



When Acute Pain Becomes Chronic

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Disclosures

- Ferring Pharmaceuticals: Consultant and Speaker
- One Source Regulatory: Consultant
- Your Encore: Consultant
- Janssen Pharmaceuticals: Consultant



Learning Objectives

- Review pain classifications
- Briefly review pain physiology and anatomy
- Describe the phenomenon of the transition from acute to chronic pain
- Review risk factors and predictors
- Discuss some clinical strategies that may reduce conversion of acute postoperative to chronic pain



Pain Management

“We must acknowledge, to ourselves
and to our nonhospice/palliative care
colleagues, that providing optimal
pain care is difficult.
... the trap ... is to minimize how hard pain
management truly is”

Weissman, 2004.



Pain Classifications

- Pain has been, and is classified:
 - Temporal: acute, subacute, chronic
 - Frequency: intermittent and consistent ...
 - Etiology: cancer and noncancer
 - Location: headache, low back pain ...
 - Functional or initiating: inflammation, post nerve injury etc ...
 - Mechanism: peripheral neuropathic pain, small fiber neuropathy, etc ...
- Proper diagnosis critical for treatment

PainWEEK.

Acute Pain

- Generally sudden onset
 - Usually obvious identifiable cause
 - Injury/disease/iatrogenic (eg, surgery)
 - Short duration 3-6 months
 - Intensity generally variable and indicative of severity of underlying condition or situation
 - Characteristic symptoms
 - Redness, swelling, throbbing
 - Characteristic behaviors
 - Rubbing, moaning, crying, etc

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Acute Pain

- Pain is not benign

- Pulmonary

- ↑ TV ↓ RR
 - Pneumonia

- Immune system

- Delays healing

- Cardiovascular

- Hypertension
 - Tachycardia

- Genitourinary

- H₂O & Na retention

- Gastrointestinal

- Ileus, constipation

- Neurologic

- Delirium

- Musculoskeletal

- Muscle spasms

- Psychological

- Depression
 - Anxiety

PainWEEK.

Chronic Pain

- Persistent (>3-6 months)

- Frequently a thorough evaluation will elucidate cause

- Prolonged functional impairment

- Physical

- Psychological

- Characteristic behavior may or may not be associated

- Insomnia, anorexia, irritability, and depression

- More difficult to manage than acute pain

PainWEEK.

Pain Treatment and Definitions

- Mechanism-based treatment elusive
 - Comprehensive mechanism based pain taxonomy, definitions, and physiology elusive
- Treatment algorithm elusive
- Selective drugs affect multiple pain types
 - “Broad spectrum approaches”
 - “Broad spectrum analgesics”



Pain Models: Biomedical

- Probably oversimplified
- Incomplete
- Explains pain through etiology
- May lead to unrealistic expectations
 - Both clinician and patient
- Pain is usually nociceptive or neuropathic



Linton S. A review of psychological risk factors in back and neck pain. *Spine*. 2000;25(9):1148-1156.

Pain Models: Biopsychosocial

- More complex
- Recognizes pathophysiology and psychological combined role
- Cultural background
- Social interactions
 - Workplace
 - Home
 - Health system



State of California Department of Industrial Relations Medical Treatment Utilization Schedule.
Chronic Pain Medical Treatment Guidelines, 2009.

