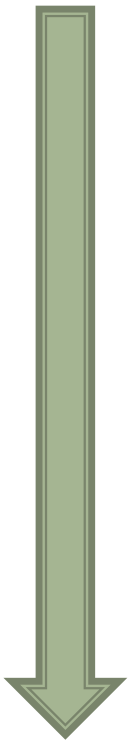
Eisenberg E, et al. JAMA. 2005;293(24):3043-52.

Efficacy of mu-opioid agonists in the treatment of evoked neuropathic pain: Systematic review of randomized controlled trials

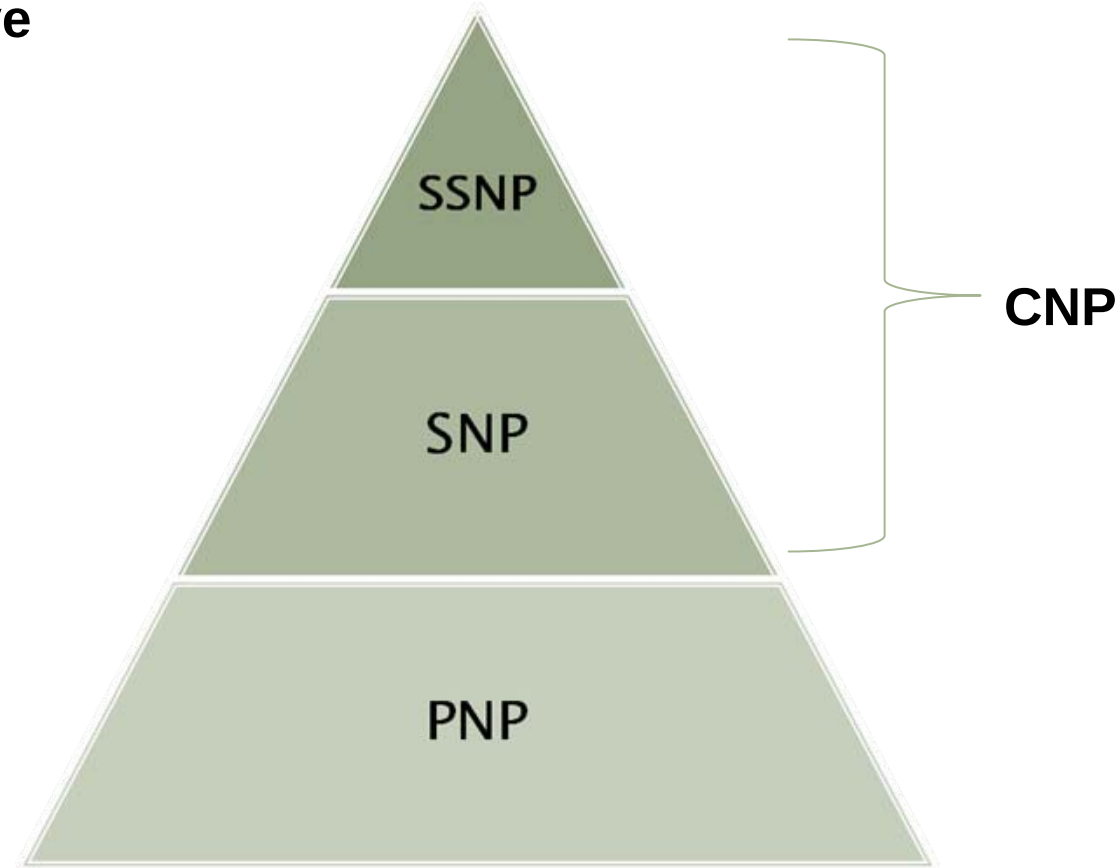
- Short-term studies show that opioids can reduce the intensity of dynamic mechanical allodynia and perhaps of cold allodynia in peripheral NP.
- Insufficient evidence precludes drawing conclusions regarding the effect of opioids on other forms of evoked NP.
- A meta-analysis of intermediate-term studies demonstrates the efficacy of opioids over placebo for evoked NP.

Eisenberg E, et al. Eur J Pain. 2006 Nov;10(8):667-76.

Poorly Opioid Responsive

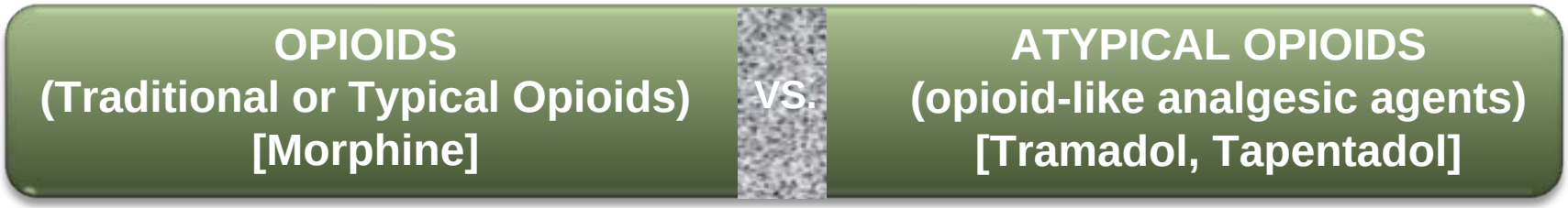


Opioid Responsive



Not all opioids are created equally---?

Some opioids are particularly useful for providing analgesia from neuropathic pain



OPIOIDS

- **Morphine**
- **Tramadol**
- **Tapentadol**

TRAMADOL

Clinical Pharmacology of Tramadol

Tramadol, a centrally acting analgesic structurally related to codeine and morphine, consists of two enantiomers, both of which contribute to analgesic activity via different mechanisms.

Grond S, Sablotzki A. Clin Pharmacokinet. 2004;43(13):879-923

Clinical Pharmacology of Tramadol

- (+)-Tramadol and the metabolite (+)-O-desmethyl-tramadol (M1) are agonists of the mu opioid receptor. (+)-Tramadol inhibits serotonin reuptake and (-)-tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord.

- Tramadol is available as drops, capsules and sustained-release formulations for oral use, suppositories for rectal use and solution for intramuscular, intravenous and subcutaneous injection.

Grond S, Sablotzki A. Clin Pharmacokinet. 2004;43(13):879-923

Tramadol hydrochloride tables

PHARMACOKINETICS	
Bioavailability*	75%
Onset of activity	1 h
Time to peak serum concentration	2 – 3 h
Protein Binding	20%
Metabolism	Extensively metabolized. One active metabolite – M1
Urinary excretion	30% unchanged, 70% metabolites
Elimination half-life	6.3 h for the parent compound 7.4 h for the M1 Metabolite
**Unaffected by food*	

The results of this placebo-controlled trial showed that tramadol was effective and safe in treating the pain of diabetic neuropathy.

