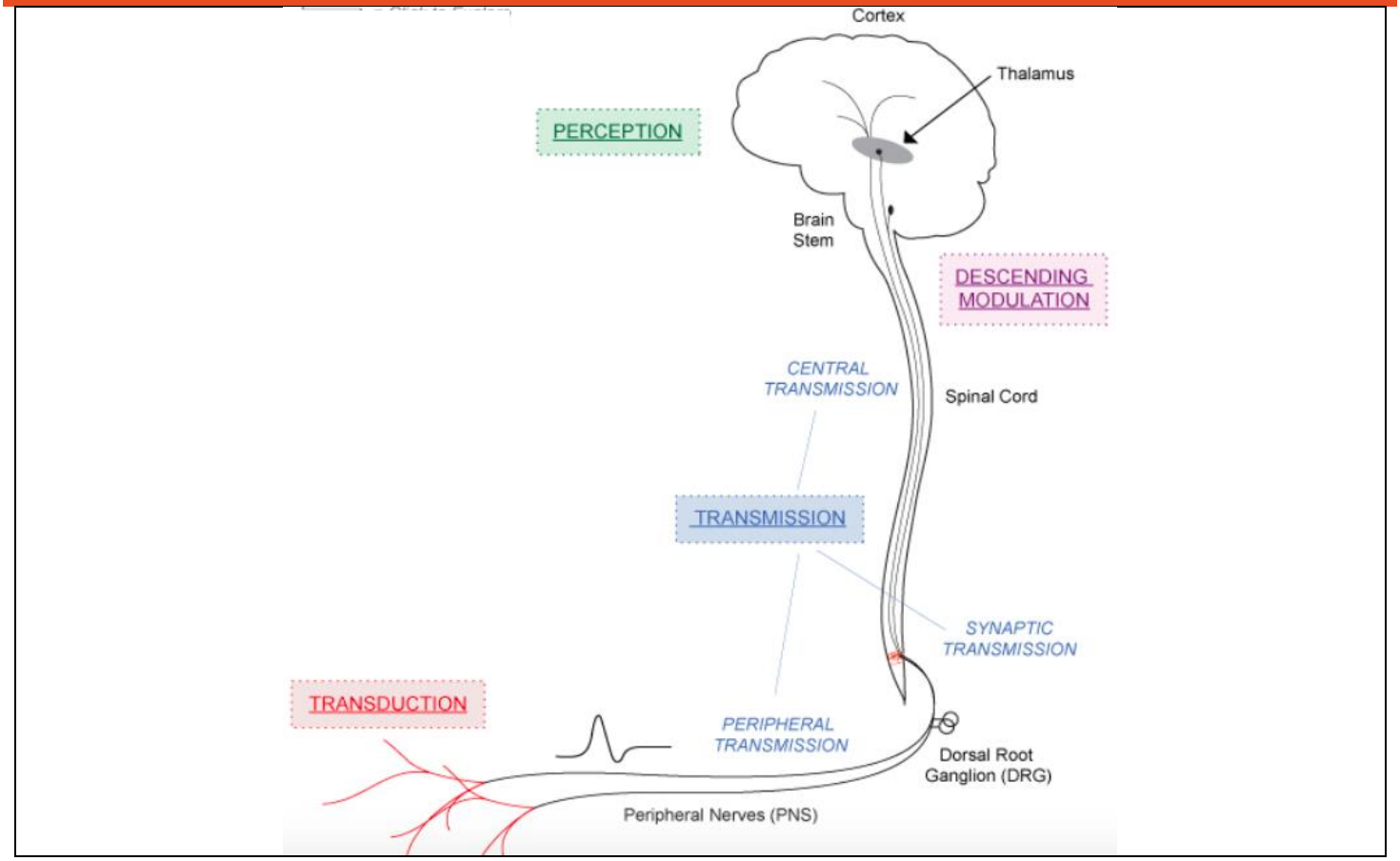
PAIN PATHOPHYSIOLOGY AND NEUROPATHIC PAIN PHARMACOTHERAPY

Compiled by Dr. Rebecca Chu, Pharm.D., reviewed and edited by Dr. Mena Raouf and Dr. Jeffrey Fudin.