Types of Pain

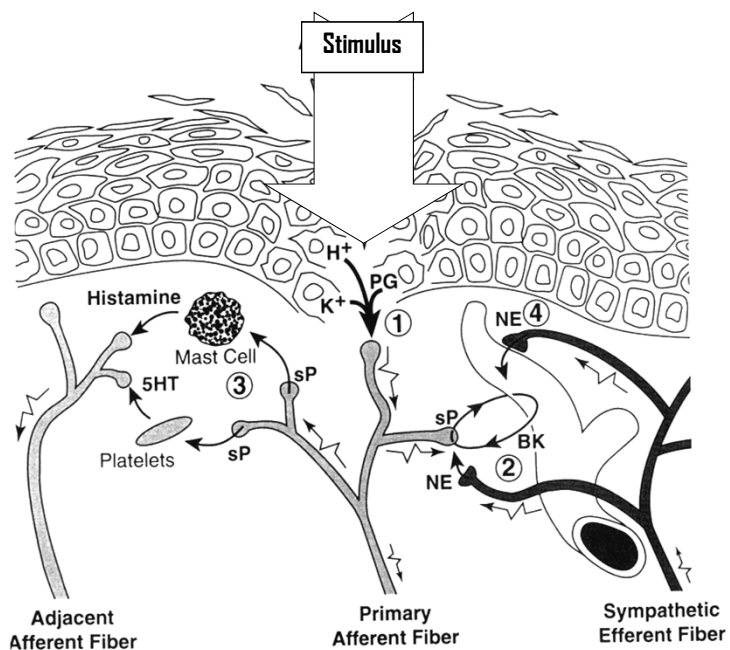
- Nociceptive pain
 - Activation of high-threshold peripheral neurons by noxious stimuli (eg, mechanical, chemical, thermal)
 - Fades once peripheral source is removed
- Neuropathic pain
 - Arises after CNS sensory transmitting nerve injury to nerves
 - Combined sensory loss and paradoxical hypersensitivity
 - If nerve injury occurs during surgery, a neuropathic pain component may persist
- Descriptive terminology:
 - “The meaning and connotation of these different terms may vary widely” (Turk & Okifuji, 2001)



Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367:1618-1625.

Pain Physiology

Painweek.



Painweek.

Pain Physiology and Anatomy

▪Peripheral sensitization

- Tissue damage \Rightarrow Increased nociceptor sensitivity
 - Nociceptor firing sensitivity increased
 - Nociceptor spontaneous activity
 - Lowered thresholds
 - Heightened responsiveness
 - Responsiveness depends on receptor history

PainWeek.

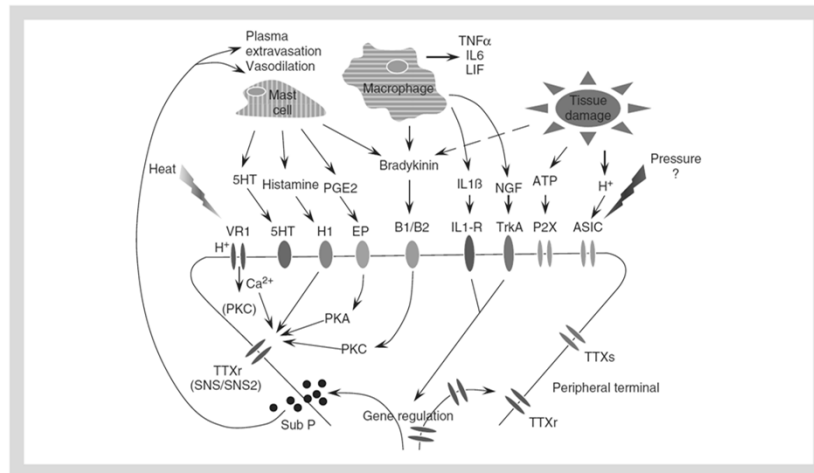
Pain Physiology and Anatomy (cont'd)

▪Peripheral sensitization

- Allogenic peptides couple with receptors
 - Bradykinin, substance P, prostaglandins
 - G-protein-coupled subtype
 - Triggers phosphorylation
 - TXR sodium channels
 - Calcium channels
- Increased neuronal barrage to CNS
 - Resultant functional changes in CNS and spinal cord