- Harati Y, et al. Neurology. 1998; 50:1842-1846.

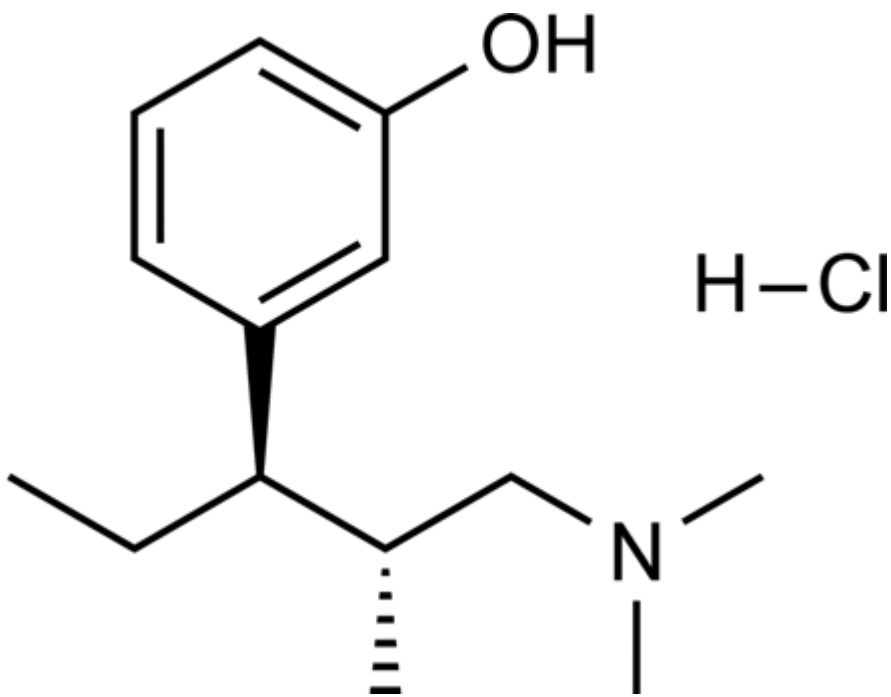
Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy.

Tramadol/APAP was more effective than placebo and was well tolerated in the management of painful DPN.

Freeman R, et al. Curr Med Res Opin. 2007; 23:147-161.

Tapentadol Hydrochloride

Chemical structure of tapentadol HCl



Tzschentke TM, et al. J Pharmacol Exp Ther. 2007; 323(1):265-276.

Tapentadol extended-release for treatment of chronic pain: a review.

Background

- Tapentadol is a novel centrally acting analgesic, initially formulated as an immediate-release preparation. It is a potent Schedule II analgesic approved for use by the US Food and Drug Administration (FDA) in 2009.
- Tapentadol immediate-release is available as 50, 75, and 100 mg tablets and provides 4–6 hours of analgesia. Tapentadol immediate-release was shown to provide analgesia comparable with that of 10–15 mg of immediate-release oxycodone in patients recovering from dental extraction pain3 and pain following bunionectomy.
- It was also as effective as oxycodone in patients presenting with chronic osteoarthritis pain and chronic low back pain.
- Of importance in the comparator trials was the finding that patients treated with tapentadol had a lower incidence of adverse gastrointestinal events, including nausea, vomiting, and constipation, than those treated with oxycodone.

Vadovelu N, et al. J Pain Res. 2011;4:211-8.

Tapentadol extended-release for treatment of chronic pain: a review. *Pharmacology*

- Tapentadol produces potent analgesic effects via its dual mechanism of action, i.e., mu receptor agonism and norepinephrine reuptake inhibition.
- In animal models, tapentadol behaves as a weak opioid agonist, with 50 times less affinity than morphine for the mu receptor.
- Tapentadol exists as a single active enantiomer and is metabolized mainly by O-glucuronidation.
- Its principal metabolite is inactive, having no affinity for the mu receptor or the norepinephrine transporter.
- Because the analgesic activity of tapentadol is limited to the primary molecule, no enzymes are needed to convert it to an active metabolite, as is the case for tramadol and codeine.

Vadovelu N, et al. J Pain Res. 2011;4:211-8.

Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial

Compared with placebo, tapentadol ER 100–250 mg bid provided a statistically significant difference in the maintenance of a clinically important improvement in pain and was well-tolerated by patients with painful DPN.

Schwartz S, et al. Curr Med Res Opin. 2011; 27:151-162.

Tapentadol extended-release for treatment of chronic pain: a review.

Extended-release preparation

- The controlled release formulation provides a 12-hour duration of activity, as well as the convenience and analgesic uniformity associated with twice per day dosing.

Vadovelu N, et al. J Pain Res. 2011;4:211-8.

The effects of hepatic dysfunction on Tapentadol Pharmacokinetics

Pharmacokinetic Parameter	Mild Hepatic Dysfunction	Moderate Hepatic Dysfunction
AUC	1.7x	4.2x
Cmax	1.4x	2.5x
T½β	1.2x	1.4x

With respect to neuropathic pain – ALL OPIOIDS MAY NOT BE CREATED EQUALLY

- Certain opioids may be particularly well suited for the treatment of neuropathic pain
  - Tapentadol
  - Methadone
  - Buprenorphine

Methadone in the management of intractable neuropathic noncancer pain

- A case series of 50 consecutive noncancer pain patients who were seen at a tertiary care centre who had failed multiple treatments including: antidepressants, anticonvulsants, opioids, spinal cord stimulation were treated with oral methadone for a variety of intractable neuropathic pain states.
- Twenty-six patients (52%) reported mild (4), moderate (15), marked (6) or complete (1) pain relief and continued on methadone at a mean maintenance dose of 159.8 mg/day for a mean duration of 21.3 months. Fourteen patients (28%) reported improved function on methadone relative to previous treatments.

Moulin DE, et al. Can J Neurol Sco. 2005; 32: 340-343.

- Methadone to treat non-oncologic neuropathic pain. Case reports.
  - Juver JP, et al. Rev Bras Anestesiol. 2005; 55:450-459.

- Management of chronic neuropathic pain with methadone: a review of 13 cases.
  - Altier N, et al. Clin J Pain. 2005; 21:364-369.

