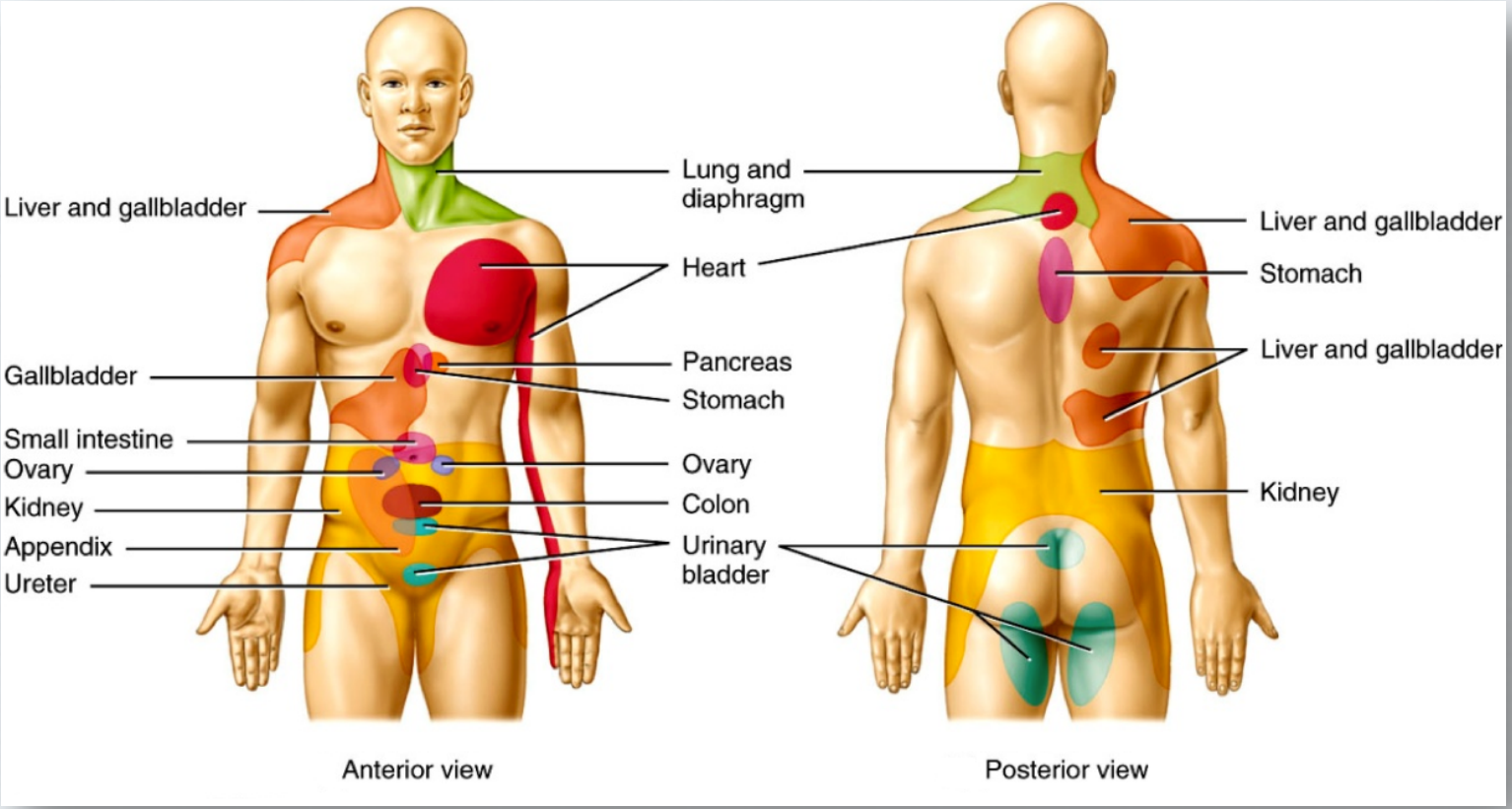

KNOW
VISCERAL
PAIN

Learning Objectives

- After completing this module, participants will be able to:
  - Discuss the types, prevalence, and causes of visceral pain
  - Understand the patient burden caused by visceral pain
  - Explain the pathophysiological mechanisms of visceral pain
  - Describe the mechanisms, benefits, and adverse effects of various pharmacological treatments for visceral pain
  - Select appropriate pharmacological and non-pharmacological strategies for the management of visceral pain

What Is Visceral Pain?

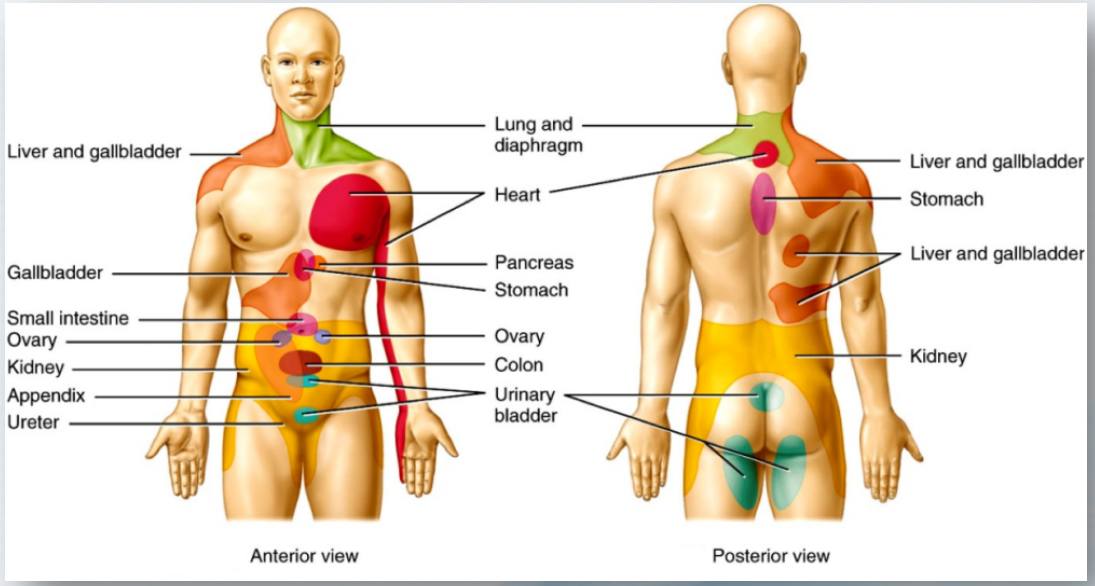


- **Results when nociceptors in the thoracic, abdominal, or pelvic viscera are activated**
- **Can occur when internal organs are injured/damaged due to inflammation, distention, or hypoxia.**

1. IASP. Available at http://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/VisceralPainFactSheets/2-Neurobiology.pdf. Accessed 1 December, 2014; 2. Collett B. *Br J Pain*. 2013;7(1):6-7;

Examples of Visceral Pain

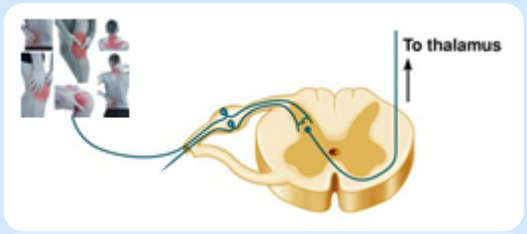
- Myocardial ischemia[1]
- Kidney and ureteral stones[1]
- Peptic ulcer
- Inflammatory bowel diseases (Crohn's disease[3], Ulcerative colitis)
- Biliary colic/ cholecystitis
- Appendicitis, diverticulitis[6]
- Pancreatitis[3]
- Cancer[3]
- Irritable bowel syndrome[1]
- Functional dyspepsia[3]
- Endometriosis[5]
- Vulvodynia[2]
- Interstitial cystitis[4]

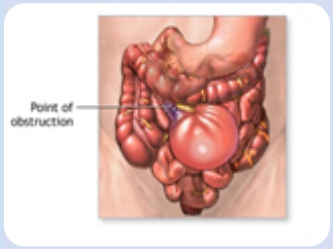


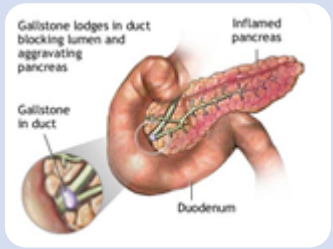
1. ISAP. Visceral Pain. Available at: http://iasp.files.cms-plus.com/Content/ContentFolders/Publications2/PainClinicalUpdates/Archives/PCU05-6_1390263870315_22.pdf. Accessed 5 March, 2015; 2. Wesselmann U *et al*. *Drug Discov Today Ther Strateg*. 2009;6(3):89-95; 3. Davis MP. *Pain Res Treat.* 2012;2012:265605; 4. Wesselmann U. *Urology*. 2001;57(6 Suppl 1):32-9; 5. Issa B *et al. Gut.* 2012;61(3):367-72; 6. Humes DJ *et al. Neurogastroenterol Motil.* 2012;24(4):318-e163.

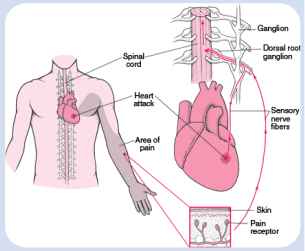
Somatic vs. Visceral Pain

Somatic	Visceral
• Can be superficial (skin, muscle) or deep (joints, tendons, bones) • Nociceptors are involved • Often well localized • Usually described as throbbing or aching	• Involves hollow organ and smooth muscle nociceptors that are sensitive to stretching, hypoxia and inflammation • Pain is usually referred, poorly localized, vague and diffuse • May be associated with autonomic symptoms (*e.g.*, pallor, sweating, nausea, blood pressure and heart rate changes)









McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
Sikandar S, Dickenson AH. *Curr Opin Support Palliat Care* 2012; 6(1):17-26.

Acute vs. Chronic Visceral Pain

Acute

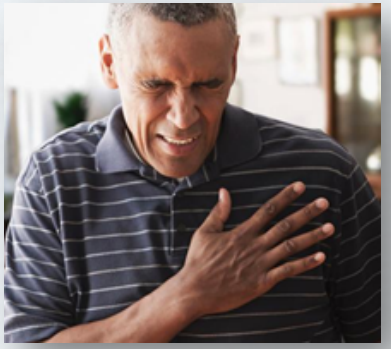
Rapid onset
Severe/intense attacks
Rapid progression
Duration <3 months
Commonly due to hypoxia, distention, inflammation

Chronic

Duration ≥3 months
Continuous sometimes accompanied by flare up/ exacerbations

Speiser P. *Wien Med Wochenschr.* 2001;151(21-23):565-7; Karnath BM, Breitkopf, DM. *Hospital Physician*. 2007;July:41-8.