CLASSIFICAITON OF PAIN

Norciceptive	• The normal response to insult or injury of tissues such as skin, muscles, visceral organs, joints, tendons, or bones ○ Somatic: musculoskeletal (joint pain, mysofacial pain), cutaneous ▪ Often well localized ○ Visceral: hollow organs and smooth muscle ▪ Usually referred
Neuropathic	• Initiated or caused by a primary lesion or disease in the somatosensory nervous system ○ Sensory abnormalities range from deficits perceived as **numbness** to **hypersensitivity** (hyperalgesia or allodynia), and to **paresthesia** such as **tingling** ○ Ex: **diabetic neuropathy,** postherpetic neuralgia, **spinal cord injury pain**, phantom limb (post amputation), and post-stroke central pain
Inflammatory	• Result of activation and sensitization of the nociceptive pain pathway by a variety of mediators released at a site of tissue inflammation ○ Key players are proinflammatory cytokines, such as IL-1 alpha, IL-1 beta, IL-6, TNF alpha, chemokines, reactive oxygen species, vasoactive amines, lipids, ATP, acid, and other factors released by infiltrating leukocytes, vascular endothelial cells, or tissue resident mast cells ○ Ex: appendicitis, **rheumatoid arthritis**, inflammatory bowel disease, and herpes zoster

PAIN PATHWAY



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Adapted from the University of Wisconsin School of Medicine and Public Health, http://projects.hsl.wisc.edu/GME/PainManagement/index.html

Preception	• The process by which a noxious event is recognized as pain by a conscious person and results in multiple areas in the brain being affected *All pain has an affective-emotional component that influences the individuals' behavioral response; may present with increased pain behaviors anxiety and depression that must be treated in order to achieve effective pain control*
Descending Modulation	• Influences central nociceptive transmission in the spinal cord by ascending noriceptive impulses and influences the brain results in descending modulation inhibition of norciceptive through the release of neurotransmitters (serotonin, norepinephrine, and endogenous opioids ***Tricyclics and SNRIs that inhibit the reuptake of serotonin and norepinephrine enhance descending inhibition**; may explain their effectiveness in neuropathic and other types of pain* *Spinal cord stimulation, epidural, and intrathecal delivery of drugs such as opioids also modify descending modulation*
Transmission	Action potentials (nerve impulses) are conducted to the central nervous system primarily via two types of primary afferent neurons: • thinly myelinated, faster conducting A delta fibers • unmyelinated, slowly conducing C fibers Action potentials result from activation of specific sodium channels Norciceptive impulses travel along these peripheral nerve fibers to the dosal horn of the spinal cord where they synapse with the second order neurons Impulse travels across the spinal cord and ascent to the thalamus and branches to the brainstem nuclei (central transmission) Noriceptive impulses are relayed to the multuple ares of the brain including the somatosensory cortex, the insula, frontal lobes, and limbic system ***Local anesthetics and some antiepileptic drugs block sodium channels and inhibit the production of action potentials along the nociceptive afferents.*** ***Opioids bind to presynaptic receptors in the dorsal horn and decrease release of neurotransmitters such as glutamate.*** *Peripheral and spinal nerve blocks interfere with propagation of action potentials and pain transmission into the CNS (at the nociceptors, along the nerve, at the dorsal root ganglion and along the spinothalamic tracts)* *Epidurally and intrathecally administered analgesics may provide presynaptic and postsynaptic inhibition of receptors at the level of dorsal horn neurons and affect the transmission of nociceptive impulses*