- Methadone for cancer-related neuropathic pain: a review of the literature.
  - Mannino R, et al. J Opioid Manag. 2006; 2:269-276.

Characteristics of Buprenorphine

Partial mu receptor
NoCiceptin Opioid Peptide (NOP) Receptor (Orphan-related ligand—1 receptor partial/full agonist)
Kappa receptor antagonist
Different G protein interactions than potent opioids
Blocks central sensitization by several mechanisms
Prolonged receptor occupancy
Highly lipophilic
Large volume of distribution
Long half-life
Slow clearance by liver via CYP3A4 and conjugases
Non-cross tolerant to potent analgesics

Induru RR, et al. 2009; 26:470-3

Buprenorphine for Neuropathic Pain—Targeting Hyperalgesia

- The difference in analgesic responses between buprenorphine and other potent opioids may be due to different receptor G protein interactions.
- Buprenorphine and methadone demonstrate significant differences in activation of G proteins; G-a i1, G-a o1, and G-a 11 are necessary for methadone-induced analgesia but not buprenorphine antinociception.
- In turn, buprenorphine requires G-a o2 and G-a Q.

Induru RR, et al. 2009; 26:470-3

Buprenorphine Transdermal System

- Do not cut
- Worn for 7 days
- Apply upper outer arm, upper back, upper chest or the side of the chest (8 possible sites)
- Rotate sides --- wait 21 days before re-using same site; clip hairs as needed

Opioid-Naive

Oral Morphine Equivalent < 30 mg → *Buprenorphine Transdermal System* **5 mcg/h**

↓

After 72 hrs

↓

Oral Morphine Equivalent 30-80 mg/d → *Buprenorphine Transdermal System* **10 mcg/h**

↓

After 72 hrs

↓

Buprenorphine Transdermal System **20 mcg/h**

||

Maximum Dose

Higher doses may ↑ QTc prolongation

Buprenorphine may show a distinct benefit in improving neuropathic pain symptoms, which is considered a result of its specific pharmacological profile.

Pergolizzi J, et al. Pain Pract. 2008; 8: 287-313.

- Buprenorphine—a review of its role in neuropathic pain.
  - Hans G. J Opioid Manag. 2007; 3:195-206.
- Transdermal Buprenorphine for Central Neuropathic Pain: Clinical Reports.
  - Guetti C, et al. Pain Pract. 2010; In press.
- Buprenorphine for Neuropathic Pain --- Targeting Hyperalgesia.
  - Induru RR, et al. Am J Josp Palliat Care. 2009; 26:470-473.

TOPICAL THERAPIES

Lidocaine Patch

- 5% Lidocaine Patch
- 10x14 cm
- Contains 700mg Lidocaine
- 12 hours per day

Lidocaine Patch

Long term use ---

3 Patches/Day

Max Lido Bld Conc $\leq$ 0.13 mcg/ml

~ 1/10 Therapeutic conc (204 mcg/ml)

~ 1/32 Toxic conc

---

4 Patches/Day (18 h/d) x3d

Max conc < (0.3 mcg/ml)

---

4 Patches/Day x (24h/d) x 3d

conc $\approx$ (0.186 mcg/ml)

4 Patches/Day --- (12hon/12hon) x3d

conc $\approx$ (0.225 mcg/ml)

Gammaitoni AR, et al
Am J Health Syst Pharm. 2001

Cancer Pt 10 Patches/Day (24h/d)

x4mon conc $\approx$ (0.47 mcg/ml)

Wilhelm IR, et al
J Pain Sympt Mgt. 2005

An open-label study of the lidocaine patch 5% in painful idiopathic sensory polyneuropathy.

Herrmann DN, et al. Pain Med. 2005; 6(5): 379-84

Topical lidocaine for the treatment of postherpetic neuralgia

- There is insufficient evidence to recommend topical lidocaine as a first-line agent in the treatment of postherpetic neuralgia with allodynia.

Khaliq W, et al. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD004846.

A New Combination Cream for the Treatment of Severe Neuropathic Pain

A novel combination topical cream, consisting of isosorbide dinitrate (ISDN) 04%, capsaicin 0.075%, and lidocaine 3% appeared effective in ameliorating severe neuropathic pain with DPN.

Kopsky DJ, et al. Letters 2010; 29:e9.

TOPICAL CAPSAICIN

- A high potency (8%) capsaicin patch is FDA approved for the treatment of postherpetic neuralgia pain.
- It is thought to diminish pain sensation by reducing transient receptor potential vanilloid 1 (TRPV1) expression and decreasing the density of epidermal nerve fibers in the application area.
- A single sixty minute application may provide up to twelve weeks of analgesia.

Tolerability of NGX-4010, capsaicin 8% patch, in conjunction with three topical anesthetic formulations for the treatment of neuropathic pain

- Up to four NGX-4010 patches of 280 cm^2 could be used (maximum treatment area of 1120 cm^2).

Webster L, et al. J Pain Res. 2011; In Press.

NGX-4010, a high-concentration capsaicin dermal patch for lasting relief of peripheral neuropathic pain

- NGX-4010 contains (640 mcg/cm (2) [8% trans-capsaicin]) that can be applied for 60 minutes to the painful skin area up to a total surface area of 1120 cm2. In phase I/II trials, NGX-4010 was well tolerated and effective in reducing pain in patients with post-herpetic neuralgia (PHN).

Noto C, et al. Curr Opin Investig Drugs. 2009; 10(7):702-710.

NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind study

- In a randomized, double-blind study, one 60-min application of NGX-4010 provided rapid and sustained pain relief in patients with postherpetic neuralgia. No adverse events were associated with treatment except for local reactions at the site of application and those related to treatment-associated pain.
- Patients with postherpetic neuralgia who were randomly assigned to NGX-4010 (n=206) had a significantly greater reduction in pain during weeks two to eight than did patients who had the control patch (n=196). The mean changes in NPRS score were -29.6%vs -19.9% (difference -9.7%, 95% CI -15.47 to -3.95; p=0.001). 87 (42%) patients who received NGX-4010 and 63 (32%) controls had a 30% or greater reduction in mean NPRS score (odds ratio [OR] 1.56, 95% CI 1.03 to 2.37; p=0.03).

Backonja M, et al. Lancet Neurol. 2008;7(12):1106-12

- Derry and colleagues performed a Cochrane Review in 2009 which included six studies (389 participants) comparing 0.075% capsaicin cream with placebo cream and two studies comparing 8% capsaicin patch with placebo patch.
- They concluded that capsaicin, either as repeated application of a low dose (0.075%) cream or a single application of an 8% patch may provide a clinically significant degree of pain relief to some patients with neuropathic pain.

