Goals of treatment in managing visceral pain

Goals in the Management of Visceral Pain

Address underlying pathology

Alleviate symptoms

Treatment *should not be delayed* unless it would obscure the diagnostic workup

Giamberardino MA. *Pain Clinical Updates.* 2005;XIII(6):1-6; IASP. Available at: http://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/VisceralPainFactSheets/3-AcuteVsChronic.pdf. Accessed 1 December, 2014.

Goals in the Management of Visceral Pain

Address underlying pathology ← **Parallel treatment** → **Alleviate symptoms**

- In **theory**, can defer pain management until symptom cause identified
  - Masking pain may confound diagnostic process and delay recognition of a potentially life-threatening condition
- In **practice**, a clear cause of each symptom may never be proven
- Symptomatic treatment should not be withheld when a treatable condition has been identified

Prolonged/repetitive visceral afferent barrage into CNS increases risk of long-term sensitization and consequences *(e.g.*, referred hyperalgesia, trophic changes)

Giamberardino MA. *Pain Clinical Updates.* 2005;XIII(6):1-6.

Overview of the Treatment of Visceral Pain

- Symptomatic treatment relies mainly on pharmacotherapy
  - Analgesics
    - Acetaminophen
    - NSAIDs/coxib
    - Opioids
  - Non-analgesic agents
    - Antidepressants
    - $\alpha_2\delta$ ligands
    - Nitrates for angina
    - Histamine receptor agonists or PPIs for ulcer/gastritis
    - Deep infiltration of muscle layer of referred area with local anesthetic may be helpful
- Non-pharmacological treatments are also important
  - Cognitive behavioral therapy
  - Meditation
  - Psychotherapy

PPI = proton pump inhibitor

Giamberardino MA. *Pain Clinical Updates.* 2005;XIII(6):1-6.

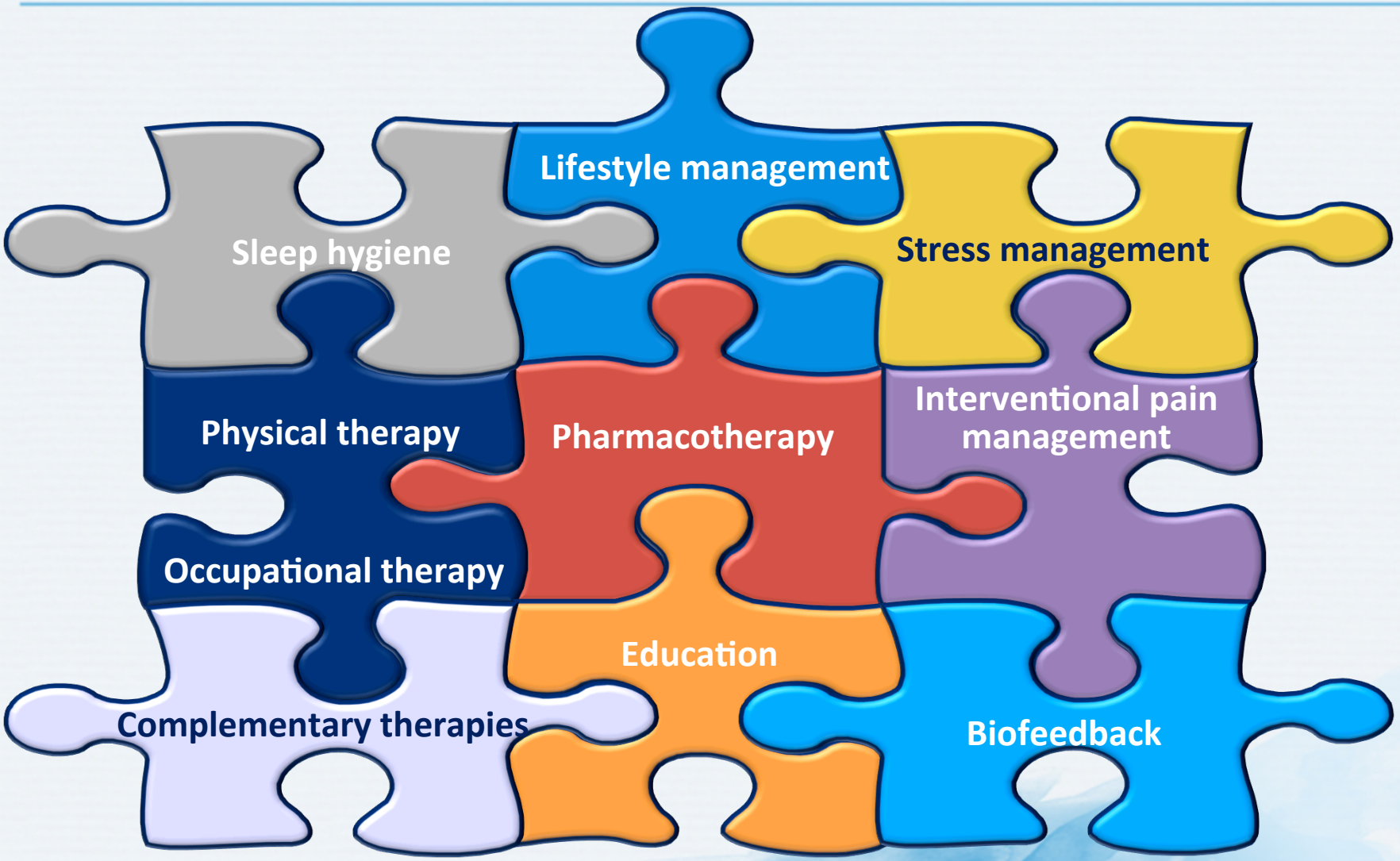
Non-pharmacological Management of Visceral Pain

Benefits of Non-pharmacological Methods in Treating Visceral Pain

- Increase individual's feeling of control
- Decrease the feeling of weakness
- Improve activity level and functional capacity
- Reduce stress and anxiety
- Reduce pain behavior and focused pain level
- Reduce needed dosage of analgesic drugs → decrease drug adverse effects

Demir Y. 2012. Available at: http://www.intechopen.com/books/pain-management-current-issues-and-opinions/non-pharmacological-therapies-in-pain-management. Accessed 8 January 2015.

Multimodal Treatment of Pain Based on Biopsychosocial Approach



Gatchel RJ *et al. Psychol Bull* 2007; 133(4):581-624; Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.*; National Academies Press; Washington, DC: 2011; Mayo Foundation for Medical Education and Research. *Comprehensive Pain Rehabilitation Center Program Guide.* Mayo Clinic; Rochester, MN: 2006.