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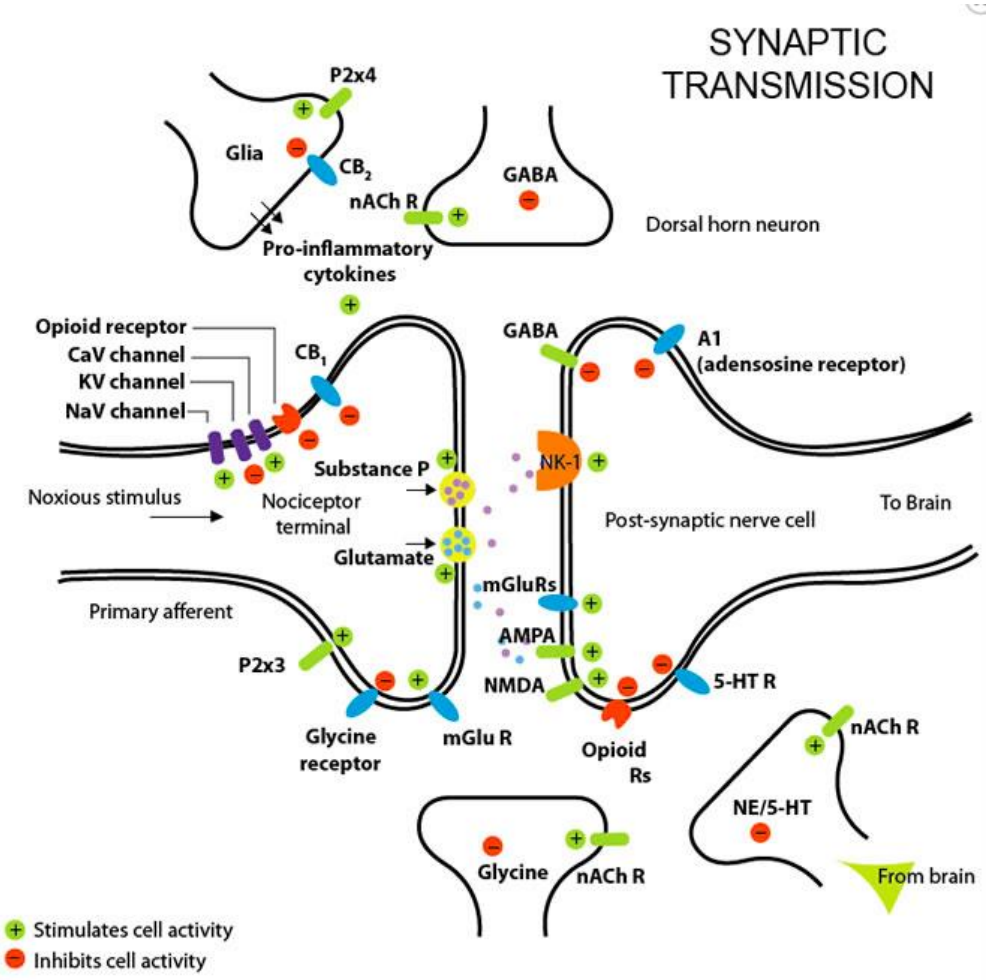
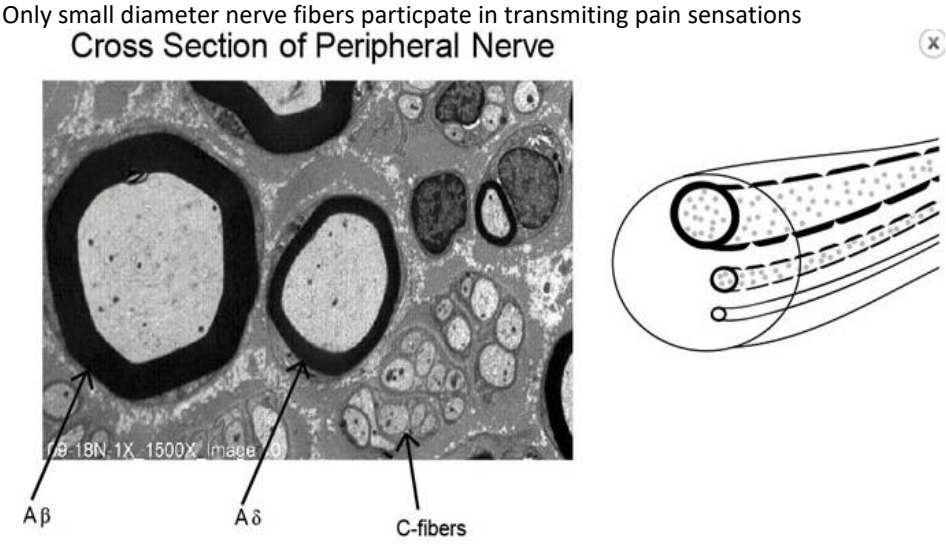
Synaptic Transmission	• Once the action potential from the periphery reaches the first synapse at the dorsal horn of the spinal cord, neuroactive substances are released: excitatory and inhibitory neurotransmitters and glial derived chemicals that illicit immune responses (astrocytes and microglia) • Lead to generation of action potentials and central transmission of pain signals to higher centers 
Peripheral transmission	• Only small diameter nerve fibers particpate in transmiting pain sensations 