NGX-4010, a Capsaicin 8% Dermal Patch, Administered Alone or in Combination With Systemic Neuropathic Pain Medications, Reduces Pain in Patients With Postherpetic Neuralgia

- A single 60-minute NGX-4010 treatment reduces PHN for up to 12 weeks regardless of concomitant systemic neuropathic pain medication use.

Irving GA, et al. Clin J Pain. 2001; In Press.

Tolerability of NGX-4010, capsaicin 8% patch, in conjunction with three topical anesthetic formulations for the treatment of neuropathic pain

- Established treatments for neuropathic pain are limited as they provide only partial pain relief in an estimated 40–60% of patients, and many are associated with a variety of unwanted systemic effects and intensive daily regimens.
- Capsaicin results in defunctionalization of TRPV1-expressing sensory nerve endings and reduced epidermal nerve fiber density.

Webster L, et al. J Pain Res. 2011; In Press.

Tolerability of NGX-4010, capsaicin 8% patch, in conjunction with three topical anesthetic formulations for the treatment of neuropathic pain

- Webster et al. conducted an open-label study to determine whether similar tolerability could be achieved with other commonly available 4% lidocaine formulations, and assessed the safety, tolerability, and efficacy of NGX-4010 following pre-treatment with either L.M.X.4, or the alternative products Topicaine Gel or Betacaine Enhanced Gel 4 and found there was little or no difference.

Webster L, et al. J Pain Res. 2011; In Press.

NMDA RECEPTOR ANTAGONISTS

Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials

- In the efficacy trial, among patients with DN, 400of dextromethorphan reduced pain intensity by a mean of 33% from baseline, memantine reduced pain intensity by a mean of 17%, and lorazepam reduced pain intensity by a mean of 16%; the proportions of subjects achieving greater than moderate pain relief were 68% with dextromethorphan, 47% with memantine, and 37% with lorazepam.
- Dextromethorphan is effective in a dose-related fashion in selected patients with DN. This was not true of PHN.

Sang CN, et al. Anesthesiology. 2002; 96:1053-1061.

ALPHA-2 AGONISTS

Current Therapy: Pharmacologic Properties of α_2-Agonists

Drug	Clonidine	Tizanidine	Dexmedetomidine
Formulations available	Oral (Catapres) Transdermal (Catapres TTS) Epidural (Duraclon)	Oral: tablet, capsule (Zanaflex)	Intravenous (Precedex)
Time to peak effect	Oral: 3-5 hours Transdermal: 48 hours Epidural: 19 minutes	1 hour (fasted state) 1.5-3 hours (fed state)	60 minutes
$T_{1/2}$	Elimination: 12-16 hours	2-2.5 hours	Distribution: 6 minutes Elimination: 2 hours
Route of metabolism/ elimination	Hepatic: 50% Renal: 40-60%	Hepatic: 95% with renal (60%) and fecal (20%) excretion of metabolites	Hepatic (nearly 100%)
Dosage	Oral: 0.2-2.4 mg/day Transdermal: 0.1-0.6 mg/day Epidural: 30-40 mcg/hour; maximum single dose 700 mcg	4-36 mg total per day (limited information exists for long term use of single doses greater than 8-12 mg or total daily doses greater than 24-36 mg)	Loading: 1 mcg/kg Maintenance: 0.2-0.7 mcg/kg/hour

Elliott J. In: Current Therapy in Pain. Smith HS (ed). Elsevier. Philadelphia, PA. 2009; pp3476-480.

Dexmedetomidine and clonidine inhibit the function of Na(V)1.7 indendent of α (2)-adrenoceptor in adrenal chromaffin cells

- Dexmedetomidine and clonidine inhibit the function of Na(v)1.7 independent of α (2)-adrenoceptor.

Marura T, et al. J Anesth. 2011; 25:549-557.

OTHER AEDS

Carbamazepine for acute and chronic pain in adults

- Carbamazepine is effective in chronic neuropathic pain

Wiffen PJ, et al. Cochrane Database Syst Rev. 2011 Jan 19; (1):CD005451

Topiramate

- Topiramate is a sulfamate-substituted monosaccharide. Electrophysiological and biochemical studies show it to be associated with voltage-dependent Na^+ and $Ca2^+$ channel blockade, increased GABA activity and inhibition of a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptors.

Smith HS, et al. Drugs. 2011; 71:557-589.

Topiramate vs. placebo in painful diabetic neuropathy: analgesic and metabolic effects

Conclusions:

Topiramate monotherapy reduced pain and body weight more effectively than placebo in patients with painful diabetic neuropathy.

Baskin P, et al. Neurology. 2004; 63: 865-73

Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials

Conclusion:

These studies did not find topiramate to be significantly more effective than placebo in reducing pain scores in patients with painful diabetic polyneuropathy.

Thienel U, et al.
Acta Neurol Scand. 2004; 110: 221-31

SKELETAL MUSCLE RELAXANTS

- Most muscle relaxants are FDA approved for either spasticity (baclofen, dantrolene and tizanidine) or musculoskeletal conditions (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol or orphenadrine) . The mechanism of action for the latter category of agents is unclear, but may be related in part to sedative effects.

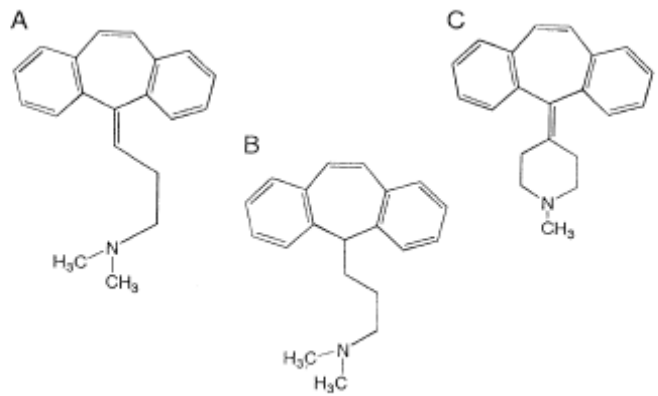
Chou R, et al. (2004) J Pain Symptom Manage 28:140-175

Orphenadrine

- Methylated Derivation of Diphenhydramine
- Doses
  - Oral: 100 mg
  - Parent: 60 mg

Orphenadrine is known to have the following pharmacology:

- mACh receptor antagonist (anticholinergic)
- H_1 receptor antagonist (antihistamine)
- NMDA receptor antagonist
- NET blocker (norepinephrine reuptake inhibitor)
- Na_v 1.7, Na_v 1.8, and Na_v 1.9 sodium channel blocker
- HERG potassium channel blocker



Chemical structures of cyclobenzaprine (A), amitriptyline (B) and cyproheptadine (C).