Various Non-pharmacological Treatments Are Available for Visceral Pain

No modality is universally recommended

CBT = cognitive behavioral therapy

Pharmacological Management of Visceral Pain

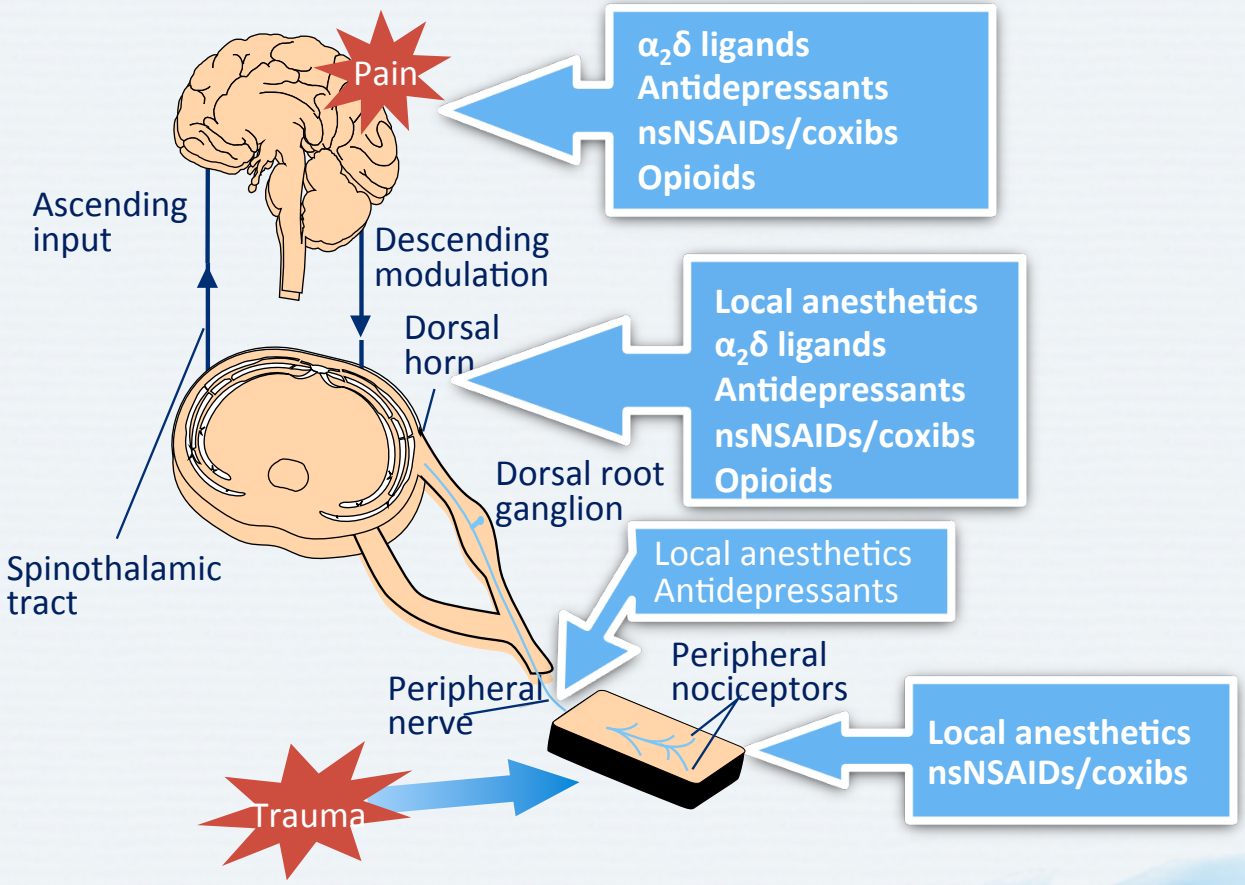
Overview of Pharmacological Management of Visceral Pain

- Visceral pain is included with somatic and nociceptive pain in most clinical trials
  - Difficult to select appropriate drug choices for visceral pain
- There may be differences in responses to analgesics
- Analgesic combinations likely to be more effective than single agents
- Analgesic dose-response relationships for visceral pain may be different than those for somatic pain

Unlikely that one analgesic or targeted agent will significantly reduce most visceral pain because multiple neurotransmitters, channels, and receptors are responsible

Davis MP. *Pain Res Treat.* 2012;2012:265605.

Analgesics Affect Different Parts of the Pain Pathway



Coxib = COX-2 inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Adapted from: Gottschalk A *et al. Am Fam Physician* 2001; 63(10):1979-84; Verdu B *et al. Drugs* 2008; 68(18):2611-32.

Overview of Pharmacological Treatments for Visceral Pain

Drug(s)	Comments
Acetaminophen	• Weak COX-2 inhibitor and selective COX-3 inhibitor • Little known about efficacy in managing visceral pain • More effective in combination with NSAIDs
NSAIDs/coxibs	• Block COX-1 (NSAIDs) and COX-2 (NSAIDs, coxibs) • Alleviate pain but adverse events (especially GI) preclude chronic use • More effective in combination with acetaminophen
Opioids	• Modify perception, modulate transmission, and affect pain signal transduction • May cause hyperalgesia – dose reduction may improve pain control • Adverse events, risk of abuse, addiction, tolerance, and physical dependence limit use
Antidepressants	• Modulate interactions between CNS and enteric nervous system; ↓ visceral hypersensitivity • TCAs most studied – agents that modify serotonergic transmission may be useful • Help with anxiety and depression often experienced with visceral pain
$\alpha_2\delta$ Ligands	• Anticonvulsants: gabapentin, pregabalin • Bind to $\alpha_2\delta$ subunit of voltage-dependent Ca^{2+} ion channels in CNS • May be helpful in managing visceral pain but little data supports use • All use in treating visceral pain is considered off-label

COX = cyclooxygenase; coxib = COX inhibitor; CNS = central nervous system; NSAID = non-steroidal anti-inflammatory drug; TCA = tricyclic antidepressant

Davis MP. *Pain Res Treat.* 2012;2012:265605; Patrizi F *et al. The Scientific World J.* 2006;6:472-90; Davis MP. *Pain Res Treat.* 2012;2012:265605; Gastrosource. Available at: http://www.gastrosource.com/11674565?itemId=11674565; Vane JR, Botting RM. *Inflamm Res.* 1995; 44(1):1-10; Clemett D, Goa KL. *Drugs.* 2000; 59(4):957-80; Grosser T *et al.* In: Brunton L et al (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. (online version). McGraw-Hill; New York, NY: 2010; Crowell MD *et al. Curr Opin Investig Drugs.* 2004;5(7):736-42; Fioramonti J, Bueno L. *Gut.* 2002; 51(Suppl 1): i91–i95; Dalton CB, Drossman DA. Available at: https://www.med.unc.edu/ibs/files/educational-gi-handouts/IBS%20and%20Antidepressants.pdf.; Attal N, Finnerup NB. *Pain Clinical Updates*. 2010; 18(9):1-8; Lacy BE *et al. Therap Adv Gastroenterol.* 2009;2(4):221-38.