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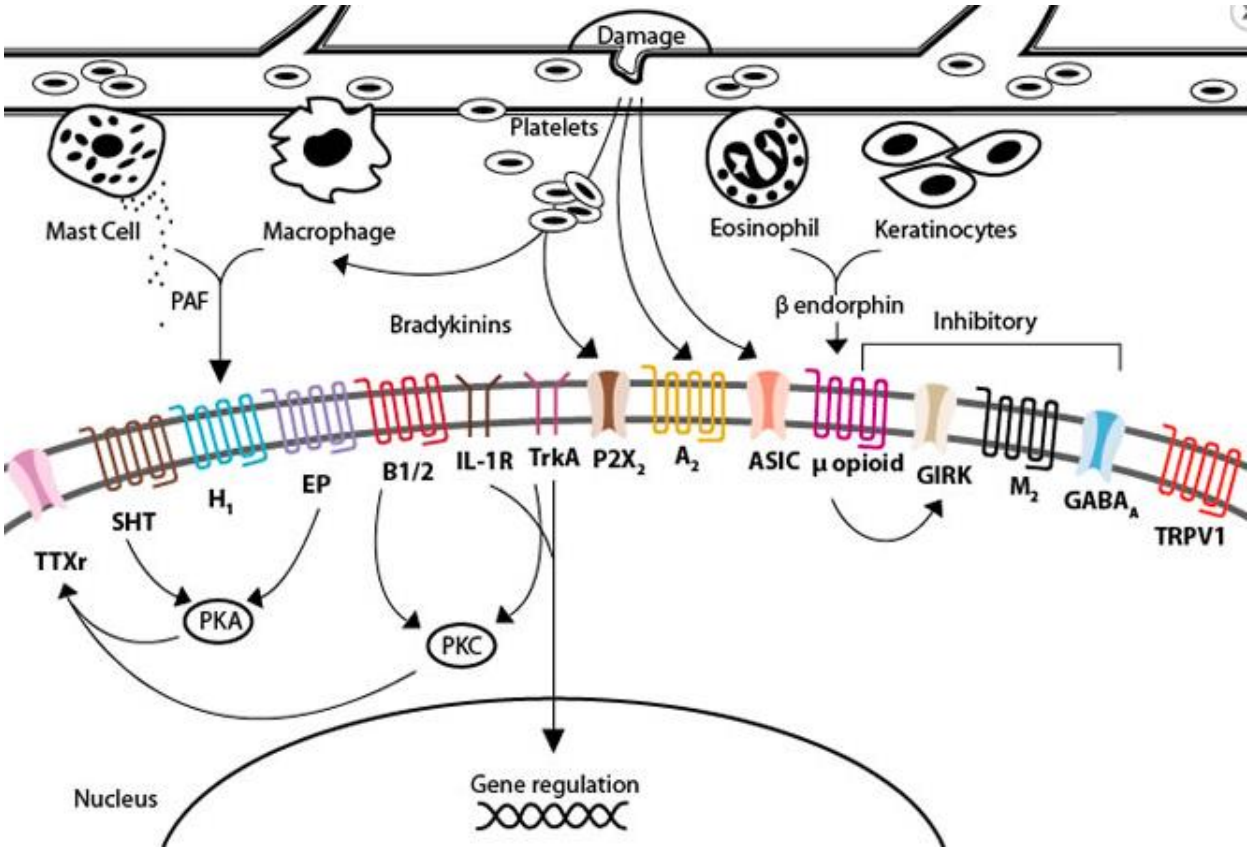
Transduction	• Physiological process whereby a noxious mechanical, chemical, or thermal stimulus is converted (transduced) via specialized receptors on primary afferents into an electrical impulse (action potential) • Nociceptors, a subpopulation of primary sensory neurons, are activated by intense stimuli, such as pressure, heat, mechanical insults (a surgical incision) or irritant chemicals ○ Irritant chemicals: bradykinin, cholecystokinin and prostaglandins *Use of non-steroidal anti-inflammatory drugs inhibit the synthesis of prostaglandins, normally produced and released at the site of injury, and which in turn make neighboring nociceptors more responsible to noxious and innocuous stimuli* 