Baclofen

- GABA-B Agonist
- Pre- and Post-synaptic action
- Pre-synaptic $\downarrow Ca^{++}$ conduction with resultant $\downarrow$ EAA/SP release
- Post-synaptic $\downarrow K^{+}$ Conductance
  $\rightarrow$ Neuronal hyperpolarization

Baclofen as an adjuvant analgesic for cancer pain

- Of the cancer patients reviewed, 80% had a component of neuropathic pain such as paroxysmal or lancing, sharp, or like an electric shock. Overall, baclofen was effective in 84% of patients and significantly reduced Numeric rating Scale pain Score, 0–10; $P > .0001$).

Yomiya K, et al. Am J Hosp Palliat Care. 2009; 26:112-118.

INTRAVENOUS LIDOCAINE

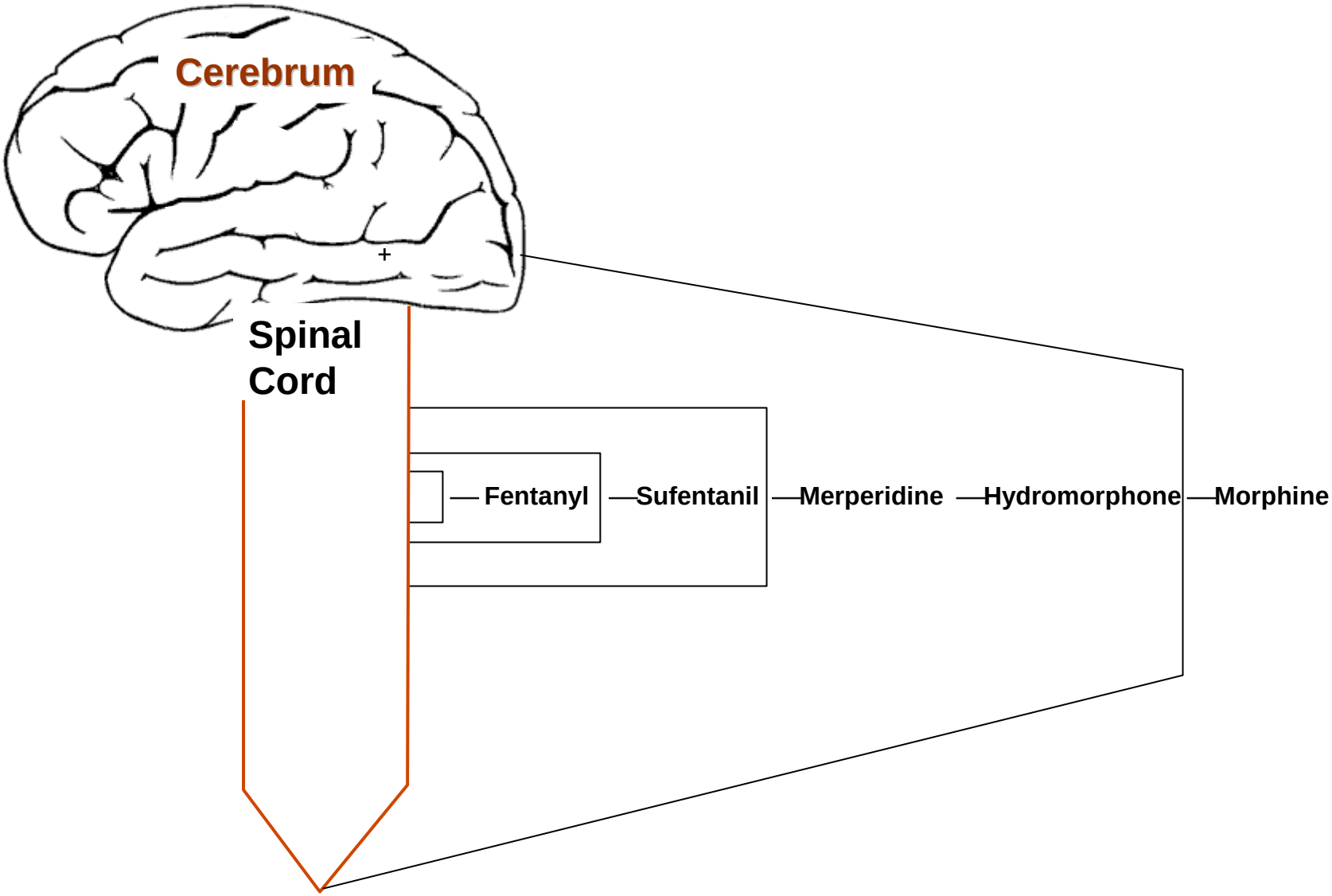
Systematic administration of local anesthetic agents to relieve neuropathic pain

Lidocaine and oral analogs were safe drugs in controlled clinical trials for neuropathic pain, were better than placebo, and were as effective as other analgesics