Acetaminophen in the Management of Visceral Pain

- Weak COX-2 inhibitor and selective COX-3 inhibitor
  - Increases brainstem serotonin neurotransmission
  - Redirects beta-endorphin
  - Inhibits 5-HT 3 receptors, which are pronociceptive
- Although commonly used for pain, little is known about its efficacy in managing visceral pain
  - Most studies do not focus on visceral pain
- May be more efficacious in **combination** with NSAIDs
  - Systematic review: NSAID + acetaminophen combinations superior to acetaminophen alone in 85% of studies and to NSAIDs alone in 64% of studies

Acetaminophen is more effective in managing visceral pain when used in combination with NSAIDs

5-HT = serotonin; COX = cyclooxygenase; NSAID = non-steroidal anti-inflammatory drug

Davis MP. *Pain Res Treat.* 2012;2012:265605.

NSAIDs/coxibs in the Management of Visceral Pain

- Most-used analgesic drugs[1]
- Effective but cause several side effects that preclude chronic use[1]
- May fail to relieve chronic pain completely[1]
- Act by inhibiting production of prostaglandins[1]
- In renal or biliary colic, NSAIDs may involve acetylcholine blockade[2]
- May be more efficacious in **combination** with acetaminophen[2]
  - NSAID + acetaminophen combinations superior to acetaminophen alone in 85% of studies and to NSAIDs alone in 64% of studies
- NSAIDs superior to anticholinergics and opioids in relieving renal colic[2]

Because chronic visceral pain is not usually associated with injury and inflammation, NSAIDs/coxibs might not be suitable for this condition[1]

1. Patrizi F *et al. The Scientific World J.* 2006;6:472-90; 2. Davis MP. *Pain Res Treat.* 2012;2012:265605.

COX-2 Is Involved in Central Sensitization

- Central induction of COX-2 increases prostaglandin production
- PGE2 stimulation of EP receptors in the dorsal horn will:
  - Activate PKC, phosphorylating and further enhancing NMDA channel opening
  - Directly activate certain dorsal horn neurons by opening EP2 receptor linked ion channels
  - Reduced inhibitory transmission of glycinergic inter-neurons
  - Increased depolarization and excitability of dorsal horn neurons

NMDA = N-methyl-D-aspartate; PGE2 = prostaglandin E2; PKC = protein kinase C

Ahmadi S *et al. Nat Neurosci* 2002; 5(1):34-40; Baba H *et al. J Neurosci* 2001; 21(5):1750-6;
Samad TA *et al. Nature* 2001; 410(6827):471-5; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

COX-2 Inhibition Minimizes Sensitization

- Signal for COX-2 induction likely to persist with peripheral inflammation
- To minimize sensitization, COX-2 should be inhibited centrally and in the periphery
  - As early as possible
  - Continued until peripheral inflammation resolved
- Ideal COX-2 inhibitor should be able to act in periphery as well as centrally
  - Should readily cross blood-brain barrier

Samad TA *et al. Nature* 2001; 410(6827):471-5; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Opioids in the Management of Visceral Pain

- May cause hyperalgesia
  - Increased pain intensity extent of pain area
  - Radiation with reduced responsiveness to opioids
  - Mimics pain associated with progression of underlying pathology
  - **Physicians who are unaware of this phenomenon may increase opioid dose, only to worsen the visceral pain**
- Addition of adjuvant analgesics or opioid rotation useful in in managing opioid-induced hyperalgesia
- NSAID, acetaminophen, and opioid combinations may be additive or synergistic
- Antidepressants + opioids may reduce visceral pain due to inhibition of sodium channels, NMDA receptors, P2X channels, and prostaglandins

Paradoxically, opioid dose reduction may improve pain control

NMDA = N-methyl-D-aspartate; NSAID = non-steroidal anti-inflammatory drug

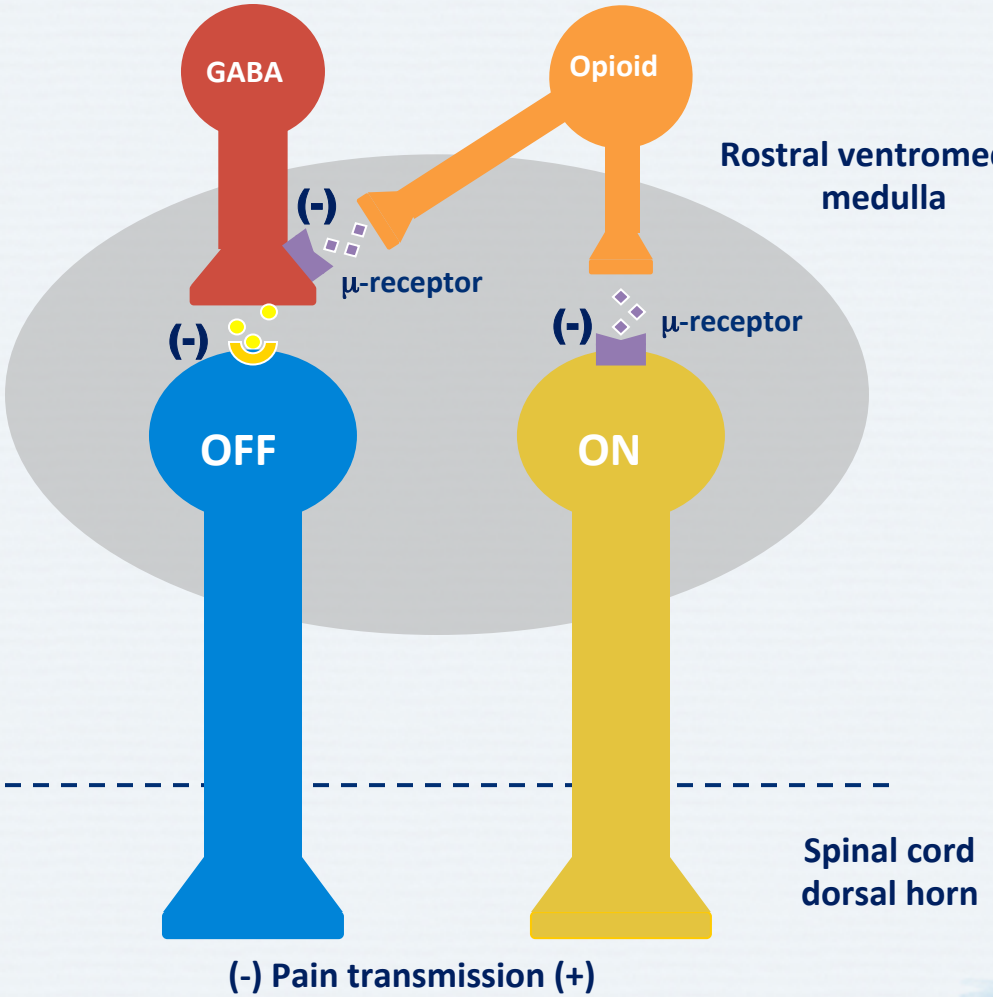
Davis MP. *Pain Res Treat.* 2012;2012:265605.