PATHOPHYSIOLOGY

- The sensation of pain is a normal response to injury or disease; is a result of normal physiological processes within the nociceptive system
- Other manifestations of pain including
  - **Hyperalgesia**: an exaggerated response to a noxious stimulus
  - **Allodynia**: the perception of pain from normally stimuli
- Genetic and environmental factors contribute to sensitization resulting in persistent chronic pain
  - Nociceptors not only signal acute pain, but when chronically sensitized, contribute to persistent pathological pain disorder from previous injury or ongoing disease
- Chronic pain is also characterized by the abnormal state and function of the spinal cord neurons which become hyperactive
  - Hyperactivity results of increased transmitter release by spontaneously active primary afferent neurons and an increased responsiveness of polysynaptic receptors (due to phosphorylation
    - The state of hyperexcitability is aggravated by the loss of inhibitory interneurons involved in the modulation of pain
- Imaging studies have shown that chronic pain is accompanied by permanent structural alterations in specific brain areas that play a crucial role in nociception

ASSESSMENT AND DIAGONSIS

Pain is a subjective experience		
Q	**Quality**	1. What were your first symptoms? 2. What words would you use to describe the pain? (achy, sharp, burning, squeezing, dull, icy, etc…)
I	**Impact**	1. How does the pain affect you? 2. How does the pain impact your sleep, activity, mood, appetite (other – work, relationships, exercise, etc.) 3. What does the pain prevent you from doing? 4. Have you been particularly anxious about anything?
S	**Site**	1. Where does the pain move/radiate? 2. Has the location changed over time?
S	**Severity**	1. On a scale of 0-10, how much pain are you in right now? 2. What is the least pain you have had in the past…? 3. What is the worst pain you have had in the past…? 4. How often are you in severe pain?
T	**Temporal Characteristics**	1. When did the pain start? 2. Was there a clear triggering event? 3. Is the pain constant or intermittent? 4. Does it come spontaneously or is it provoked? 5. Is there a predictable pattern? (e.g. always worst in the morning or in the evening?)
A	**Aggravating and Alleviating Factors**	1. What makes the pain better? 2. What makes the pain worse? 3. When do you get the best relief? 4. How much relief do you get and how long does it last?
P	**Past Response, Preferences**	1. How have you managed your pain in the past? (Ask about both drug and non-drug methods) 2. What helped? What did not help? 3. What medications have you tried? Was the dose increased until you had pain relief or side effects? How long did you take the drug? 4. Have you tried physical or occupation therapy? What was done? Was it helpful? 5. Have you tried spinal or other injections for pain treatment?
E	**Expectations, Goals, Meaning**	1. What do you think is causing the pain? 2. What do you hope the treatment will accomplish? 3. What do you want to do that pain keeps you from doing? 4. What are you most afraid of?
D	**Diagnostics and Physical Exam**	1. Examine and inspect the site 2. Review imaging, laboratory and/or other test results as indicated