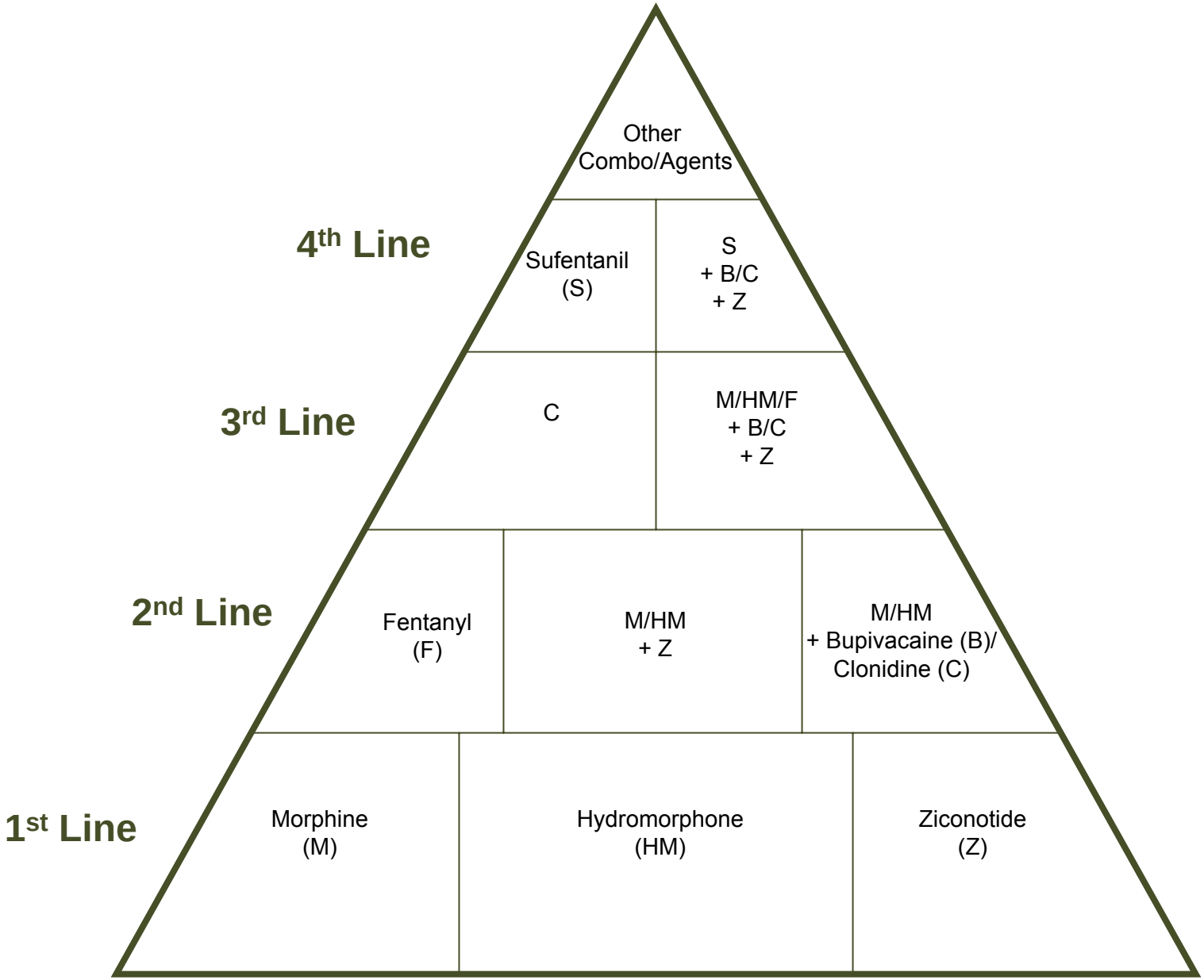
Challapalli V, et al. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD003345.

INTRATHECAL ANALGESICS

Intrathecal Opioids



Smith HS. Pain Physician. 2009, 12: 269-280.



Intrathecal Analgesic Therapies

Smith HS, et al. Pain Physician. 2008, 11:S89-S104.

Recommended Maximum Intrathecal Dosages and Concentrations

Drug	Dosage (mg/day)	Concentration (mg/mL)
Morphine	15	30
Hydromorphone	10	30
Bupivacaine	30	38
Clonidine	1.0	2.0

Hassenbush S, et al.
Journal of Pain and Symptom Management. 2004; 27: 540-63

Botulinum Toxins for Analgesia

- In a landmark 2008 article in *Annals of Neurology, Ranoux* et al.have convincingly demonstrated that botulinum toxin type A (BTX-A) may provide direct analgesic effects in patients with focal chronic neuropathic pain independent of its effects on tone.

Smith HS. Pain Physician 2009; 12:479-481

Subcutaneous injection of botulinum toxin a is beneficial in postherpetic neuralgia

Subcutaneous administration of BTX-A significantly decreased pain in PHN and reduced opioid use compared with lidocaine and placebo at day 7 and 3 months post-treatment. It also increased subjects' sleep times.

Xiao L, et al. Pain Med. 2010; 11:1827-1833.

Mechanisms underlying purinergic P2X3 receptor-mediated mechanical allodynia induced in diabetic rats

- The mechanical allodynia was significantly attenuated by peripheral administration of the P2X receptor antagonists, PPADS or TNP-ATP.
- The expression of P2X3 receptor proteins in the plasma membrane of L4-6 DRGs of STZ rats was significantly enhanced while the total expression of P2X3 receptors remained unaltered.
- Suggesting that an increase in the membrane expression of P2X3 receptors contribute to the development of chronic pain in STZ-induced diabetic rats .

Xu GY, et al. Mol Pain. 2011; In Press.

Botulinum Toxin Decreases Hyperalgesia and Inhibits P2X(3) Receptor Over-Expression in Sensory Neurons Induced by Ventral Root Transection in Rats

Xiao L, et al. Pain Med. 2011; In Press.

INTRATHECAL ZICONOTIDE

Safety and efficacy of intrathecal ziconotide in the management of severe chronic pain

- The US Food and Drug Administration (FDA) approved ziconotide on December 28, 2004 for the management of severe chronic pain in patients whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatments, such as systemic analgesics, adjunctive therapies, or IT morphine

Smith HS, et al. Ther Clin Risk Manag. 2009 ;5(3):521-34.

Possible side effects of ziconotide may include:

- an allergic reaction,
- nausea, vomiting, seizures, fever, headache, and/or stiff neck (e.g., meningitis),
- a change in mental status (cognitive and neuropsychiatric alterations) (extreme tiredness, asthenia, confusion, disorientation or decreased alertness),
- a change in mood or perception (hallucinations, unusual feelings in the mouth),
- postural hypotension, abnormal gait, urinary retention, nystagmus/amblyopia
- drowsiness/somnolence (reduced level of consciousness),
- dizziness or lightheadedness, weakness,
- visual problems (e.g., double vision),
- elevation of serum creatine kinase, or
- vestibular side effects.

Vestibular side effects may be due to ziconotide blocking N-type calcium channels in the granular cell layer of the cerebellum.

Smith HS, et al. Ther Clin Risk Manag. 2009 ;5(3):521-34.

Regulation of spinal substance p release by intrathecal calcium channel blockade

- Takasuski and Yaksh suggested that ziconotide contributes to antinociception at least in part by inhibiting spinal N-type not voltage sensitive calcium channel resultant with inhibition of the stimulus-evoked substance P release from small primary afferents.

Talasuski T, et al. Anesthesiology. 2011; 115:153-164.

Experience in treatment of patients with neuropathic facial pain using ziconotide

Lux EA, et al. Schmerz. 2011; 25:434–439.

Trigeminal neuralgia relief with intrathecal ziconotide

- Michiels WB, et al. Clin J Pain. 2011; 27:352-354.