Visceral Pain and Gender



- Gallbladder disease
- Irritable bowel syndrome
- Interstitial cystitis
- Vulvodynia
- Dysmenorrhea
- Bladder pain

- Coronary heart disease
- Prostate pain syndrome/prostatitis
- Scrotal pain

Gender differences exist in the perception of pain from internal organs

Giamberardino MA. *Pain Clinical Updates.* 2005;XIII(6):1-6; Pappagallo M. In: Chronic Pain: A Primer for Physicians. 1st Edition. 2008. (Andrew Ward) Remedica, London; Wesselmann U *et al*. *Drug Discov Today Ther Strateg*. 2009;6(3):89-95.

Discussion Question

WHAT PROPORTION OF YOUR PATIENTS SUFFER FROM VISCERAL PAIN?

Prevalence of Chronic Visceral Pain

- By far the most common type of pain[1]
- Prevalence
  - Endometriosis: 10%[2]
  - Irritable bowel syndrome: 11%[3]
  - Vulvodynia: 10-28%[4]*
  - Interstitial cystitis: 6.5%[5]*
- Abdominal pain with no definite explanation:
  - 6th most common cause of hospital admission for any reason in women
  - 10th most common reason in men[1]

*True prevalence unknown and published prevalence rates likely underestimate the true prevalence

1. Collett B. *Br J Pain*. 2013;7(1):6-7; 2. Halder S and Locke GR III. Epidemiology and social impact of visceral pain. In: Giamberardino MA (ed) Visceral pain: clinical, pathophysiological and therapeutic aspects. Oxford University Press. 2009; 1-7; 2. WHO. Endometriosis: an overview of Cochrane Reviews. 2014. Available at: http://apps.who.int/rhl/gynaecology/gynaecology_infertility/cd009590/en/index.html. Accessed February 19, 2015; 3. Canavan C *et al*. *Clin Epidemiol.* 2014;6:71-80; 4. Harlow BL *et al. J Women's Health (Larchmt).* 2009;18(9):1333-40; 5. Berry SH *et al*. *J Urol*. 2011;186(2):540-4.

Burden of IBS, IC, Vulvodynia, and Endometriosis

- Reduced quality of life
  - Physical and social functioning
  - Psychological disturbances
  - Absenteeism and presenteeism
- Various co-existing conditions
  - Fibromyalgia
  - Celiac disease
  - GERD
  - Chronic fatigue syndrome
  - Chronic yeast infection
  - Dyspareunia
  - Infertility
- Significant direct and indirect health care costs

Pain from internal organs is widespread and its social burden may surpass that of somatic pain

GERD = gastroesophageal reflux disease; IBS = Irritable bowel syndrome; IC = Interstitial cystitis

Giamberardino MA. *Pain Clinical Updates.* 2005;XIII(6):1-6; Hanno PM. *Rev Urol.* 2002; 4(Suppl 1): S3-S8; Rothrock NE *et al. J Urol.* 2002;167(4):1763-7; Nickel JC *et al. J Urol.* 2007;177(5):1832-6; Arnold LD *et al. Obstet Gynecol.* 2006;107(3):617-24; Reed BD *et al. Obstet Gynecol*. 2012;120(1):145-51; Xie Y *et al. Curr Med Res Opin.* 2012;28(4): 601-8; Levy AR *et al. J Obstet Gynaecol Can.* 2011;33(8):830-7; Simoens S *et al. Hum Reprod.* 2012;27(5):1292-9; Hulisz D. *J Manag Care Pharm.* 2004;10(4):299-309.

Impact of Chronic Visceral Pain

- **Irritable Bowel Syndrome**[1]
  - QoL poorer than patients with asthma, migraine, GERD
    - In most domains, poorer than in patients with diabetes
  - Associated costs are about 50% higher than for population controls
  - **Endometriosis**[2]
  - Quality-adjusted life years per woman = 0.809
  - Economic burden similar to that for diabetes, Crohn's disease, and rheumatoid arthritis
  - **Vulvodynia**[3]
  - QoL poorer than kidney transplant recipients and people with prior osteoporosis-related fracture
  - **Interstitial cystitis**[4]
  - QoL poorer than dialysis patients with ESRD

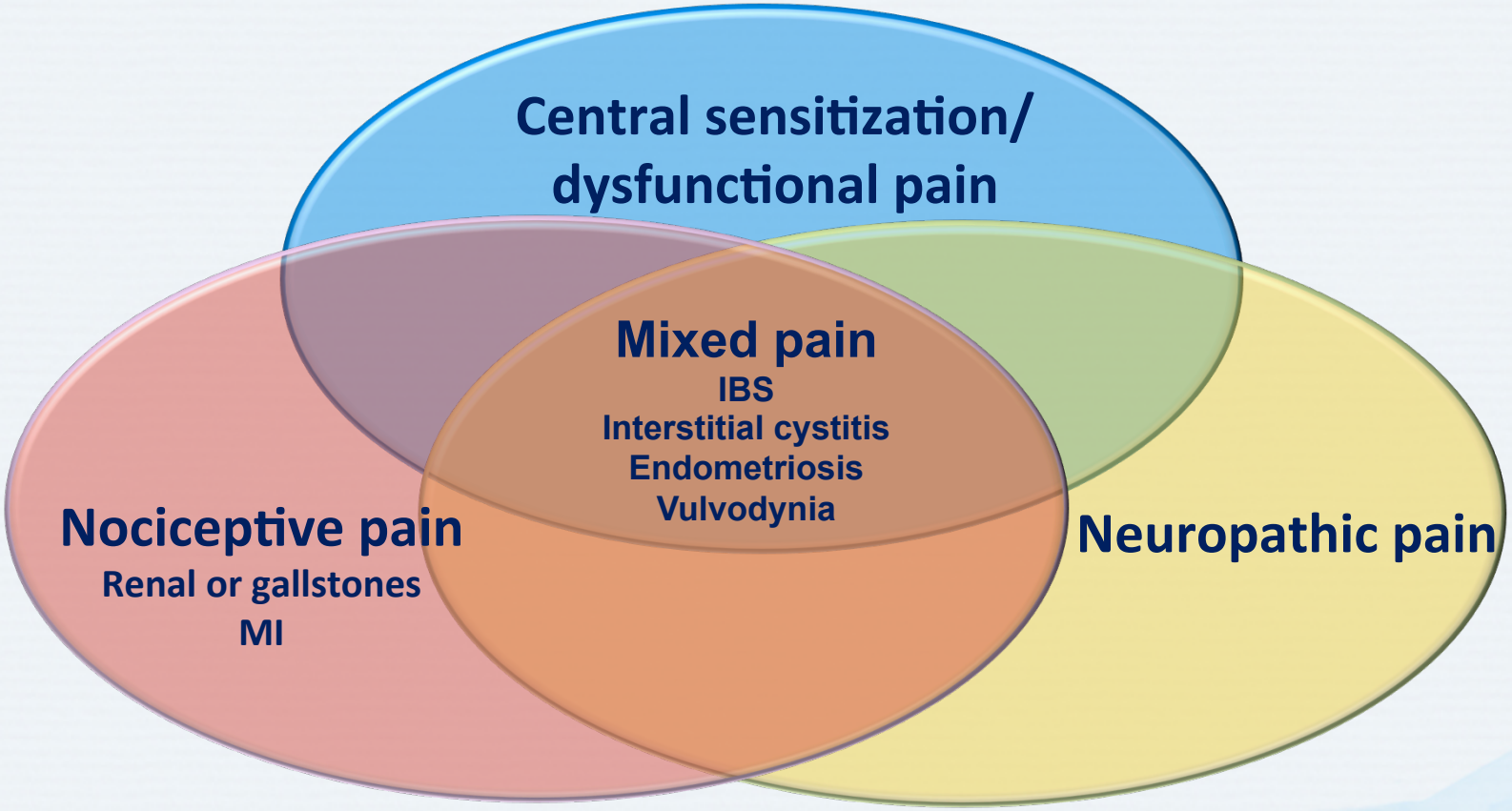
Visceral pain disorders can be very costly and significantly negatively impact patients' lives with psychological distress, disturbance of work and sleep and sexual dysfunction

GERD = gastroesophageal reflux disease; QoL = quality of life; ESRD = end-stage renal disease

1. Collett B. *Br J Pain*. 2013;7(1):6-7; 2. Halder S and Locke GR III. Epidemiology and social impact of visceral pain. In: Giamberardino MA (ed) Visceral pain: clinical, pathophysiological and therapeutic aspects. Oxford University Press. 2009; 1-7; Sikandar S, Dickenson AH. Curr Opin Support Palliat Care. 2012;6(1):17-26.

Pathophysiology of Visceral Pain

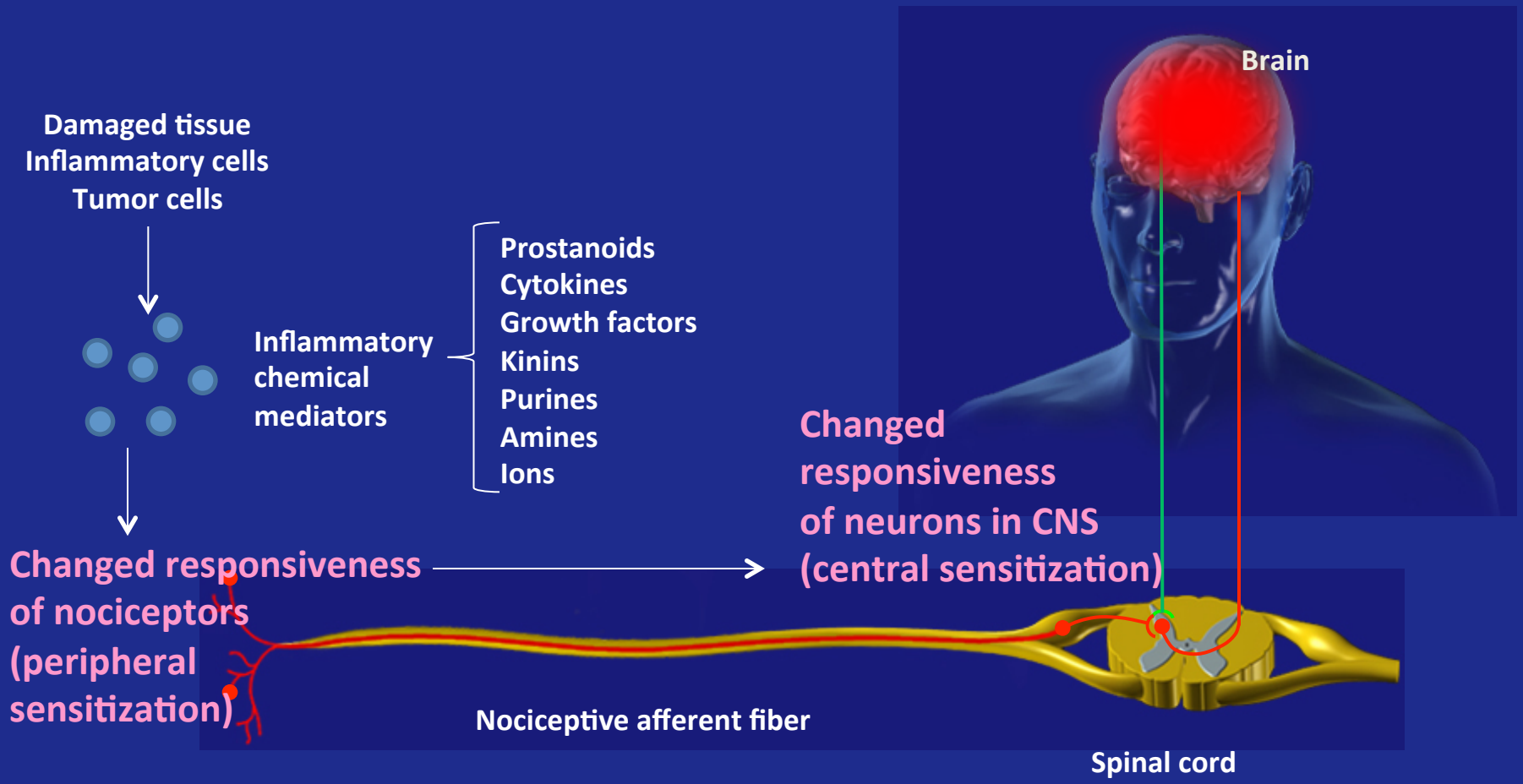
Pathophysiological Classification of Pain