TREATMENT OF PAIN

Acute Pain	Chronic Pain
• Identify and treat the underlying disease and enhance healing and recovery • Adequate management of acute pain may also prevent the development of chronic pain • Analgesics are the mainstay of acute pain treatment, but nondrug methods are essential too	• Multiple mechanisms are at play and the cause of the pain may be difficult to identify and cannot be completely eliminated • Pain relief is still primary but the goals of improvement in function and quality of life gain even greater importance **Pain Flare** •Transient increases in pain that can least for hours to days •Extremely common and generally benign although may be precieved as hamful by the patient •Pain intensity eventually returns to baseline •Care should be used with additional short-acting analgesics since they are not apprropriate from a mechanisitic standpoint **Disease Progression** •pain is exacerbated and dose not remit with flare manaagement techinques, look for treat anychange in the causative disease process

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"Breakthrough Pain"
• Describe a transitory exacerbation of pain (predictable or spontaneous) that occurs on a background of otherwise stable pain in a cancer patient receiving chronic opioid therapy • Increases in pain may be categorized as incident related, (i.e. caused by movement, cough, defecation), end-dose failure, or idiopathic

REGULATORY ISSUES AND ADDICTION

Addiction	• Primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations
	• Characterized by behaviors that include one or more of the following:
	  ○ Impaired control over drug use
	  ○ Compulsive use
	  ○ Continued use despite harm
	  ○ Craving

Physical dependence	• State of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist
Tolerance	• State of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time

COMMON REGIMENS FOR NEUROPATHIC PAIN MANAGEMENT

Name	Effective Dosing *	Metabolism	Medication Pearls
Anti-eptics			
MOA: binds to alpha2 subunit on voltage gated channels; decrease substance P, norepinephrine and glutamate			
Gabapentin	1800-3600mg	None – eliminated unchanged in the urine	Renal dose adjustments; drowsiness ; bioavailability decreases with increasing dose
• Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia. JAMA 1998;280:1837-42. • Rice AS, Maton S, Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. Pain 2001;94:215-24.			
Pregabalin	≥ 150mg/day	None – eliminated unchanged in the urine	Renal dose adjustments; Improved GI tolerability than gabapentin because of improved bioavailability; has a higher binding affinity to receptor than gabapentin
• Lesser H, Sharma U, LaMoreaux L, et al. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004;63:2104-10. • Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110(3):628-38. • Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. Drugs 2005;65:111-8. • Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003;60:1274-83.			
MOA: block sodium channels			
Carbamazepine	600-1200mg/day	3A4 and 2C8 → carbamazepine 10,11 epoxide	CYP inducer (1A2, 2C and 3A4); monitor blood count for aplastic anemia and agranulocytosis; monitor liver function needs HLA testing; trigeminal neuralgia; induce its own metabolism
• Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. Cochrane Database Syst Rev. 2011; (1); CD005451. • Vinik A. Clinical review: use of antiepileptic drugs in the treatment of chronic painful diabetic neuropathy. J Clin Endocrinol Metab. 2005;90:4936–45.			
Lamotrigine	200-400mg/day	Phase II glucoronidation	Decrease release of glutamate; risk of teratogenicity; start low and titrate slowly to decrease incidence of skin rashes
• Wiffen PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain in adults. Cochrane Database Syst Rev. 20011; (1); CD00604. • Devulder, Jacques et al. Lamotrigine in the Treatment of Chronic Refractory Neuropathic Pain. 19(5):398-403. • Eisenberg, E, Alon, N, Ishay, A, Daoud, D, Yarnibsky, D. Lamotrigine in the treatment of painful diabetic neuropathy. Eur J Neurol. 1998;5:167–173. • di Vadi, P, Hamann, W. The use of lamotrigine in neuropathic pain. Anaesthesia. 1998;53:808–809.			
Oxcarbazepine	900-2400mg/day	Cystolic enzymes → 10 monohydroxocy methaboite (active) Phase II glucoronidation Oxidized → 10,11 dihydroxy metabolite (DHD)	CYP inducer (2C19; fewer than carbamazepine); risk for Steven-Johnson Syndrome; trigeminal neuralgia; monitor blood count for aplastic anemia and agranulocytosis; may induce hyponatremia
• Grant SM, Faulds D. Oxcarbazepine: a review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. Drugs 1992;43:873-888. • Zhou M, Chen N, He L, Yang M, Zhu C, Wu F. Oxcarbazepine for neuropathic pain. Cochrane Database of Syst Rev. 2013 (3). CD007963. • Magenta P, Arghetti S. Di Palma F, Jann S, Sterilcchino M, Bianconi C, et al. Oxcarbazepine is effective and safe in the treatment of neuropathic pain: pooled analysis of seven clinical studies. Neurol Sci. 2005 Oct; 26(4): 218-26.			
Topiramate	≥200mg/day	Phase II hydroxylation, hydrolysis, glucoronidaiton	Migraine prophylaxis and weight loss; renal dose adjustments; metabolic acidosis; glaucoma precaution; risk for kidney stones and increased ocular pressure; also affects GABA and glutamate receptors; weak carbonic anhydrase inhibitor; CYP inducer (3A4)