Intrathecal ziconotide for neuropathic pain: a review

- Twenty-eight articles met the inclusion criteria: 5 were preclinical studies and 23 were clinical studies. In the preclinical studies, ziconotide demonstrated antiallodynic effects on neuropathic pain. Data from double-blind, placebo-controlled (DBPC) trials indicated that patients with neuropathic pain reported a mean percent improvement in pain score with ziconotide monotherapy that ranged from 15.7% to 31.6%.
- A low starting dose and slow titration of ziconotide resulted in an improved safety profile in the aforementioned trials. Common AEs associated with ziconotide include nausea and/or vomiting, dizziness, confusion, urinary retention, and somnolence. Evidence from DBPC trials, open-label studies, case series, and case studies suggests that ziconotide, as either monotherapy or in combination with other IT drugs, is a potential therapeutic option for patients with refractory neuropathic pain.
- Additional studies are needed to establish the long-term efficacy and safety of ziconotide for neuropathic pain.

Rauck RL, et al. Pain Pract. 2009; 9: 327-337.

Ziconotide or MVIIA in Rat Models of Neuropathic Pain

Reference	Model(s) Studied	Results
Bowersox et al.	SSNL	Both bolus IT injections and continuous IT infusions of ziconotide reversibly blocked mechanical allodynia; no evidence of tolerance was noted
Chaplan et al.	SSNL	IT bolus injections of ziconotide produced dose-dependent suppression of tactile allodynia
Scott et al.	SSNL	IT bolus injections of MVIIA attenuated tactile allodynia in a dose-dependent manner
Xiao and Bennett	CCI	Ziconotide applied to the site of nerve injury reduced heat hyperalgesia and mechanical allodynia; mechanical hyperalgesia was not affected by ziconotide
Yamamoto and Sakashita	CCI PSNL	Bolus IT injection of MVIIA decreased thermal hyperalgesia Bolus IT injection of MVIIA had no significant effect on thermal hyperalgesia

SSNL, segmental spinal nerve ligation; IT, intrathecal; CCI, chronic constriction injury; PSNL, partial sciatic nerve ligation.

Rauck RL, et al. Pain Pract. 2009; 9:327-337.

Efficacy of Ziconotide in the Treatment of Neuropathic Pain Among Populations in Double-blind, Placebo-Controlled Studies

Reference	Ziconotide-Treated Patients With Neuropathic Pain, No.	Duration of Titration Period	Mean Improvement in VASPI Score From Baseline to End of Titration, %*
Rauck et al.	85	3 weeks	15.7
Wallace et al.	124	6 days	31.6
Collins et al.†	NA	Varied	29.1

† Analyses included patients from 3 double-blind, placebo-controlled trials of ziconotide.
NA, not available.

Rauck RL, et al. Pain Pract. 2009; 9:327-337.

The efficacy of most agents against neuropathic pain is roughly in the same ball park

Gabapentin versus notriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial---the GONIP Trial

- Gabapentin was shown to be equally efficacious but was better tolerated to nortriptyline and can be considered a suitable alternative for the treatment of PHN.

Chandra K, et al. Int J Clin Pharmacol Ther. 2006; 44:358-363.

Comparison of the efficacy and safety of tramadol/acetaminophen combination therapy and gabapentin in the treatment of painful diabetic neuropathy

- Subjects were randomized to receive either tramadol (37.5 mg)/acetaminophen (325 mg) or gabapentin (300 mg) for 6 weeks.
- At the final visit, the mean doses were 1575 mg/day for gabapentin and 4.22 tablets/day for T/A
- Both groups had similar improvements in every Short Form Health Survey category and Brief Pain Inventory subcategory, and in the mean pain relief scores.
- This study suggests that the T/A combination treatment is as effective as gabapentin in the treatment of painful diabetic neuropathy in patients with Type 2 diabetes.

Ko Sh, et al. Diabet Med. 2010; 27:1033-1040.

Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study.

Venlafaxine ER appears effective and safe in relieving pain associated with diabetic neuropathy. NNT values for higher dose venlafaxine ER are comparable to those of tricyclic antidepressants and the anticonvulsant gabapentin.

Rowbotham MC, et al. Pain. 2004; 110:697-706..

Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain

- Although both drugs provide pain relief, mean pain score and global pain score data indicate no significant difference between gabapentin and amitriptyline.

Morello CM, et al. Arch Intern Med. 1999; 159:1931-1937.

Toward a definition of pharmacoresistant neuropathic pain

‘‘A neuropathic pain condition is resistant to pharmacotherapy when mono- or a rational combination treatment using drugs proven efficacious in RCTs fails in inducing useful pain relief from the patients/physicians point of view after an appropriate duration of treatment with adequate dosage, or if intolerable side effects occur”.

Hansson PT. Eur J Pain. 2009; 13: 439-440.

Toward a definition of pharmacoresistant neuropathic pain

Drug classes that have proven efficacious in RCTs including tricyclic antidepressants (e.g., amitriptyline and nortriptyline), serotonin norepinephrine reuptake inhibitors (duloxetine and venlafaxine), alpha-2-delta ligands (gabapentin and pregabalin) and opioids (oxycodone, morphine, methadone and tramadol). Also, topical lidocaine for small areas of pain/mechanical allodynia and sodium channel blockers (carbamazepine and oxcarbazepine) in trigeminal neuralgia should be considered.

Hansson PT. Eur J Pain. 2009; 13: 439-440.

Polypharmacy

- Controlled studies have only provided evidence in favour of combining gabapentin with opioids or gabapentin and venlafaxine. A rational approach would be to combine drugs from the drug classes that have proved efficacious in relieving neuropathic pain

Hansson PT. Eur J Pain. 2009; 13: 439-440.

Rational Polypharmacy

"Combination Treatment"

"Cocktail Therapy"

Morphine, gabapentin, or their combination for neuropathic pain

Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent, with constipation, sedation, an dry mouth as the most frequent adverse effects.

Gilron I, et al. N Engl J Med. 2005; 352:1324-1334.

Anti-nociceptive synergism of morphine and gabapentin in neuropathic pain induced by chronic constriction injury.

- In a rat model of neuropathic pain (Bennett model), gabapentin did not produce an anti-allodynic effect, whereas the morphine and gabapentin combination completely decreased allodynia behavior at 30 min post-injection, an effect that PERSISTED UNTIL 120 MIN. The area under the curve (AUC) of the anti-allodynic or anti-hyperalgesic effects produced by the combinations were significantly greater than the theoretical sum of effects produced by each drug alone or similar to the theoretical sum.