IBS = irritable bowel syndrome; MI = myocardial infarction

Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90; Jensen TS *et al. Pain* 2011; 152(10):2204-5;
Julius D *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
Ross E. *Expert Opin Pharmacother* 2001; 2(1):1529-30; Webster LR. *Am J Manag Care* 2008; 14(5 Suppl 1):S116-22; Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

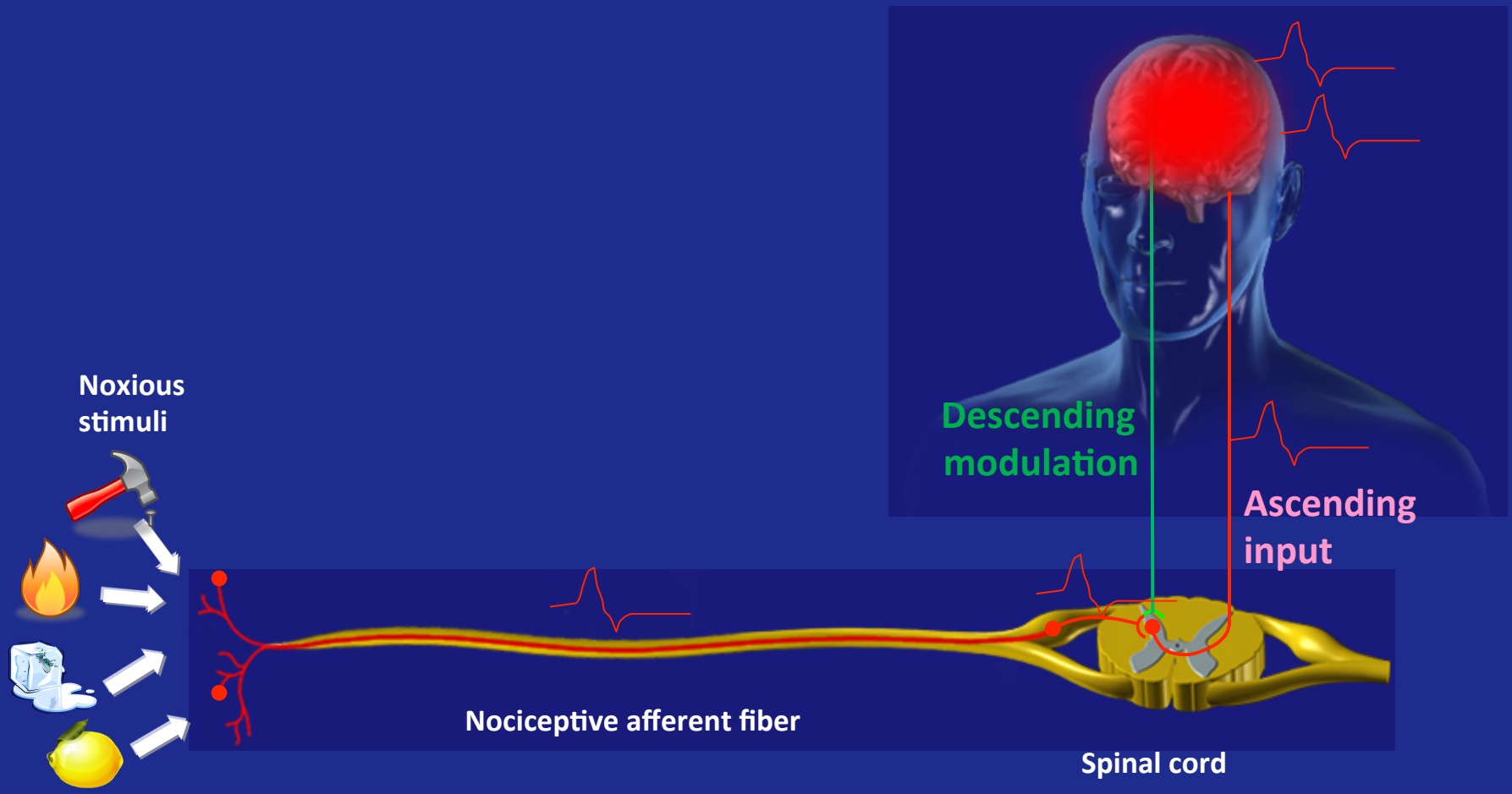
Inflammation



CNS = central nervous system

Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7.

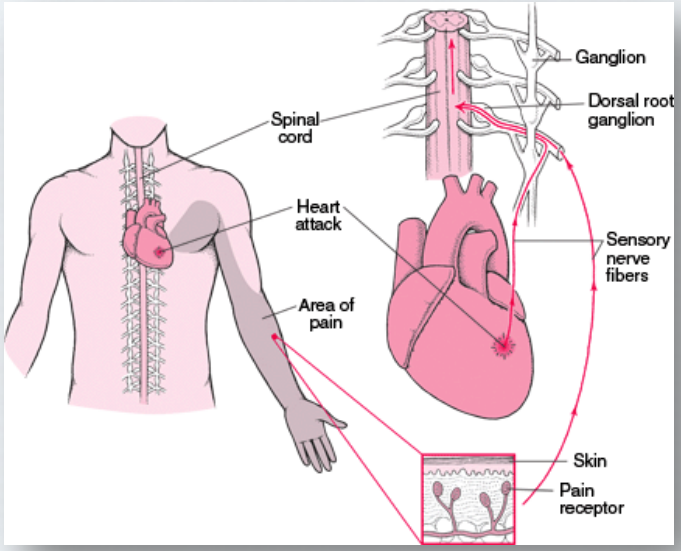
Nociception: Neural Process of Encoding Noxious Stimuli

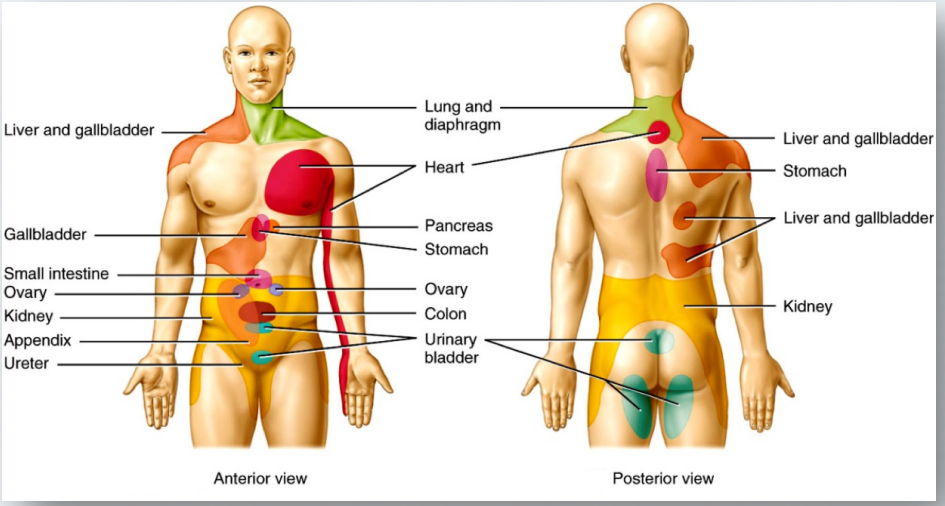


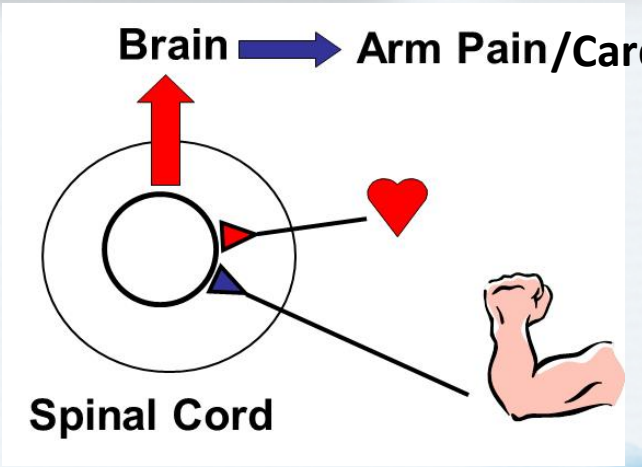
Consequences of encoding may be autonomic (*e.g.*, elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain perception is not necessarily implied.

Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7.