Opioids and Pain Management

Opioid Receptor	Response
Mu	Supraspinal analgesia, respiratory depression, sedation, miosis, euphoria, cardiovascular effects, pruritis, nausea/ vomiting, decreased gastrointestinal motility, dependence, tolerance
Delta	Analgesia, euphoria, dysphoria, psychotomimetic effects
Kappa	Spinal analgesia, dysphoria, psychotomimetic effects, miosis, respiratory depression, sedation

Gourlay GK. *Support Care Cancer* 2005; 13(3):153-9.;Reisine T *et al.* In: Hardman JG *et al* (eds). *Goodman and Gilman's: The Pharmacological Basics of Therapeutics.* 9th ed. McGraw-Hill; New York, NY: 1996.; Trescot AM *et al. Pain Physician* 2008; 11(2 Suppl):S133-53. Gourlay GK. *Supp Care Cancer*. 2005;13:153-9.

Opioids Modulate Control of "ON" and "OFF" Cells



- **Opioid stimulation of mu-receptors on "ON" cells**
  - Reduced "ON" cell activity
  - Reduced facilitation of pain transmission at dorsal horn
  - **Less pain**
- **Opioid stimulation of mu-receptors on GABA-ergic interneurons innervating "OFF" cells**
  - Reduced GABA-ergic interneuron activity
  - Reduced inhibition of "OFF" cells
  - Increased "OFF" cell inhibition of pain transmission at dorsal horn
  - **Less pain**

GABA = γ-aminobutyric acid

Fields HL *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006.

Opioids Can Induce Hyperalgesia

- Primary hyperalgesia
  - Sensitization of primary neurons → decrease threshold to noxious stimuli within site of injury
  - May include response to innocuous stimuli
  - Increase pain from suprathreshold stimuli
  - Spontaneous pain
- Secondary hyperalgesia
  - Sensitization of primary neurons in surrounding uninjured areas
  - May involve peripheral and central sensitization

Dolan S, Nolan AM. *Neuroreport* 1999; 10(3):449-52; Raja SN *et al.* In: Wall PB, Melzack R (eds). *Textbook of Pain*. 4th ed. Churchhill Livingstone; London, UK: 1999; Woolf CJ. *Drugs* 1994; 47(Suppl 5):1-9.

Opioids Can Induce Allodynia

- Pain evoked by innocuous stimuli
- Central sensitization → pain produced by Aβ fibers
- Possibly mediated by spinal NMDA receptors

NMDA = N-methyl-D-aspartate

Dolan S, Nolan AM. *Neuroreport* 1999; 10(3):449-52; Raja SN *et al.* In: Wall PB, Melzack R (eds). *Textbook of Pain*. 4th ed. Churchhill Livingstone; London, UK: 1999; Woolf CJ. *Drugs* 1994; 47(Suppl 5):1-9.

Adverse Effects of Opioids

System	Adverse effects
Gastrointestinal	Nausea, vomiting, constipation
CNS	Cognitive impairment, sedation, lightheadedness, dizziness
Respiratory	Respiratory depression
Cardiovascular	Orthostatic hypotension, fainting
Other	Urticaria, miosis, sweating, urinary retention

Additional Opioid Use Concerns

- Abuse and addictive potential
- Tolerance and physical dependence
- Administrative burden in distribution and monitoring due to scheduled status

CNS = central nervous system

Moreland LW, St Clair EW. *Rheum Dis Clin North Am* 1999; 25(1):153-91; Yaksh TL, Wallace MS. In: Brunton L *et al* (eds). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. (online version). McGraw-Hill; New York, NY: 2010; World Health Organization. *Understanding Health Professionals' Fear of Opioids.* Available at: http://www.whocancerpain.wisc.edu/?q=node/332. Accessed: October 17, 2013.

Additional Opioid Concerns

- Abuse and addictive potential
- Tolerance and physical dependence
- Administrative burden in distribution and monitoring due to scheduled status

World Health Organization. *Understanding Health Professionals' Fear of Opioids.*
Available at: http://www.whocancerpain.wisc.edu/?q=node/332. Accessed: October 17, 2013.

Antidepressants in the Management of Visceral Pain

- Visceral pain syndromes may be effectively treated by a number of therapies that modulate interactions between the central and enteric nervous systems
- Antidepressants may be efficacious for treatment of these syndromes
- TCAs most studied
  - Other antidepressants may be useful because serotonin modifies sensation in the gut
- Agents that modify serotonergic transmission may be useful in the moderation of visceral pain syndromes
  - Selective serotonin reuptake inhibitors may be useful

Crowell MD *et al. Curr Opin Investig Drugs.* 2004;5(7):736-42; Fioramonti J, Bueno L. *Gut*. 2002; 51(Suppl 1): i91–i95.

Antidepressants in the Management of Visceral Pain

- Antidepressants work at the level of brain and spinal cord to block pain messages between the gastrointestinal tract and the brain → reduces visceral hypersensitivity
- May help recover the brain's ability to respond to pain signals properly
- May stimulate nerve cell growth and possibly restore more normal nerve function in the in the brain and intestines over time
- Patients may require antidepressant treatment for 6 months to 1 year
  - Therapy may need to be extended in patients with a longer history of visceral pain

Using antidepressants can also help with the anxiety and depression often experienced by individuals with visceral pain

Dalton CB, Drossman DA. Available at: https://www.med.unc.edu/ibs/files/educational-gi-handouts/IBS%20and%20Antidepressants.pdf. Accessed 8 January, 2015.

Antidepressants Used in the Management of Visceral Pain

Class and Drug	Adverse Effects	
TCA Amitriptyline Imipramine Desipramine Nortriptyline	Dry mouth Difficulty sleeping Difficulty urinating	Sexual difficulties Constipation Dizziness Drowsiness
SSRI Citalopram Escitalopram Paroxetine Sertraline Fluoxetine	Nervousness Vivid dreams	Sleep disturbances Sexual difficulties Diarrhea
SNRI Venlafaxine Duloxetine Desvenlafaxine Milnacipram	Nausea Headache	Changes in liver chemistry (rare)

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

Dalton CB, Drossman DA. Available at: https://www.med.unc.edu/ibs/files/educational-gi-handouts/IBS%20and%20Antidepressants.pdf. Accessed 8 January, 2015.