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- Raskin P, Donofrio PD, Rosenthal NR, et al. Topiramate vs. placebo in painful diabetic neuropathy: analgesic and metabolic effects. Neurology 2004;63:865-873.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy. Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011;76:1758-1765.
- Donofrio PD, Raskin P, Rosenthal NR, et al. Safety and effectiveness of topiramate for the management of painful diabetic peripheral neuropathy in an open-label extension study. Clin Ther. 2005 Sep; 27(9):1420-31.

Valproic Acid	≥ 1200mg/day	Phase II glucoronidation	Safety Considerations/BBW: hepatotoxicity, teratogenicity, pancreatitis ; monitor for LFTs and troughs levels; caution that this may increase ammonia levels and lead to encephalopathies

- Kochar DK, Rawat N, Agrawal RP, et al. Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. Q J Med 2004;97:33-38.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy. Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011;76:1758-1765.
- Kochar DK, Jain N, Agrawal RP, et al. Sodium valproate in the management of painful neuropathy in type 2 diabetes – a randomized placebo controlled study. Acta Neurol Scand 2002; 106:248-252.
- Argawal RP, Goswami J, Jain S, et al. Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: A prospective double-blind randomized placebo-controlled study. Diabetes Res Clin Pr 2009; 83:371-378.

Name	Effective Dosing	Metabolism	Medication Pearls
Selective Serotonin and Norepinephrine Reuptake Inhibitor (SSNRI) (cardiac risk i.e. Qtc, BP, HR)			
MOA: dual reuptake inhibitors of serotonin and norepinephrine in the presynaptic cleft			
Duloxetine	≥60mg/day	2D6 1A2	Indicated for diabetic neuropathy and fibromyalgia; 5HT x10 > NE; fewer antiplatelet effect
• Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014;CD007115.			
Milnacipran	100-200mg/day	Phase II glucoronidation	5HT=NR
• Cording M, Derry S, Phillips T, et al. Milnacipran for pain in fibromyalgia in adults. Cochrane Database Syst Rev. 2015.			
Levomilnacipran	N/A	Phase II glucoronidation	NE 2x > 5HT
Venlafaxine	≥ 150mg/day	2D6 → O-desmethylvenlfaxine (active) 3A4	5HT 30x>NE; doses above 300mg inhibit dopamine
• Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain. 2004;110:697-706. • Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. Eur J Pain. 2002;6:17-24. • Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology. 2001;25:871-880. • Blier P, Saint-André E, Hébert C. Effects of different doses of venla- faxine on serotonin and norepinephrine reuptake in healthy volunteers. Int J Neuropsychopharmacol. 2007;10:41-50.			
Desvenlafaxine	200-400mg/day		5HT 14x > NE; active metabolite and enantiomer of venlafaxine
• Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. J Pain Res. 2014;7:339-351.			