Convergence and Referred Pain

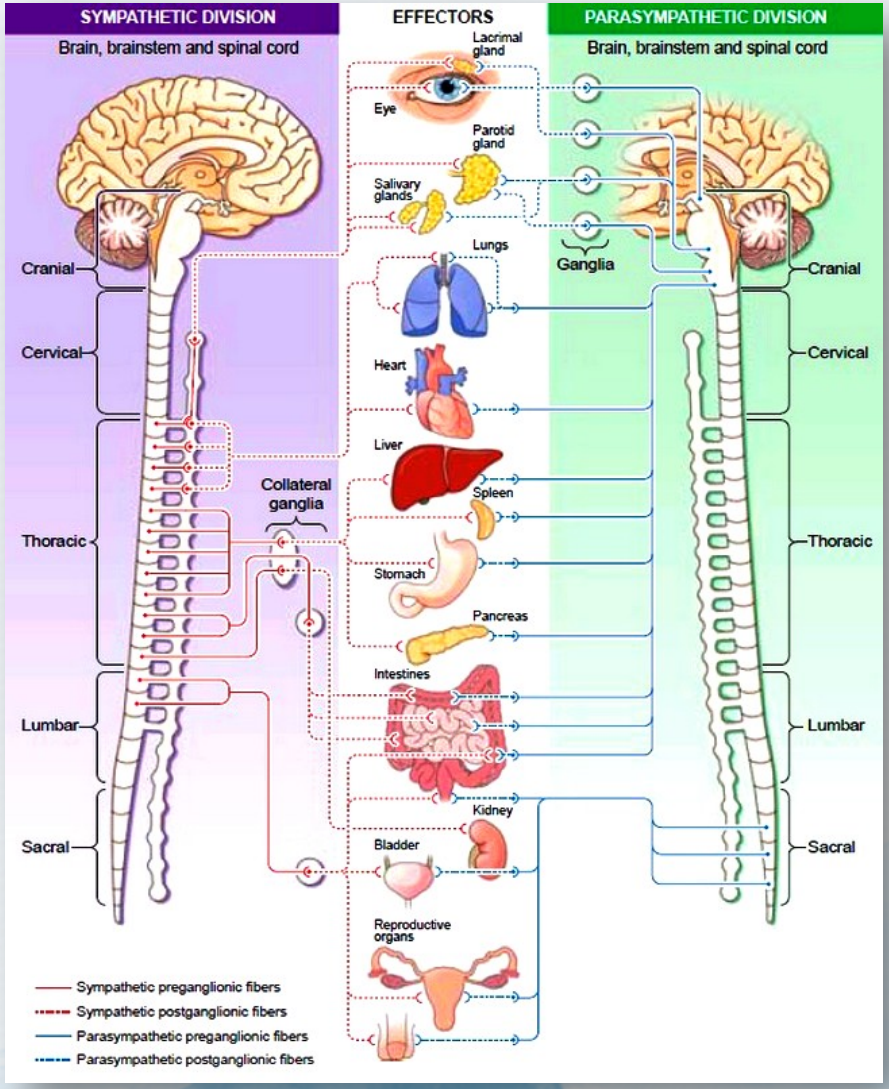




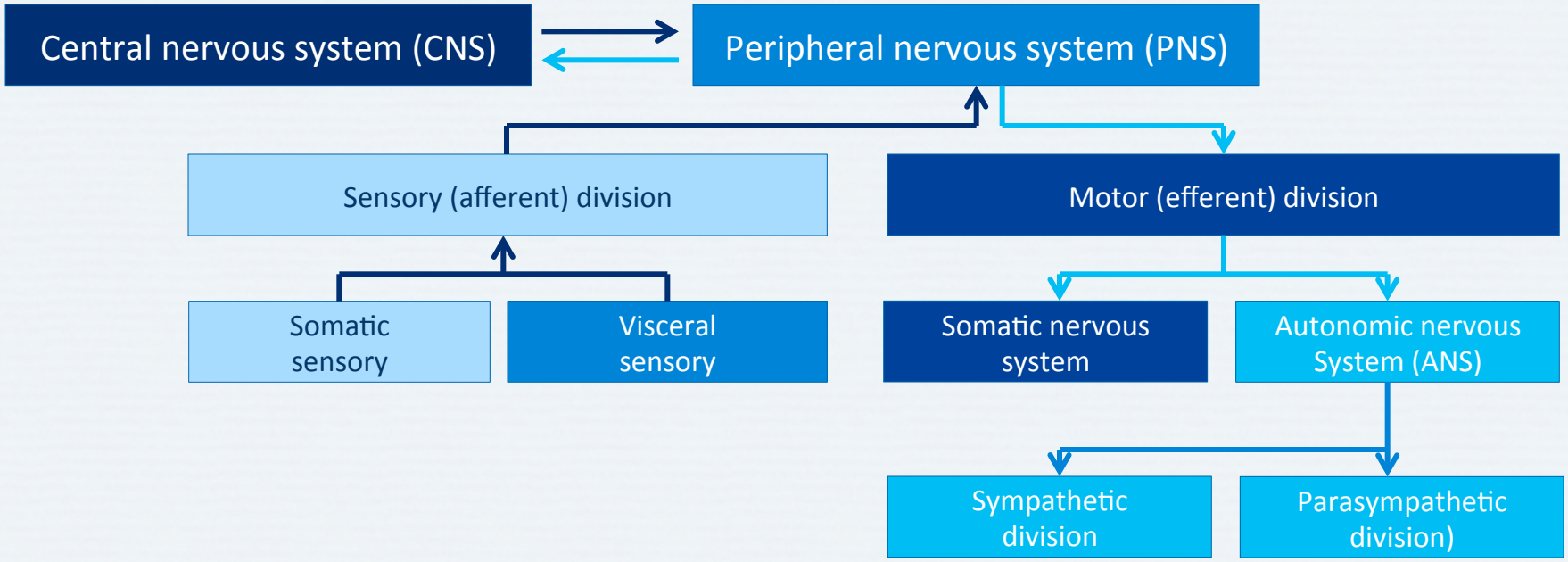


Autonomic Contributions in Visceral Pain

- Pallor
- Sweating
- Blood pressure changes
- Tachycardia
- Diarrhoea



The Autonomic Nervous System and Visceral Sensory Neurons



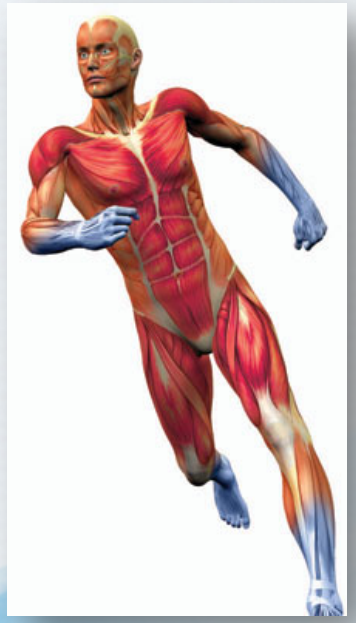
Sympathetic Nervous System: The "Fight or Flight" System

Involves activities such as exercise, excitement, emergency, embarrassment

Other activities are reduced (GI, urinary)

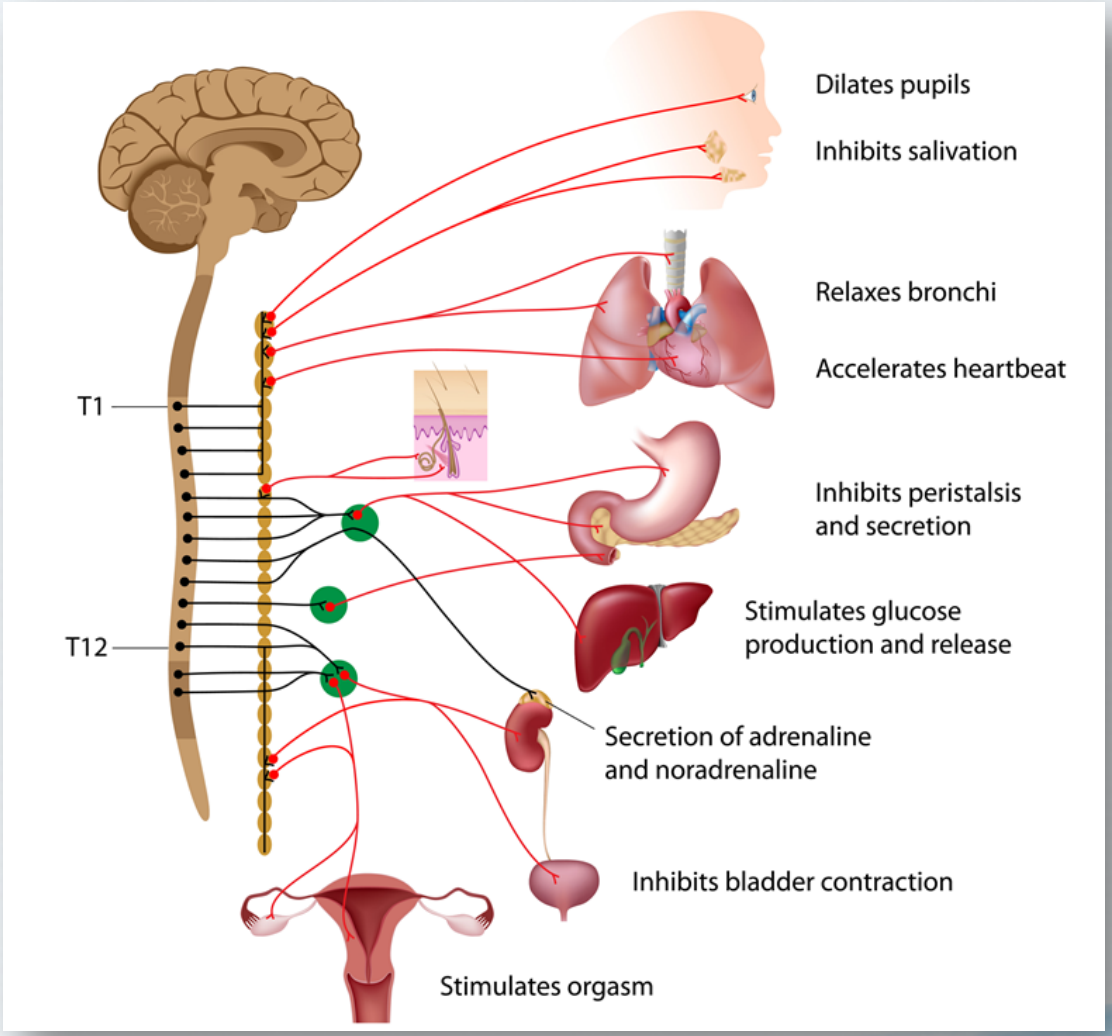
Increased blood flow to muscles

- ↑ Heart rate - ↑ breathing (rapid and deep)
- Bronchioles dilate - ↑ ventilation (deliver more oxygen to cells)
- Skin is cold and sweaty
- Pupils dilate
- Liver releases more glucose into circulation
- Lipolysis to the level of the adipocytes



GI = gastrointestinal

Sympathetic Nervous System

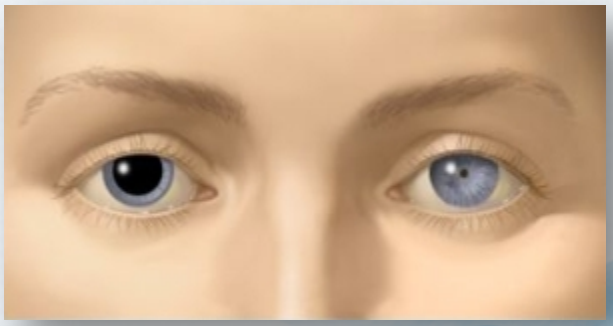


- Cervical-thoraco-lumbar division
- Short preggl/long postggl

Parasympathetic Nervous System

- Active in non-stressful situations
- Keeps the body energy

- ↑ GI tract activity (salivation, digestion, defecation, urination)
- ↓ Heart rate, blood pressure
- ↓ Respiration rate
- Constricted pupils (miosis), lacrimation, accommodation for improved close vision
- Warm skin



GI = gastrointestinal

Signs and Symptoms of Visceral Pain

General Characteristics of Visceral Pain

- Poorly localized with referral to somatic structures
- Produces nonspecific regional or whole-body motor responses
- Produces strong autonomic responses
- Leads to sensitization of somatic tissue
- Produces strong affective responses

Sikander S, Dickenson AH. *Curr Opin Support Palliat Care.* 2012;6(1):17-26.