De la O-Arciniega M, et al. Pharmacol Biochem Behav. 2009; 92:457-464.

Nortriptyline and gabepentin, alone and in combination for neuropathic pain: a double-blind, randomized controlled crossover trial

- Combined gabapentin and nortriptyline seems to be more efficacious than either drug given alone for neuropathic pain, therefore use of this combination is recommended in patients who show a partial response to either drug given alone and seek additional pain relief.

Gilron I, et al. Lancet. 2009; 374:1252-1261.

Examples of between-class combinations

Class combinations	Specific example	Example of usage
Centrally acting analgesic + opioid	Acetaminophen + Codeine	Nociceptive pain
NSAID + opioid	Ibuprofen + oxycodone	Inflammatory pain
Anti-convulsant + opioid	Gabapentin + morphine	Neuropathic pain [Gilron]
Anti-convulsant + anti-depressant	Gabapentin + amitriptyline	Neuropathic pain [Sator-Katzenschlager] [Heughan]

NSAID, nonsteroidal anti-inflammatory drug

Murison B. In: Current Therapy in Pain. Smith HS (ed). Elsevier. Philadelphia, PA. 2009; p397-402.

Efficacy of tramadol in combination with doxepin or venlafaxine in inhibition of nociceptive process in the rat model of neuropathic pain: an isobolographic analysis

Wrzosek and colleagues conducted a series of experiments which demonstrated that the nature of interaction between tramadol and doxepin is synergistic, which is not the case for tramadol and venlafaxine.

Wrzosek A, et alJ Physiol Pharmacol. 2009; 60:71-78.

Synergistic antihypersensitive effects of pregabalin and tapentadol in a rat model of neuropathic pain

The concept of dose-equivalent suggested an additive interaction of pregabalin and tapentdol (demonstrated by isobolographic analysis).

Christoph T, et al. Eur J Pharmacol. 2001; 666:72-79.

Potential Opioid Synergy

- Morphine + Gabapentin
- Morphine + Methadone
- Morphine + Clonidine or Dexmedetomedine
- Morphine + Ketamine
- Tapentadol+ Pregabalin
- Clonidine+ Dextromethorphan
- Tramadol+ Venlafaxine
- Tramadol+ Doxepin
- Gabapentin + C1-21021 (NK-1 Antagonist)

Guidelines or Algorithms for the Pharmacologic Treatment of Neuropathic Pain

Evidence-Based Recommendations for Neuropathic Pain

- 1st-line treatments
  - Certain antidepressants (ie, tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine)
  - Calcium channel alpha2-delta ligands (ie, gabapentin and pregabalin)
  - Topical lidocaine
- 2nd-line treatments that can be considered for 1st-line use in select clinical circumstances
  - Opioid analgesics
  - Tramadol
- 3rd-line treatments that could also be used as 2nd-line treatments
  - Certain antiepileptic and antidepressant medications
  - Mexiletine
  - N-methyl-D-aspartate receptor antagonists
  - Topical capsaicin
- Medication selection should be individualized, considering side effects, potential beneficial or deleterious effects on comorbidities, and whether prompt onset of pain relief is necessary

Dworkin RH, et al. *Pain.* 2007;132:237-251.

Comparison of neuropathic pain treatment guidelines, excluding trigeminal neuralgia*

Medication Class	Neuropathic Pain Special Interest Group Guidelines	Canadian Pain Society Guidelines	European Federation of Neurological Societies Guidelines
Tricyclic antidepressants	First line	First line	First line for PPN, PHN, and CP
Calcium channel α2-δ ligands (gabapentin and pregabalin)	First line	First line	First line for PPN, PHN, and CP
SSNRIs (duloxetine and venlafaxine)	First line	Second line	Second line for PPN
Topical lidocaine	First line for localized peripheral NP	Second line for localized peripheral NP	First line for PHN if small area of pain/allodynia
Opioid analgesics	Second line except in Selected circumstances†	Third line	Second-third line for PPN, PHN, and CP
Tramadol	Second line except in selected circumstances†	Third line	Second-third line for PPN and PHN

* Only medications considered first or second line in 1 of the guidelines are presented.
† Opioid analgesics and tramadol were considered first-line options in the following circumstances: for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.
CP = central pain; NP = neuropathic pain; PHN = postherpetic neuralgia; PPN = painful polyneuropathy; SSNRIs = selective serotonin and norepinephrine reuptake inhibitors.

de Leon-Casaola O. Pain Med. 2011;12 Suppl 3:S100-8

Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update

- Tricyclic antidepressants, dual reuptake inhibitors of serotonin and norepinephrine, calcium channel α_2-delta ligands (ie, gabapentin and pregablin), and topical lidocaine were recommended as first-line treatment options on the basis of the results of randomized clincial trials.

- Opioid analgesics and tramadol were recommended as second-line treatments that can be considered for first-line use in certain clinical circumstances.

Dworkin RH, et al. Mayo Clin Proc. 2010 Mar;85(3 Suppl):S3-14

Potential Future Treatment Strategies

Contribution of peripheral endothelin ET(A) and ET(B) receptors in neuropathic pain induced by spinal nerve ligation in rats

- SNL induces marked hind paw hypersensitivity to thermal stimulation in part via up-regulation of peripheral sensory nerve pronociceptive ET(A) and ET(B) receptor-operated mechanisms.

Werner MF, et al. Eur J Pain. 2010; In Press

Relief of Chronic Neuropathic Pain through Endothelin Antagonism

- A 47-year-old man was treated with the selective endothelin-A antagonist, sitaxsentan, for pulmonary arterial hypertension. He had been referred with a history of gradually increasing dyspnea.

- His sciatica had been managed with a number of medications, including paracetamol, nonsteroidal anti-inflammatory agents, and narcotic analgesia, all with limited success.

- He was given sitaxsentan 100 mg daily, with improvements in dyspnea and exercise tolerance reported at review 4 weeks later. He also volunteered that he had experienced a substantial improvement in his sciatica, allowing discontinuation of analgesia.

Murphy DM, et al. Am J Med. 2010 Mar;123(3):e7

True or False

- Opioids are not effective analgesic agents for neuropathic pain

A. True
B. False

Answer: B-False

True or False

- Pregabalin doses do not need to be adjusted in a patient with chronic kidney disease stage IV

A. True
B. False

Answer: B-False

- All of the following agents may be considered first line medications for the treatment of neuropathic pain except:

  A. Nortriptyline
  B. Duloxetine
  C. Desipramine
  D. Oxycodone CR
  E. Venlafaxine

Answer: D – Oxycodone CR