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Peripheral Sensitization



PainWeek

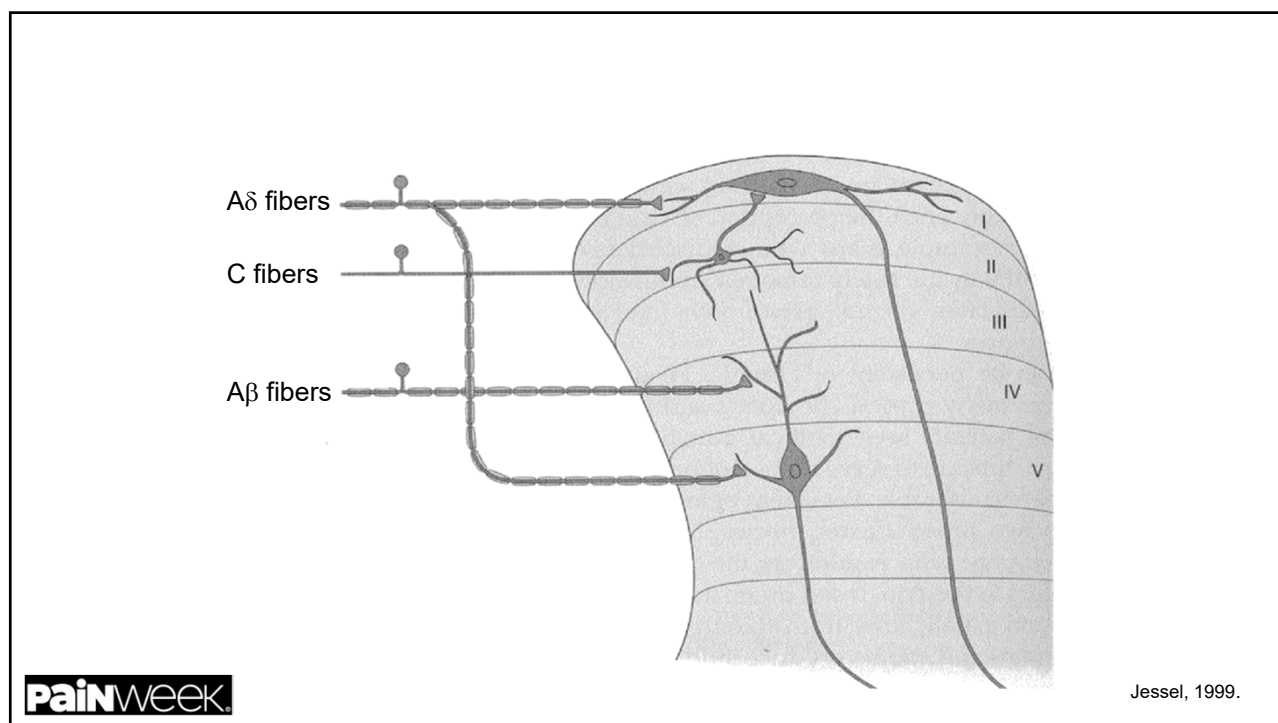
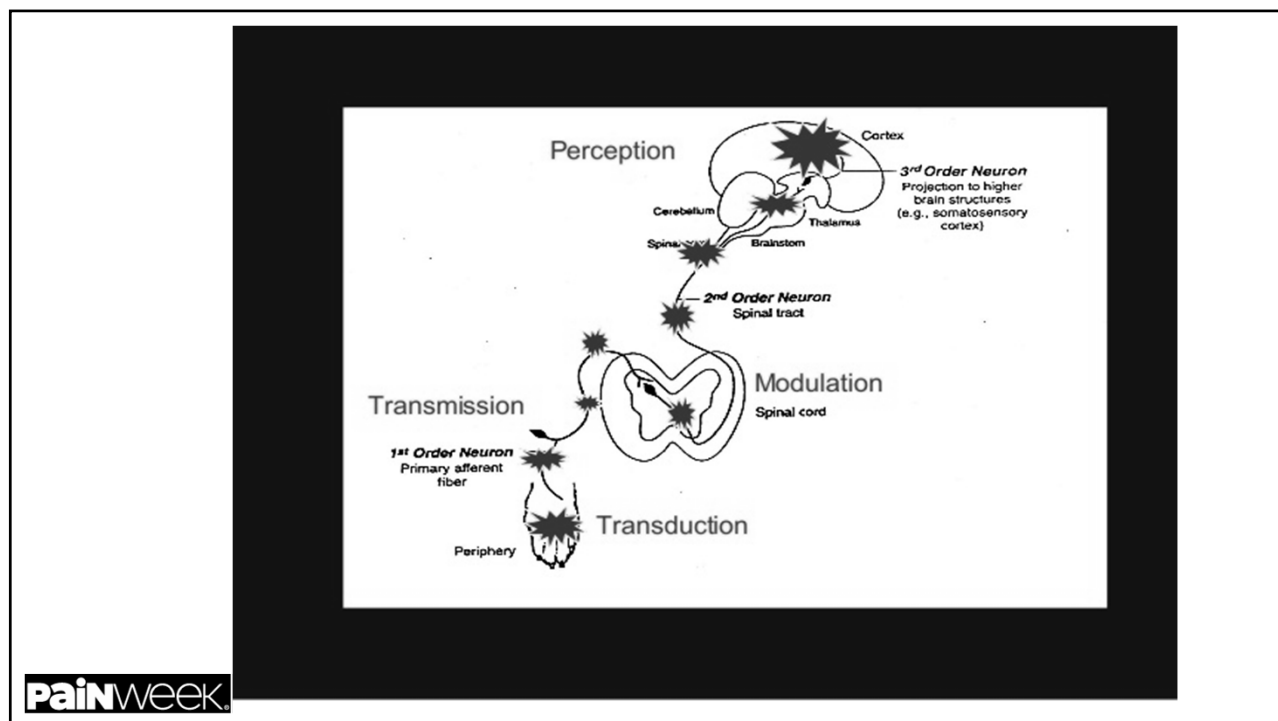
Costigan M, Woolf CJ. Pain: molecular mechanisms. *J Pain*. 2000;(suppl 3):35-44.