Importance of Diagnosing and Treating Underlying Condition

- Visceral pain symptoms may herald a life-threatening underlying cause
- Examples:
  - Myocardial infarction
  - Intestinal obstruction
  - Acute pancreatitis
  - Peritonitis

Prompt evaluation and specific diagnosis of visceral pain is mandatory

Giamberardino MA. Visceral pain. 2005;XIII(6):1-6.

Be Alert for Red Flags

- Onset after age 50
- Rebound phenomena in physical examination
- Gastrointestinal bleeding
- Anemia
- Weight loss
- Severe diarrhea
- Rectal bleeding/blood in stool
- Fever
- Family history of colorectal cancer, irritable bowel disease, celiac disease, other cancers
- Vomiting
- Recent travel to areas known for enteric pathogens
- Physical or psychological abuse is a marker for visceral pain – especially in the pelvic region

Pappagallo M. In: Chronic Pain: A Primer for Physicians. 1st Edition. 2008. (Andrew Ward) Remedica, London; Black TP et al. *J Gastrointestin Liver Dis.* 2012;21(2):153-6; Rosenberg M et al. *Cleve Clin J Med.* 2005;72(8):698-704.

Discussion Question

WHAT ARE SOME OF YOUR BIGGEST CHALLENGES IN DIAGNOSING PATIENTS WITH VISCERAL PAIN?

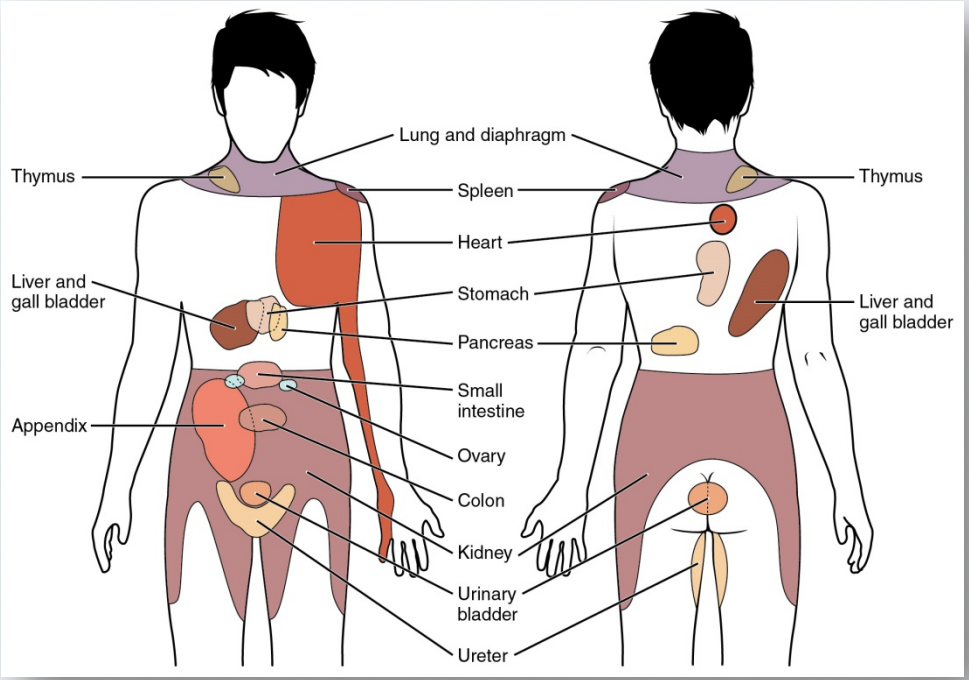
HOW DO YOU OVERCOME THESE CHALLENGES?

Diagnosis of Visceral Pain

Discussion Question

HOW DO YOU DIAGNOSE VISCERAL PAIN IN YOUR PRACTICE?

Referred Pain



- Relative to early, diffuse visceral pain, **referred** visceral pain is
  - Better localized
  - May be accompanied by neurovegetative signs
  - Less likely to be accompanied by emotional signs
  - Similar in quality to pain of deep somatic origin
- May be associated with hyperalgesia of the tissues in the painful area

Hudspith MJ *et al.* In: Hemmings HC, Hopkins PM (eds). *Foundations of Anesthesia*. 2nd ed. Elsevier; Philadelphia, PA: 2006.

The 3L Approach to Diagnosis[1]

Listen[1,2]

Patient verbal descriptors of pain

Locate[1,3]

Affected Visceral organ

Look[1,4]

Vital signs and physical examination

Fourth "L" may be lab testing

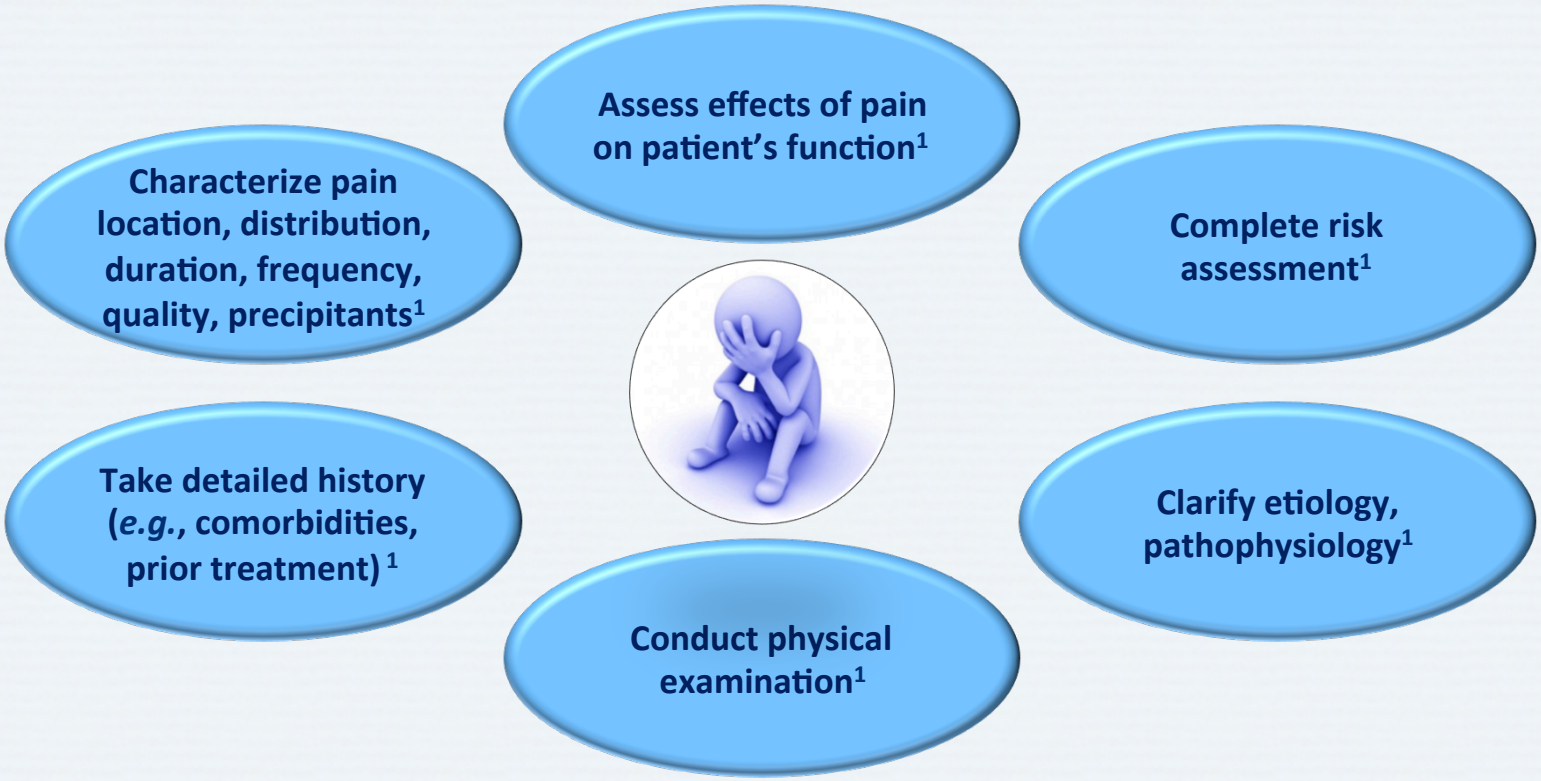
1. Freynhagen R, Bennett MI. *BMJ* 2009; 339:b3002; 2. Bennett MI *et al*. *Pain* 2007; 127(3):199-203;
3. Freynhagen R *et al*. *Pain* 2008; 135(1-2):65-74; 4. Freynhagen R *et al. Curr Pain Headache Rep* 2009; 13(3):185-90.