Suggested Mechanisms of Analgesic Action of Antidepressants

Mechanism of Action	Site of Action	TCA	SNRI
Reuptake inhibition	Serotonin Noradrenaline	+ +	+ +
Receptor antagonism	α-adrenergic NMDA	+ +	- (+) milncipran
Blocking or activation of ion channels	Sodium channel blocker Calcium channel blocker Potassium channel activator	+ + +	(+) venlafaxine/ - duloxetine ? ?
Increasing receptor function	$GABA_B$ receptor	+ amitriptyline/ desipramine	?
Opioid receptor binding/ opioid-mediated effect	Mu- and delta-opioid receptor	(+)	(+) venlafaxine
Decreasing inflammation	Decrease of PGE2 production decrease of TNFα production		

GABA = γ-aminobutyric acid; NDMA = N-methyl-D-aspartate; PGE = prostaglandin E;
SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TNF = tumor necrosis factor

Verdu B *et al. Drugs* 2008; 68(18):2611-32.

How Effective Are Antidepressants in the Management of Visceral Pain?

- Studies are rare and data are controversial
- Some studies have been conducted on healthy volunteers, which influences outcomes
  - Limited studies in patients suffering from visceral pain
  - In IBS patients, low dose amitriptyline (10 – 25 mg/day) for six weeks increased pressure thresholds needed to induce pain using rectal distension

Some antidepressants increase pain threshold but have no effect on pain perception or discomfort

IBS = irritable bowel syndrome

Fioramonti J, Bueno L. *Gut*. 2002; 51(Suppl 1): i91–i95.

$\alpha_2\delta$ Ligands (Anticonvulsants) in the Management of Visceral Pain

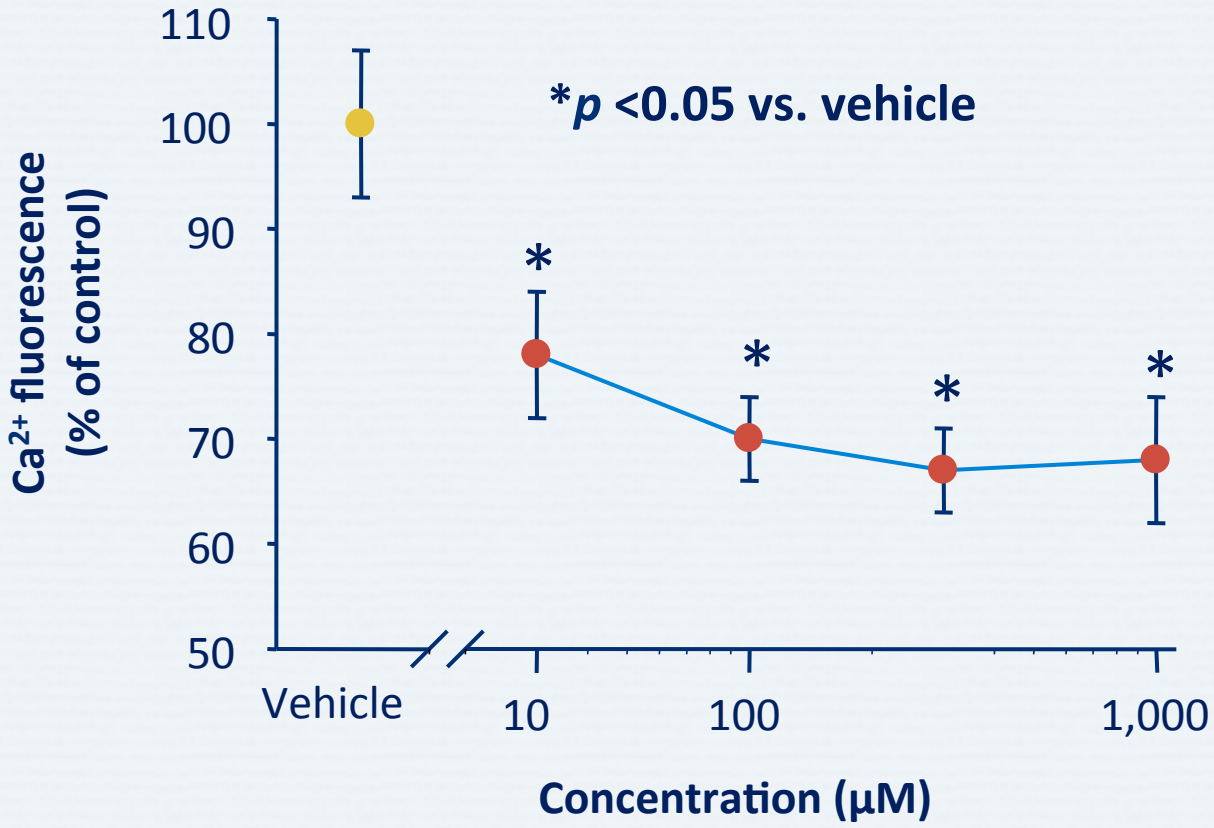
Gabapentin	Pregabalin
• Biochemically similar to GABA • MOA poorly understood • Binds to $\alpha_2\delta$ subunit of voltage-dependent calcium ion channel in CNS • May decrease Ca^{2+} influx into nerve terminal → affect release of multiple neurotransmitters, including substance P • Generally well tolerated • Dizziness, somnolence, and peripheral edema common • May increase pain threshold in IBS	• Successor to gabapentin • Binds to $\alpha_2\delta$ subunit of voltage-dependent calcium ion channel in CNS • Animal and human trials have demonstrated blunted visceral pain perception • One study in IBS patients showed an increase in sensory distension thresholds to normal levels and decreased pain

In theory, gabapentin and pregabalin may be helpful in the treatment of visceral pain. However, little data currently supports their use and all use is considered off-label.