Pain Perception

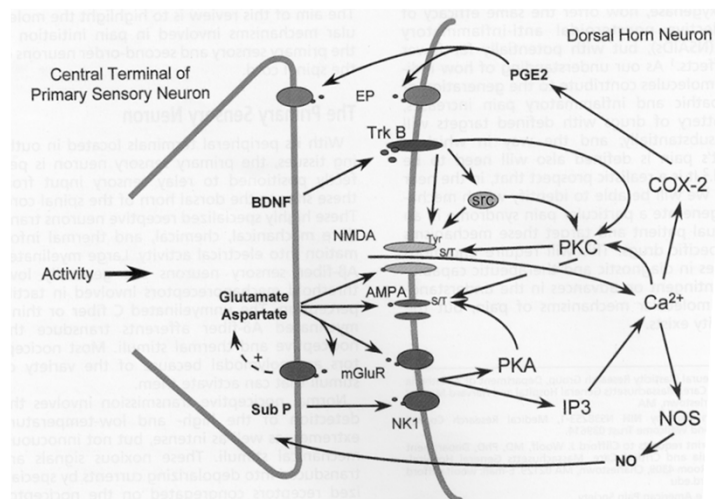
- Things necessary for nociceptors to relay pain to the CNS
 - A brain
 - Transduction
 - Action potential generation
 - Transmission
 - Signal transmission to the thalamus
 - Signal transmission to the cerebral cortex
- Each event controlled separately and may offer potential treatment targets

PainWeek

Voscopoulos C, Lema M. When does acute pain become chronic? *Br J Anaesth*. 2010;105(suppl 1):i69-i85.



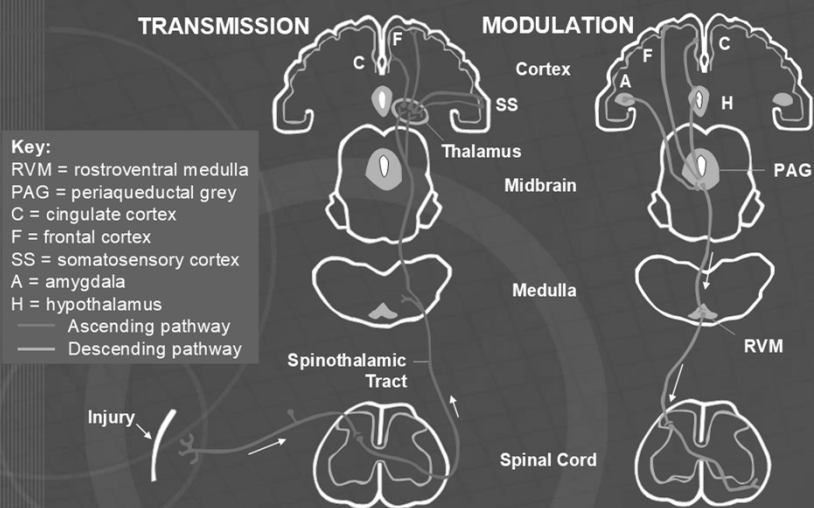
Peripheral Sensitization



PainWeek

Costigan M, Woolf CJ. Pain: molecular mechanisms. *J Pain*. 2000;(suppl 3):35-44.

Normal Pain Pathways



Adapted with permission, from Fields. In: *The Placebo Effect: An Interdisciplinary Exploration*. 1997.

Transition From Acute to Chronic Pain

▪Neuroplasticity (Voscopoulos, 2010)

- Compensatory mechanism
 - Allows the brain to compensate for injury
 - Adjust activity accordingly in response to new situations or to changes in environment
- Involves either:
 - Reversible inflammatory changes
 - Physical remodeling of neuronal cytoarchitecture
- ↓ Inhibition of pain modulation
- Ultimately leads to central sensitization (neuronal hypersensitivity)



Voscopoulos C, Lema M. When does acute pain become chronic? *Br J Anaesth.* 2010;105(suppl 1):i69-i85.