Visceral Hyperalgesia

- Very frequent in the clinical setting
- Increased sensitivity of an internal organ such that even non-pathological, normal stimuli may produce pain from that organ
- Usual cause is visceral inflammation → peripheral and central sensitization
- Examples
  - Ingestion of foods/liquids when esophagus/stomach mucosa inflamed
  - Pain from normal bladder distension with inflamed lower urinary tract

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

Comprehensive Pain Assessment



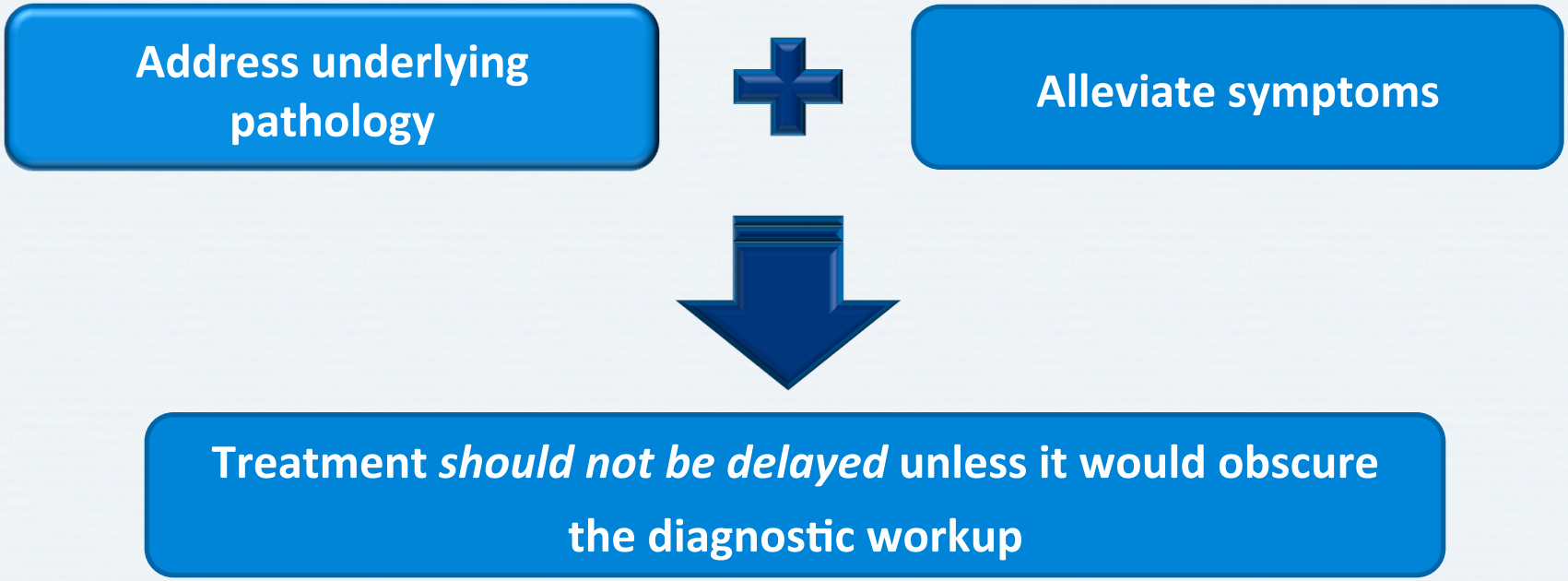
Appropriate work-up may include lab tests for infectious and inflammatory processes and imaging of sites not readily assessed by physical exam[2]

National Pharmaceutical Council, Joint Commission on Accreditation of Healthcare Organizations. *Pain: Current Understanding of Assessment, Management, and Treatments*. Reston, VA: 2001; Passik SD, Kirsh KL *CNS Drug* 2004; 18(1):13-25; 2. IASP. Available at: http://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/VisceralPainFactSheets/3-AcuteVsChronic.pdf. Accessed 1 December, 2014.

Discussion Question

WHAT TREATMENTS DO YOU USE FOR VISCERAL PAIN?

Goals in the Management of Visceral Pain



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.

Treatment of Visceral Pain: Overview

Pharmacotherapy

Non-pharmacological Treatments

Interventional Techniques

PPI = proton pump inhibitor

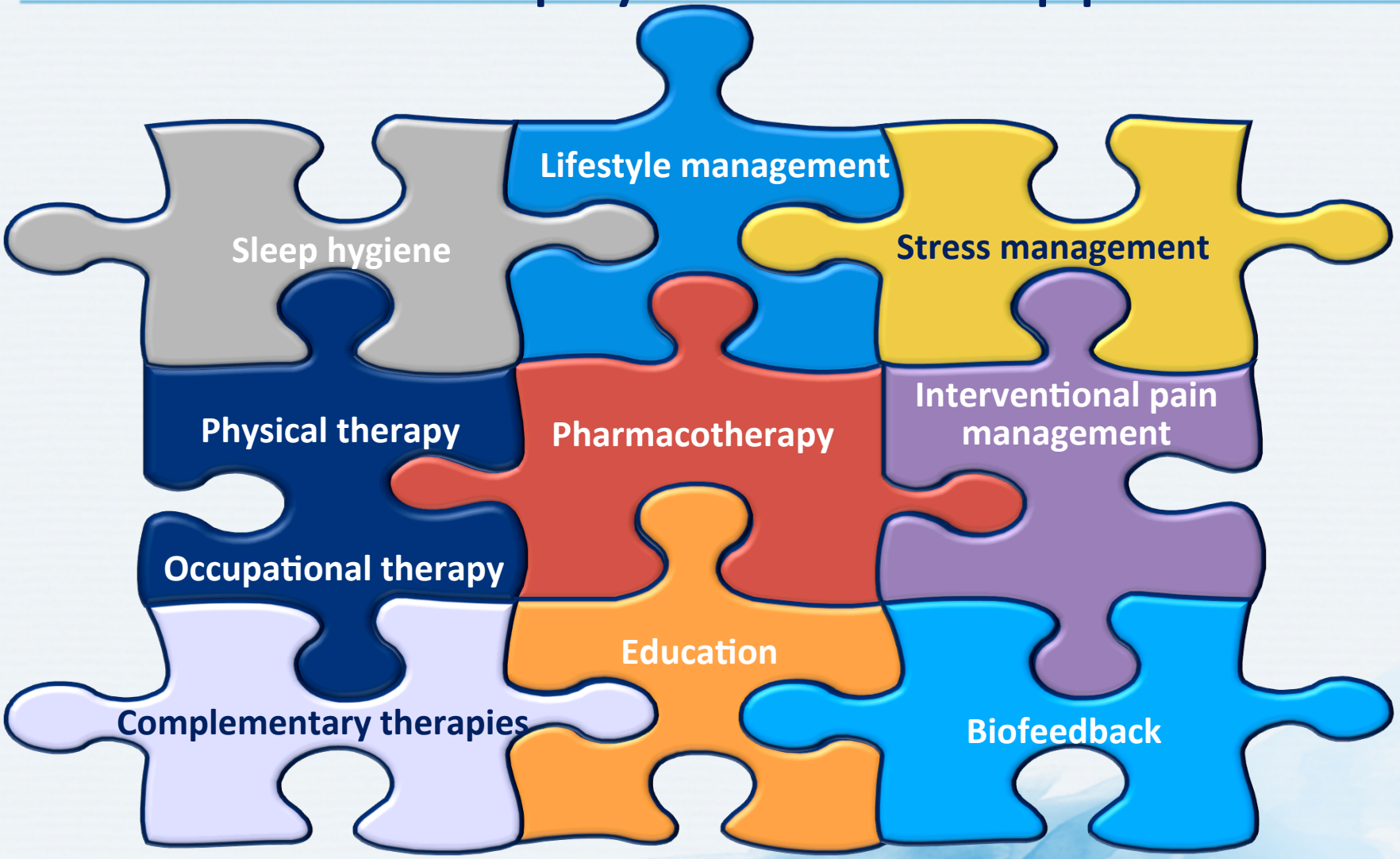
Giamberardino MA. *Pain Clinical Updates.* 2005;XIII(6):1-6.

Non-pharmacological Management of Visceral Pain

Discussion Question

WHAT NON-PHARMACOLOGICAL APPROACHES TO VISCERAL PAIN MANAGEMENT HAVE YOU FOUND HELPFUL FOR YOUR PATIENTS?

Multimodal Treatment of Visceral Pain Based on Biopsychosocial Approach



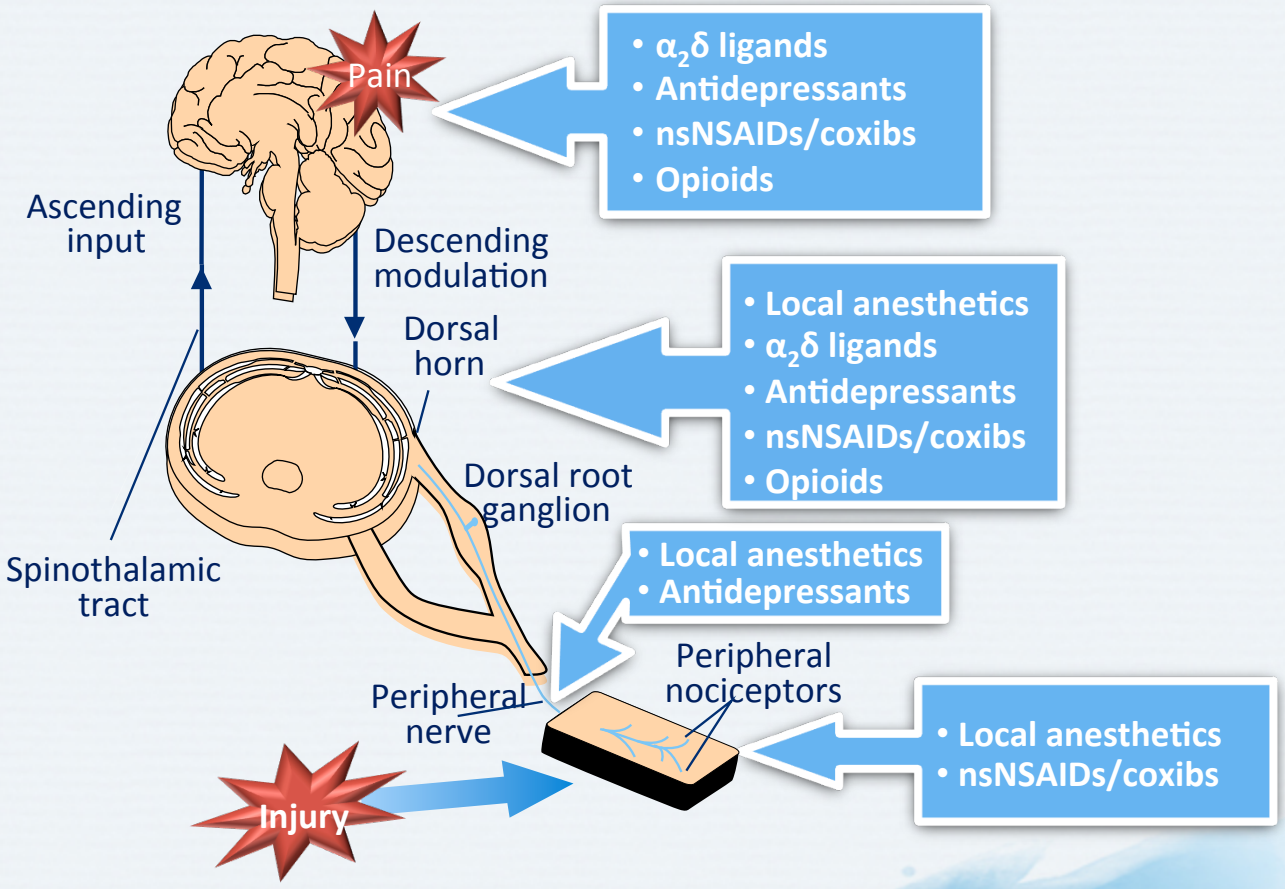
Gatchel RJ *et al. Psychol Bull* 2007; 133(4):581-624; Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.*; National Academies Press; Washington, DC: 2011; Mayo Foundation for Medical Education and Research. *Comprehensive Pain Rehabilitation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

Multimodal Pain Management

CBT = cognitive behavioral therapy

Pharmacological Management of Visceral Pain

Medications Acting on 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.