CNS = central nervous system; GABA = gamma-aminobutyric acid; IBS = irritable bowel syndrome; MOA = mechanism of action

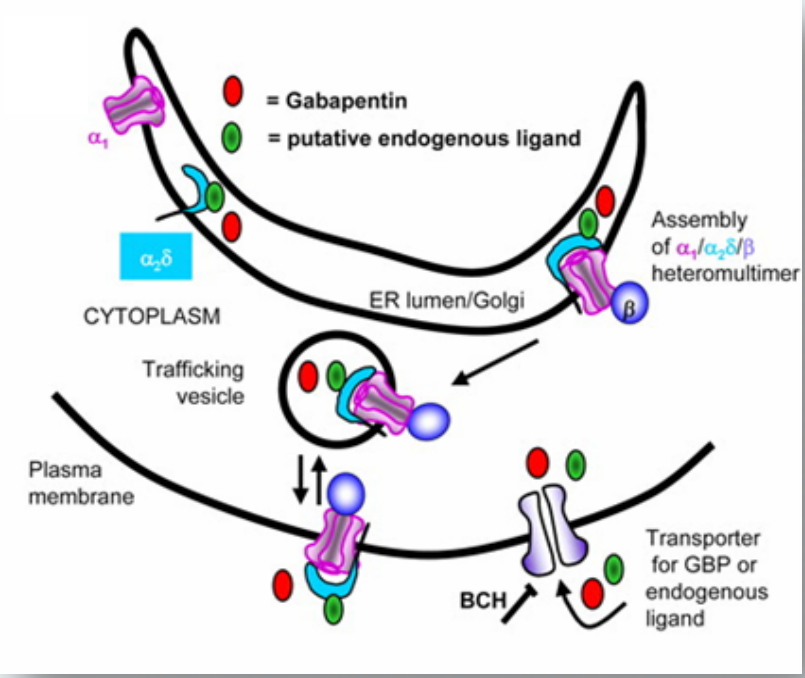
Lacy BE *et al. Therap Adv Gastroenterol*. 2009;2(4):221-38.

$\alpha_2\delta$ Ligands Reduce Calcium Influx in Depolarized Human Neocortex Synaptosomes

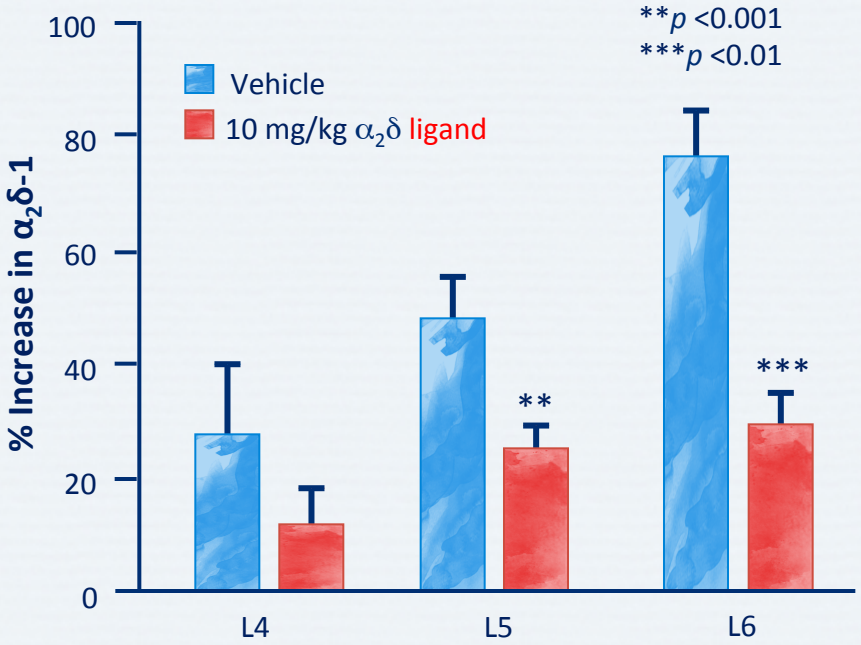


Fink K *et al. Neuropharmacology* 2002; 42(2):229-36.

$\alpha_2\delta$ Ligands Modulate Calcium Channel Trafficking



Hendrich et al. 2008



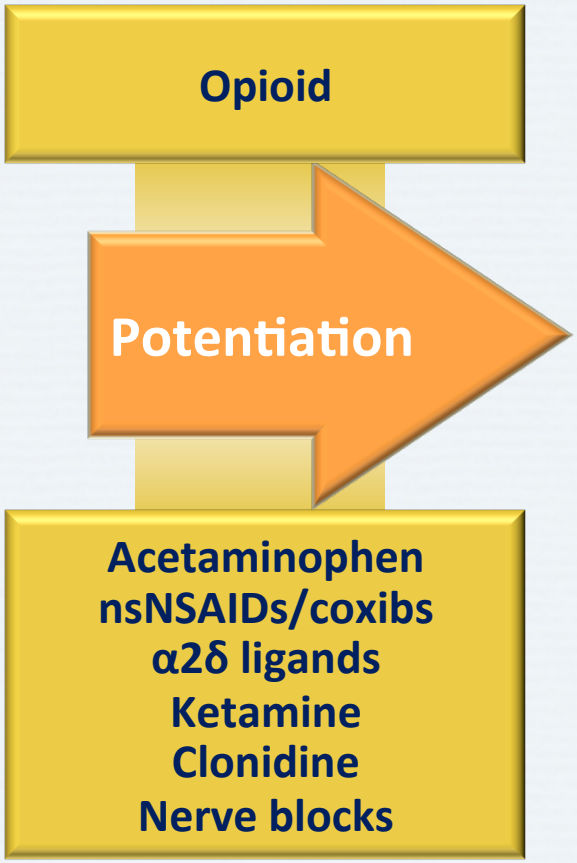
Bauer et al. 2009

- **$\alpha_2\delta$ ligands reduce trafficking of voltage-gated calcium channel complexes to cell surface *in vitro***
- **$\alpha_2\delta$ ligands prevent nerve-injury induced up-regulation of $\alpha_2\delta$ in the dorsal horn**

BCH = 2-(−)-endoamino-bicycloheptene-2-carboxylic acid; ER = endoplasmic reticulum; GBP = gabapentin

Bauer CS *et al. Neurosci* 2009; 29(13):4076-88; Hendrich J *et al. Proc Natl Acad Sci U S A* 2008; 105(9):3628-33.

Multimodal or Balanced Analgesia



- Improved analgesia
- ↓ doses of each analgesic
- ↓ severity of side effects of each drug

Coxib = COX-2 inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Kehlet H, Dahl JB. *Anesth Analg* 1993; 77(5):1048-56.