Pain Physiology and Anatomy

“..the biggest hurdle is that the exact mechanisms for pain have not been definitively established for any condition. ... the unproven assumption that important mechanistic similarities connect the many different types of neuropathic pain.”

Rowbotham, 2005



Postoperative Chronic Pain as a Model



Chronic Postoperative Pain

- Poorly understood, poorly characterized
 - Complex and no clear distinction from acute to chronic
 - Neuropathic? Inflammatory? Ongoing nociception?
 - At least in part neuropathic resulting from neuroplastic changes
- Postprocedural pain (IASP, 2018):
 - *“a persistent pain state that is apparent more than 2 months after operation and cannot be explained by other causes”*
 - But no universal definition



Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth.* 2008;101:77-86.

Chronic Postsurgery Pain

- Global volume of surgeries have increased
 - CPSP has not decreased
- CPSP causes suffering, disability, cost
- “Indeed, CPSP is now accepted as an important outcome of surgery.” (Lavand’homme, 2017)
- “CPSP develops in 1 of 10 surgical patients and becomes an intolerable pain condition after 1 of every 100 operations.” (Breivik, 2008)



Lavand’homme, P. (2017). Transition from acute to chronic pain after surgery. *Pain*, 158, S50-S54.
 Breivik H, Stubhaug A. Management of acute postoperative pain: still a long way to go! *PAIN* 2008;137:233–4.

Chronic Postsurgery Pain (cont’d)

- First reference in 1981
 - 40% of 5,130 chronic pain patients in 10 UK pain clinics posttrauma or surgery
 - Not limited to major surgery
 - Frequent problem identified postherniorrhaphy
 - Overall, the incidence of chronic pain after major surgery is estimated to lie in the range of 20% to 50%²
 - Relatively minor operations such as inguinal hernia repair or a C-section seem ~10%²



1. Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. *Pain*. 1998;76:167-171.
 2. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth*. 2008;101:77-86.

Incidence of Chronic Postoperative Pain

Surgery	Incidence of Chronic Pain (%)	Estimated % Severe (>5)
Amputation	30-85	5-10
Thoracotomy	5-65	10
Mastectomy	11-57	5-10
Inguinal hernia	5-63	2-4
CABG	30-50	5-10
C-Section	6-55	4
Cholecystectomy (open)	3-50	?
Vasectomy	0-37	?
Dental surgery	5-13	?



Macintyre PE, Schug SA, Scott DA, et al. APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. *Acute pain management: scientific evidence*, 3rd edition. Melbourne: Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine; 2010.

Chronic Postoperative Pain

■ Predisposing factors include (Voscopoulos , 2010):

- Psychosocial status (eg, anxiety)
- Pre-existing pain/recurrence/high pain sensitivity
- Genetics
- Gender (female)
- Age??
- Coping skills
- Co-existing disease/type of disease
- Adjuvant therapy (eg, radiation, chemotherapy)



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Psychosocial Status^{1,2}

- Expectation of pain
- Fear, anxiety, depression
- Past experiences
- Social environment
- Work-related factors
(eg, disability, Workers Compensation)
- Prior level of physical activity
- Neuroticism



Figure 1. Vlaeyen's cognitive-behavioral model of chronic pain pathogenesis (Source: Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain* 2000;85:317-332.)



1. Callesen T, Bech K, Kehlet H. Prospective study of chronic pain after groin hernia repair. *Br J Surg*. 1999;86:1528-1531.
2. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000;85:317-332.

Pre-existing Pain

- High correlation with the development of chronic neuropathic pain¹
 - Amputees with severe phantom pain often have more intense preamputation pain¹
 - Similar association with intensity of chronic pain after
 - Breast surgery²
 - Thoracotomy³
 - Inguinal herniorrhaphy⁴



1. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367:1618-1625.
2. Tasmuth T, Estlanderb AM, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. *Pain*. 1996;68:343-347.
3. Katz J, Jackson M, Kavanagh BP, et al. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *Clin J Pain*. 1996;12:50-55.
4. Callesen T, Bech K, Kehlet H. Prospective study of chronic pain after groin hernia repair. *Br J Surg*. 1999;86:1528-1531.