Name	Effective Dosing		Metabolism	Medication Pearls
Tricyclic Anti-depressants (TCA) (decrease seizure threshold, cardiotoxic, glaucoma, anticholinergic, BBW: suicide)				
MOA: inhibit reuptake of norepinephrine and serotonin				
	Pain	**Anti-depressant**		
Amitripytline	25-75mg	150-300mg	2C19 → nortriptyline (active) 2D6 → inactive metabolite	Tertiary amine; half-life 10-46 hours; high risk for orthostatic hypotension
• Cardenas DD, Warms CA, Turner JA. Marshall. Brooke, Loeser JD. Efficacy of amitriptyline for relief of pain in spinal cord injury:results of a randomized controlled trial . Pain 2002;96:365 – 73. • Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250 – 6. • Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. Neurology 1982;32:671 – 3. • Moore R.A., Derry S., Aldington D., et al: Amitriptyline for neuropathic pain and fibromyalgia in adults (review). Cochrane D atabase Syst Rev 2012; undefined:				
Nortripytline	25-75 mg	50-150mg	2D6 → 10-hydroxy-nortrityline (inactive) 2D6, 1A2, 2C19 → desmethyl nortrityline (inactive)	Secondary amine; half-life 13-90 hours; has less cholinergic effects, orthostatic
• Gomez - Perez FJ, Rull JA, Dies H, Rodriguez - Rivera G, Gonzlez - Barranco J, Lozano - Castaneda O. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double - blind cross - over study. Pain 1985;23:395 – 400. • Panerai AE, Monza G, Movilia P, Bianchi M, Francucci BM, Tiengo M. A randomized, within - patient, cross - over, placebo - controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain. Acta Neurol Scand 1990;82:34 – 8.				
Imipramine	50-150mg	150-300mg	2C19 → desipramine (active) 1A2, 3A4 → desipramine (active) 2D6 → 2-hydroxy-impiramine (inactive)	Tertiary amine; half-life 8-12 hours; high risk for ortherostatic hypotension
• Kvinesdal B, Molin J, Frøland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. J Am Med Assoc 1984;251:1727 – 30. • Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy. A randomized, controlled trial. Neurology 2003;60:1284 – 9.				
Despiramine	50-150mg	150-300mg	2D6 → 10-hydroxy-nortrityline (inactive) 2C19 → inactive metabolites	Secondary amine; half-life 13-90 hours
• Max MB, Kishore - Kumar R, Schafer SC, Meister B, Gracely R, Smoller B, Dubner R. Efficacy of desipramine in painful diabetic neuropathy: a placebo - controlled trial. Pain 1991;45:3 – 9. • Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250 – 6.				

Dual Mechanism Opioids			
MOA: stimulate opioid receptors in the brain and reuptake of norepinephrine			
Tapentadol		Phase II glucoronidation 2C9, 2C19	Also binds to serotonin receptors, but binding is very little; serotonin syndrome?; 18X less potent for receptor activation compared to morphine but 2-3x less potent for analgesia
Tramadol		2D6 → O-methyl → Phase II glucoronidation 3A4 and 2B6 → N-demethylation	6,000x less binding affinity to the mu-opioid receptor compared to morphine
MOA: stimulate opioid receptors in the brain, reuptake of norepinephrine, and NMDA receptor antagonist (glutamate will increase neuronal signals if agonist)			

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Levophanol		Phase II glucoronidation; Levorphanol-3 glucuronide	
Methadone		**3A4, 2B6,** 2D6, **2C19,** 2C9 EDDP (inactive)	Long half life, (8-59 hours) but short analgesic effect (4-8 hours) might be due to large volume of distribution; highly lipophilic

Name	Effective Dosing	Metabolism	Medication Pearls
Miscellaneous			
MOA: blocks initiation and condition of nerve impulses by decreasing membrane permeability to Na+ → decrease conduction			
Lidocaine	Patch: apply up to 3 patches for 12 hours, then no patches for 12 hours		
• Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy. Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011;76:1758-1765. • Fleming JA, O'Connor BD. Use of lidocaine patches for neuropathic pain in a comprehensive cancer center. Pain Res Manag. 2009 Sept-Oct; 14(5): 381-388			
MOA: depletes and prevents accumulation of substance P in peripheral sensory neurons			
Capsaicin			Active ingredient in Capzasin

** Effective dosing based on studied regimens in clinical trials that demonstrated efficacy. Different patients may have different dose requirements. Therapeutic dosing may be altered in the setting of renal or hepatic impairment, drug-drug interactions, and/or drug-food interactions. Therefore, it is advisable that dosing be guided by patient response with regards to efficacy and tolerability.