Synergistic or Additive Effects of Analgesics Used in Combination

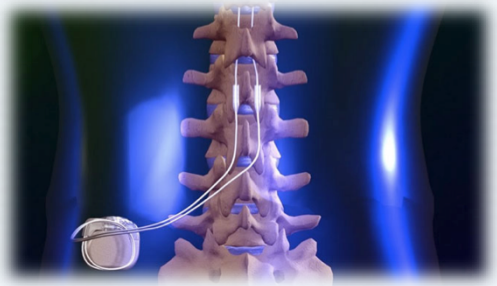
- Agents with different MOAs can potentially have additive or synergistic effects:
  - Acetaminophen/NSAIDS + opioids
  - Opioids + local anesthetics
  - Centrally acting agents + NSAIDS
  - Opioids + $\alpha_2\delta$ ligands (e.g., dexamethatomidine)

MOA = mechanism of action; NSAID = non-steroidal anti-inflammatory drug

Bader P *et al. Guidelines on Pain Management*. European Association of Urology; Arnhem, The Netherlands: 2010;
Kehlet H *et al. Acta Anaesthesiol Scand* 2010; 55(7):778-84; Paul S *et al*. Ceylon Med J 2010; 55(4):111-5; Robert B *et al. J Pain* 2010; 11(8):701-9;
Starks I *et al. ISRN Anesthesiology* 2011; 2011:742927; Vadivelu N *et al.* Yale J Biol Med 2010; 83(1):11-25.

Spinal Cord Stimulation (SCS) and Visceral Pain

- Used for >40 years to control complex intractable pain syndromes
  - Especially neuropathic pain
- Precise mechanism of analgesia is unknown
- Recent study (2015) showed SCS significantly reduced pain in IBS
  - Trend in reducing number of attacks, diarrheas
- 2014 study reported sacral nerve stimulation can significantly reduce symptoms and improve QoL of patients with IBS
- SCS is a minimally invasive treatment option IBS pain
  - Can also be used for chronic pelvic pain



IBS = irritable bowel syndrome; QoL = quality of life

Hunter C *et al*. *Pain Pract.* 2013;13(1):3-17; Lind G *et al.* Therapeutic value of spinal cord stimulation in irritable bowel syndrome – a randomized cross-over pilot study. Available at: http://ajpregu.physiology.org/content/early/2015/03/11/ajpregu.00022.2015. Accessed March 25, 2015; Abdel-Aziz S, Ghaleb A. *Pain Studies Treatment*. 2014;2:86-90.

Neuromodulation and Visceral Pain

- Sacral nerve root stimulation effective in:
  - Interstitial cystitis
  - Painful bladder syndrome
  - Chronic prostatitis
  - Coccygodynia
  - Vulvodynia
  - Anorectal pain
  - Chronic pelvic pain
  - Bladder dysfunction, incontinence, urinary retention

Abdel-Aziz S, Ghaleb A. *Pain Studies Treatment*. 2014;2:86-90.

Neuromodulation and Interstitial Cystitis (IC)

Percentage of patients with IC with ≥50% improvement in symptoms with neuromodulation

	Moderately Improved	Markedly Improved	Total Positive Response
Urinary frequency	38%	33%	71%
Urinary urgency	38%	24%	62%
Pelvic pain	35%	30%	65%
Pelvic pressure	40%	40%	80%
Quality of life	34%	38%	72%
Incontinence	38%	31%	69%
Bowel movements	34%	5%	39%
Vaginal pain	31%	23%	54%

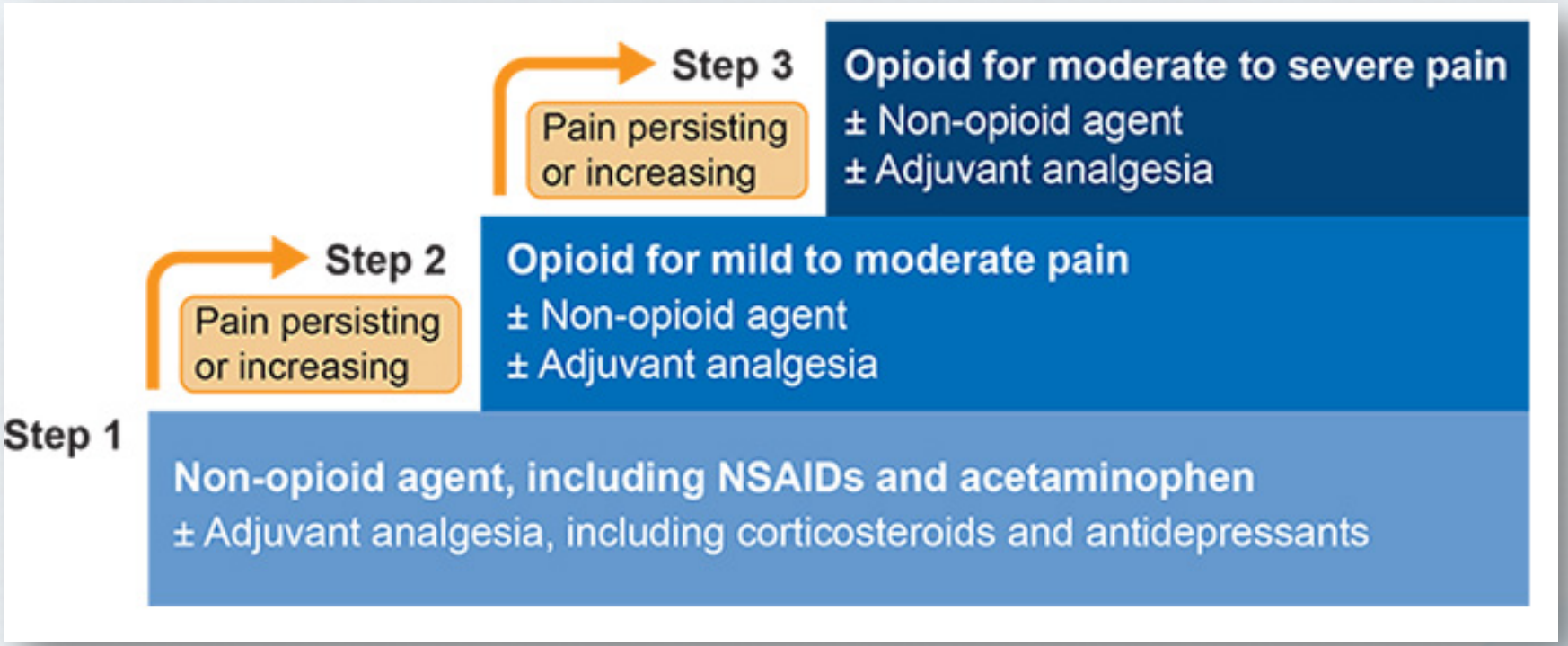
Peters KM. Neuromodulation for the Treatment of Refractory Interstitial Cystitis. *Rev Urol.* 2002;4(Suppl 1):S36-S43.