Genetics

- “Presently it is not possible to ascertain the extent to which individual genetic factors contribute to a person’s propensity to develop chronic postsurgical pain or their response to therapy.” (Clarke, 2015)
- Some suggestions:
 - High level of nociceptive sensitivity
 - Inheritable susceptibility
 - Response to analgesics
 - Polymorphisms of opioid-receptor sites
 - Catecholamine-O-methyltransferase (COMT) polymorphisms
 - Altered pain sensitivity



Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367:1618-1625.

Other Risk Factors

- Age
 - Older people less likely to transition from acute to chronic postoperative pain
 - Opposite with postherpetic neuralgia
- Gender
 - Females seem to be more likely
- Coping skills
 - Catastrophizing
- Co-existing disease/therapeutic causes



Other Effective Factors

- Anesthetic technique
- Surgical approach
 - Duration/multiple procedures
 - Nerve damage
 - Postop infection/prolonged inflammation
- Recurrence or worsening of condition



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Potential Therapeutic Approaches



Acute Pain Service

- Goal to reduce and improve postoperative pain
 - Secondary goal to decrease acute → chronic
 - Team:
 - “It has responsibility for the day to day management of patients with acute pain and for providing an appropriate level of care and monitoring, adjusted to the clinical condition of the patient and the technique used.”
(Royal College of Surgeons, 1990; Werner, 2002; Meissner, 2015)



Acute Pain Service (cont'd)

- “In the US and Western Europe, a high proportion of hospitals have an acute pain service, but the structure and responsibilities vary both within and between countries.” (Meissner, 2015)
- UK hospital survey (Powell 2004):
 - Described their acute pain service as
 - 17% no acute pain service
 - 52% as “struggling acute pain service”
 - 30% as “thriving acute pain service”



Potential Treatments of Postsurgical Pain

- Gabapentin:
 - Studies show little benefit (Clark, 2012)
- Pregabalin
 - Met-analysis showed benefit (Chaparro, 2013)
 - Intrathecal clonidine (De Kock, 2005)
- Ketamine
 - Intraoperative ketamine (Lavand'homme, 2005)
 - Results have been equivocal (Clark, 2015)
- Epidural analgesia
 - Epidural analgesia (Senturk, 2002)



Approaches

- Multimodal treatments
 - Preventing neuroplastic changes
 - Aggressively treat acute pain
 - Maintenance of activity
 - Pharmaceutical agents
 - Ice/heat
 - Topical agents
 - Physical therapy
 - Whatever works ... 😊



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Case Study

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Case Study

- 85 year old female
 - Brought into the hospital for further evaluation
 - Presents with severe left lower quadrant abdominal pain

- What are you going to do?

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Case Study (cont'd)

- History:
 - Pain has been present on and off for over 15 years
 - She has had multiple imaging and multiple endoscopies
 - She has been tried on multiple medications
 - No other serious medical or past psychiatric history
- Social history:
 - No ETOH, TOB or drug history or concerns
- What are you going to do now?

PainWEEK.

Case Study (cont'd)

- Assessment and physical examination
 - Patient states she can't remember ever having an examination
 - Trigger point in the left lower quadrant
 - Reproduced patient's pain "exactly"
 - Remainder of physical examination not significant
- What are you going to do now?

PainWEEK.

Case Study (cont'd)

- Treatment
 - Injection of bupivacaine and dexamethasone
 - Pain reproduced with the injection
 - Pain resolved within 5-10 minutes
 - Didn't recur during hospitalization

Painweek.

Conclusion

Painweek.

Conclusion

“There is a tremendous gap in the literature on postsurgical pain duration, with a great need for studies to test whether we can intervene therapeutically to reduce the duration of acute and subacute pain for the 34 million Americans undergoing surgery every year.”

Wang, 2009



Conclusion (cont'd)

- The transition from acute to chronic pain occurs in discrete pathophysiological steps involving multiple signaling pathways
- The duration and intensity of the initial stimulus leads to both peripheral and central sensitization that synergistically exacerbate pain perception
- A multimodal therapeutic approach may be best suited to target the complex mechanisms leading to the transition from acute to chronic pain



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Conclusion (cont'd)

“Physicians, like beer,
are better when they are old.”

Thomas Fuller, 1608-1661



Thank you.

Questions?