Acetaminophen

- Action at molecular level is unclear
- Potential mechanisms include:
  - Inhibition of COX enzymes (COX-2 and/or COX-3)
  - Interaction with opioid pathway
  - Activation of serotoninergic bulbospinal pathway
  - Involvement of nitric oxide pathway
  - Increase in cannabinoid-vanilloid tone

Mattia A, Coluzzi F. *Minerva Anestesiol* 2009; 75(11):644-53.

NSAIDs/Coxibs and Visceral Pain

- May fail to relieve chronic visceral pain completely[1]
  - May be more efficacious in **combination** with acetaminophen[2]
- In renal or biliary colic, NSAIDs may involve acetylcholine blockade[2]
  - 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 analgesics[1]

Coxib = cyclooxygenase inhibitor; NSAID = non-steroidal anti-inflammatory drug

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

What are NSAIDs (nsNSAIDs/coxibs)?

NSAID = **N**on-**S**teroidal **A**nti-**I**nflammatory **D**rug

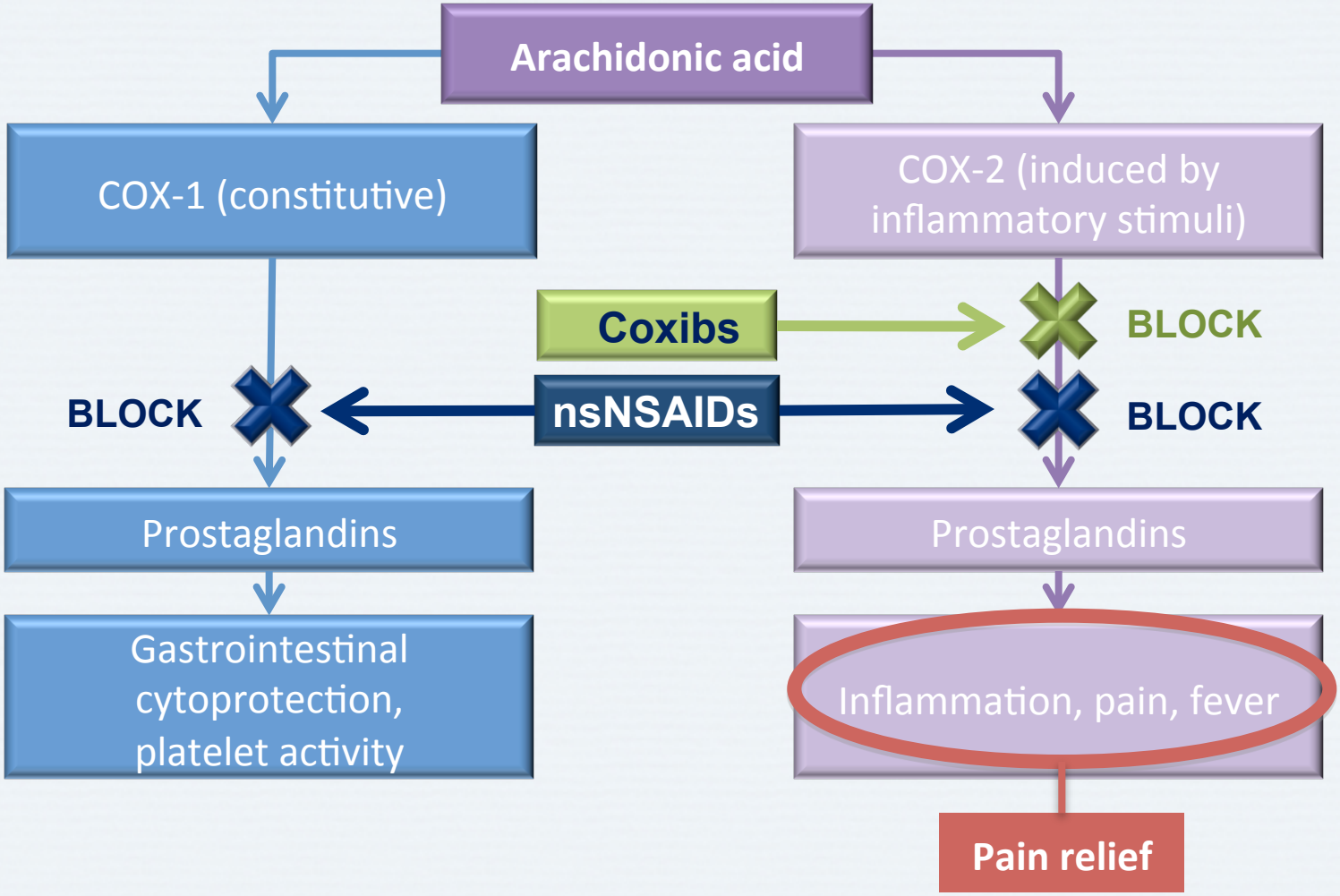
- Analgesic effect via inhibition of prostaglandin production
- Broad class incorporating many different medications:

Examples of nsNSAIDs:	*Examples of Coxibs:*
– Diclofenac	– Celecoxib
– Ibuprofen	– Etoricoxib
– Naproxen	– Parecoxib

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

Brune K. In: Kopf A *et al* (eds). *Guide to Pain Management in Low-Resource Settings.* International Association for the Study of Pain; Seattle, WA: 2010.

How Do nsNSAIDs/coxibs Work?



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

Vane JR, Botting RM. *Inflamm Res* 1995;44(1):1-10.

Adverse Effects of nsNSAIDs/Coxibs

All NSAIDs

- Gastroenteropathy
  - Gastritis, bleeding, ulceration, perforation
- Cardiovascular thrombotic events
- Renovascular effects
  - Decreased renal blood flow
  - Fluid retention/edema
  - Hypertension
- Allergic phenomenon

Cox-1-mediated NSAIDs (nsNSAIDs)

- Decreased platelet aggregation

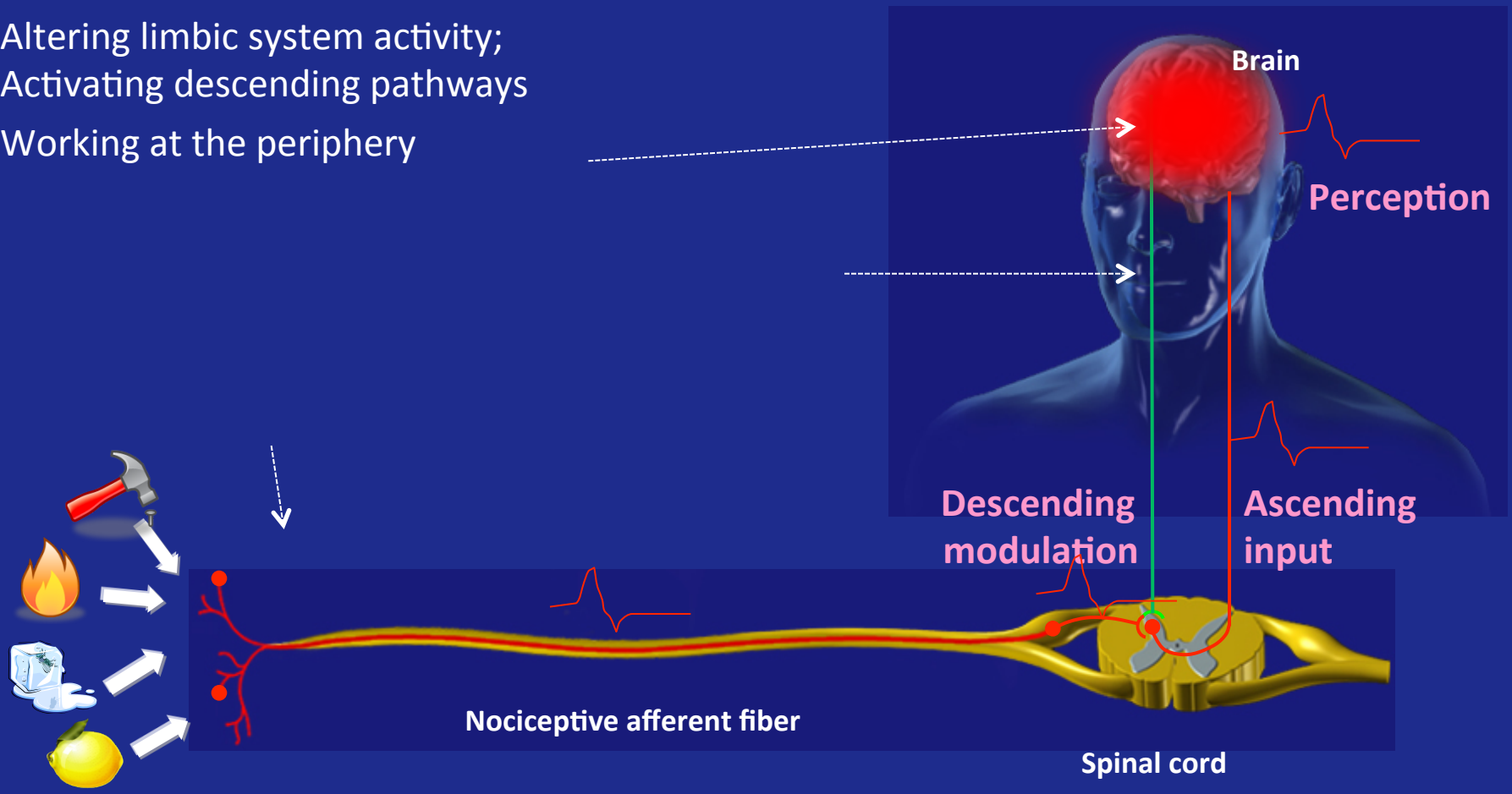
Coxib = COX-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific non-steroidal anti-inflammatory drug

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.

How Opioids Affect Pain

Reduce pain by:

- Altering limbic system activity; Activating descending pathways
- Working at the periphery



Reisine T, Pasternak G. In: Hardman JG *et al* (eds). *Goodman and Gilman's: The Pharmacological Basics of Therapeutics.* 9th ed. McGraw-Hill; New York, NY: 1996; Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7; Trescot AM *et al. Pain Physician* 2008; 11(2 Suppl):S133-53.

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	Itching, miosis, sweating, urinary retention

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.