Treatment Recommendations for Visceral Pain

Guidelines for the Management of Visceral Pain

- No consensus treatment recommendations or guidelines exist for the general management of visceral pain
- WHO analgesic ladder can be used as a guideline in managing pain
  - WHO approach may need to be combined with other treatment modalities

World Health Organization Analgesic Ladder



Literature Cited

Ahmadi, S., Lippross, S., Neuhuber, W. L., & Zeilhofer, H. U. (2002). PGE(2) selectively blocks inhibitory glycinergic neurotransmission onto rat superficial dorsal horn neurons. *Nature Neuroscience*, *5*(1), 34–40. http://doi.org/10.1038/nn778

Baba, H., Kohno, T., Moore, K. A., & Woolf, C. J. (2001). Direct activation of rat spinal dorsal horn neurons by prostaglandin E2. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *21*(5), 1750–1756.

Bauer, C. S., Nieto-Rostro, M., Rahman, W., Tran-Van-Minh, A., Ferron, L., Douglas, L., … Dolphin, A. C. (2009). The Increased Trafficking of the Calcium Channel Subunit α2δ-1 to Presynaptic Terminals in Neuropathic Pain Is Inhibited by the α2δ Ligand Pregabalin. *The Journal of Neuroscience*, *29*(13), 4076–4088. http://doi.org/10.1523/JNEUROSCI.0356-09.2009

Brunton, L., Chabner, B., & Knollman, B. (2011). *Goodman and Gilman's The Pharmacological Basis of Therapeutics, Twelfth Edition* (12 edition). New York: McGraw-Hill Education / Medical.

Clemett, D., & Goa, K. L. (2000). Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs*, *59*(4), 957–980.

Crowell, M. D., Jones, M. P., Harris, L. A., Dineen, T. N., Schettler, V. A., & Olden, K. W. (2004). Antidepressants in the treatment of irritable bowel syndrome and visceral pain syndromes. *Current Opinion in Investigational Drugs (London, England: 2000)*, *5*(7), 736–742.

Literature Cited

Dalton, C., & Drossman, D. (n.d.). The Use of Antidepressants in the Treatment of Irritable Bowel Syndrome and Other Functional GI Disorders. Retrieved June 23, 2015, from https://www.med.unc.edu/ibs/files/educational-gi-handouts/IBS%20and%20Antidepressants.pdf

Davis, M. P. (2012). Drug management of visceral pain: concepts from basic research. *Pain Research and Treatment*, *2012*, 265605. http://doi.org/10.1155/2012/265605

Dolan, S., & Nolan, A. M. (1999). N-methyl D-aspartate induced mechanical allodynia is blocked by nitric oxide synthase and cyclooxygenase-2 inhibitors. *Neuroreport*, *10*(3), 449–452.

Fink, K., Dooley, D. J., Meder, W. P., Suman-Chauhan, N., Duffy, S., Clusmann, H., & Göthert, M. (2002). Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. *Neuropharmacology*, *42*(2), 229–236.

Fioramonti, J., & Bueno, L. (2002). Centrally acting agents and visceral sensitivity. *Gut*, *51 Suppl 1*, i91–95.

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological Bulletin*, *133*(4), 581–624. http://doi.org/10.1037/0033-2909.133.4.581

Gottschalk, A., & Smith, D. S. (2001). New concepts in acute pain therapy: preemptive analgesia. *American Family Physician*, *63*(10), 1979–1984.

Literature Cited

Gourlay, G. K. (2005). Advances in opioid pharmacology. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *13*(3), 153–159. http://doi.org/10.1007/s00520-004-0690-6

Hendrich, J., Van Minh, A. T., Heblich, F., Nieto-Rostro, M., Watschinger, K., Striessnig, J., … Dolphin, A. C. (2008). Pharmacological disruption of calcium channel trafficking by the alpha2delta ligand gabapentin. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(9), 3628–3633. http://doi.org/10.1073/pnas.0708930105

Institute of Medicine. (2011). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington DC: National Academies Press.

Kehlet, H., & Dahl, J. B. (1993). The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesthesia and Analgesia*, *77*(5), 1048–1056.

Lacy, B. E., Weiser, K., & De Lee, R. (2009). The treatment of irritable bowel syndrome. *Therapeutic Advances in Gastroenterology*, *2*(4), 221–238. http://doi.org/10.1177/1756283X09104794

Literature Cited

Lind, G., Winter, J., Linderoth, B., & Hellström, P. M. (2015). Therapeutic value of spinal cord stimulation in irritable bowel syndrome: a randomized crossover pilot study. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, *308*(10), R887–R894. http://doi.org/10.1152/ajpregu.00022.2015

Mayo Foundation for Medical Education and Research. (2006). *Comprehensive Pain Rehabilitation Center Program Guide*. Rochester MN: Mayo Clinic.

McMahon, S. B. (Ed.). (2013). *Wall and Melzack's textbook of pain* (6th ed). Philadelphia, PA: Elsevier/Saunders.

Moreland, L. W., & St Clair, E. W. (1999). The use of analgesics in the management of pain in rheumatic diseases. *Rheumatic Diseases Clinics of North America*, *25*(1), 153–191, vii.

Patrizi, F., Freedman, S. D., Pascual-Leone, A., & Fregni, F. (2006). Novel therapeutic approaches to the treatment of chronic abdominal visceral pain. *TheScientificWorldJournal*, *6*, 472–490. http://doi.org/10.1100/tsw.2006.98

Peters, K. M. (2002). Neuromodulation for the treatment of refractory interstitial cystitis. *Reviews in Urology*, *4 Suppl 1*, S36–43.

Literature Cited

Samad, T. A., Moore, K. A., Sapirstein, A., Billet, S., Allchorne, A., Poole, S., … Woolf, C. J. (2001). Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature*, *410*(6827), 471–475. http://doi.org/10.1038/35068566

Trescot, A. M., Datta, S., Lee, M., & Hansen, H. (2008). Opioid pharmacology. *Pain Physician*, *11*(2 Suppl), S133–153.

Vadivelu, N., Mitra, S., & Narayan, D. (2010). Recent advances in postoperative pain management. *The Yale Journal of Biology and Medicine*, *83*(1), 11–25.

Vane, J. R., & Botting, R. M. (1995). New insights into the mode of action of anti-inflammatory drugs. *Inflammation Research: Official Journal of the European Histamine Research Society ... [et Al.]*, *44*(1), 1–10.

Verdu, B., Decosterd, I., Buclin, T., Stiefel, F., & Berney, A. (2008). Antidepressants for the treatment of chronic pain. *Drugs*, *68*(18), 2611–2632.

Wall, P., & Melzack, R. (1999). *Textbook of Pain*. London: Churchill Livingstone.

Woolf, C. J. (1994). A new strategy for the treatment of inflammatory pain. Prevention or elimination of central sensitization. *Drugs*, *47 Suppl 5*, 1–9; discussion 46–47.

Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: increasing the gain in pain. *Science (New York, N.Y.)*, *288*(5472), 1765–1769.