Antidepressants Used in the Management of Visceral Pain

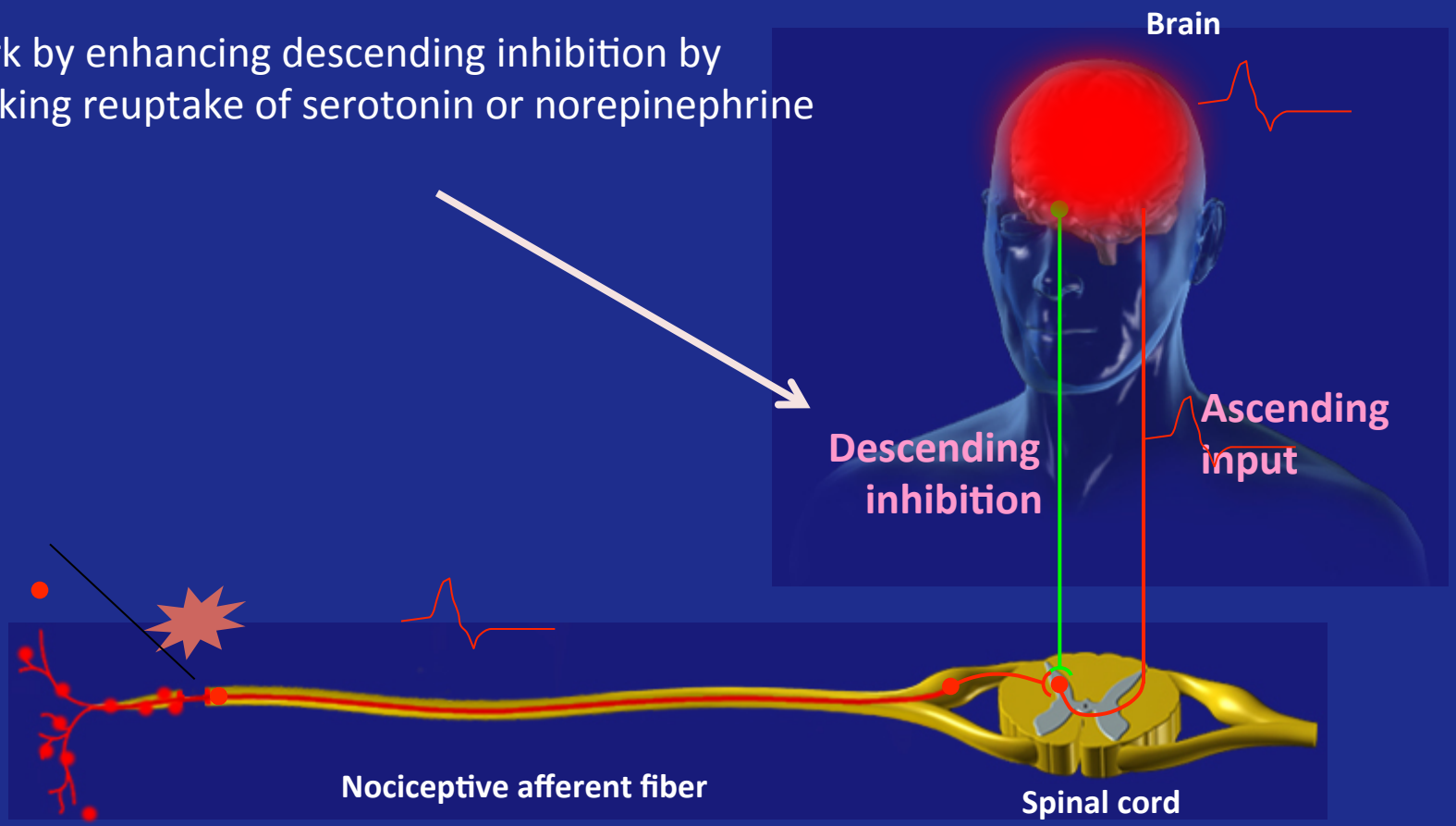
Class and Drug	Adverse Effects	
TCA Amitriptyline Imipramine Desipramine Nortriptyline	• Dry mouth • Difficulty sleeping • Difficulty urinating	• Sexual difficulties • Constipation • Dizziness • Drowsiness
SNRI Venlafaxine Duloxetine Desvenlafaxine Milnacipram	• Nausea • Headache	• Changes in liver chemistry (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.

How Antidepressants Modulate Pain

- Work by enhancing descending inhibition by blocking reuptake of serotonin or norepinephrine



Verdu B *et al. Drugs* 2008; 68(18):2611-2632.

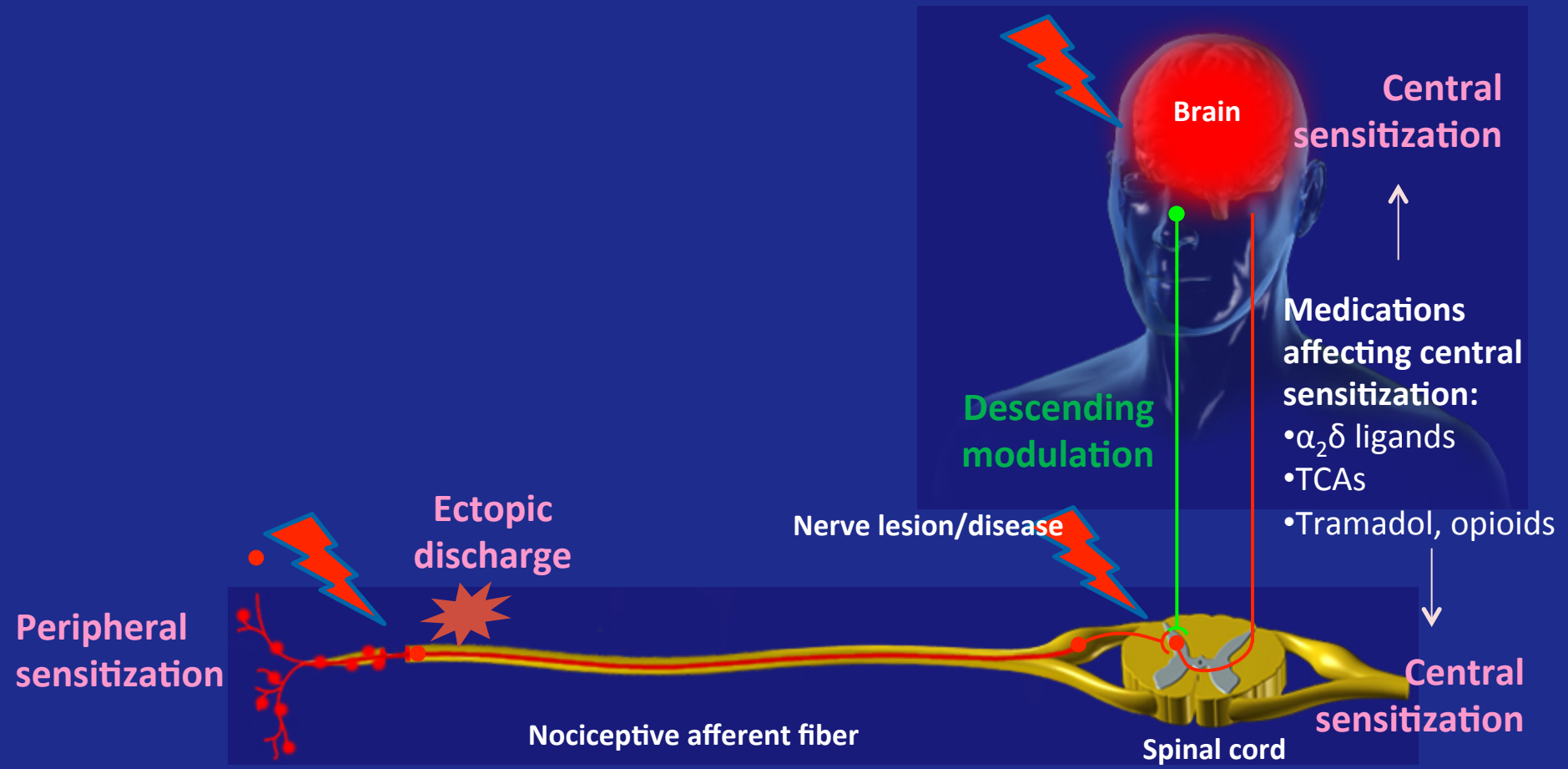
Adverse Effects of Antidepressants

System	TCAs	SNRIs
Digestive system	• Constipation • Dry mouth • Urinary retention	• Constipation • Diarrhea • Dry mouth • Nausea • Reduced appetite
CNS	• Cognitive disorders • Dizziness • Drowsiness • Sedation	• Dizziness • Somnolence
Cardiovascular	• Orthostatic hypotension • Palpitations	• Hypertension
Other	• Blurred vision • Falls • Gait disturbance • Seating • Impotence • Reduced libido	• Elevated liver enzymes • Elevated plasma glucose • Sweating • Impotence • Reduced libido

CNS = central nervous system; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor

Attal N, Finnerup NB. Pain Clinical Updates 2010; 18(9):1-8.

Mechanism-Based Pharmacological Treatment of Neuropathic Pain



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

Adapted from: Attal N *et al. Eur J Neurol* 2010; 17(9):1113-e88; Beydoun A, Backonja MM. *J Pain Symptom Manage* 2003; 25(5 Suppl):S18-30; Jarvis MF, Boyce-Rustay JM. *Curr Pharm Des* 2009; 15(15):1711-6; Gilron I *et al. CMAJ* 2006; 175(3):265-75; Moisset X, Bouhassira D. NeuroImage 2007; 37(Suppl 1):S80-8; Morlion B. Curr Med Res Opin 2011; 27(1):11-33; Scholz J, Woolf CJ. Nat Neurosci 2002; 5(Suppl):1062-7.

Adverse Effects of $\alpha_2\delta$ Ligands

System	Adverse effects
Digestive system	• Dry mouth
CNS	• Dizziness • Somnolence
Other	• Asthenia • Headache • Peripheral edema • Weight gain

$\alpha_2\delta$ ligands include gabapentin and pregabalin
CNS = central nervous system
Attal N, Finnerup NB. *Pain Clinical Updates* 2010; 18(9):1-8.

Interventional Methods

- Nerve/Ganglion blocks
- Intrathecal pumps
- Spinal cord stimulation
- Onabotulinium toxin injections

When to Refer to a Specialist

1. When the diagnosis is in doubt and requires further tests.
2. When patient's therapeutic expectations have barely been met.
3. When an interdisciplinary team approach may be in order.
4. When patient continues to adhere to his or her beliefs regarding the disorder and the therapy

Key Messages

- Visceral pain:
  - Emanates from internal organs
  - Is poorly localized
  - Can be referred somatically
  - May be accompanied by autonomic features
  - Is associated with comorbidities
  - Has a negative impact on the patient's quality of life
- Patients should be assessed using a multimodal approach
  - Consider psychological and physical aspects
  - Be watchful for red flags
- Treatment should be pain- and disease-specific

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