Treating chronic pain in patients is difficult, how can you manage these patients within your specialty or practice?

Sarah Rebstock M.D.

Disclosures

- Financial: no relevant disclosures

- Thank you to Kathy Sheehy
- Thank you to the Complex pain Medicine Team for their support

The Aphorisms of Hippocrates include the axiom:

"Those who are used to bearing an accustomed pain, even if they be weak and old, bear it more easily than the young and strong who are unaccustomed."

If I were quoted:

Treating chronic and complex pain: It is a difficult job, every specialty is affected, and all physicians prepared to recognize it and start the treatment process.

Sarah Rebstock 09.17.2013

Objectives:

1.Describe how to recognize and initiate treatment for your patients with complex pain, and when to refer.

2. Describe how mechanisms in complex pain can be mitigated by different treatment modalities

3. Describe the role of neuroplasticity in complex pain

4. Order the appropriate medication to manage complex/chronic pain

5. Identify multimodal therapies that optimize pain management

Food for Thought

Otherwise healthy 16 Y.O. female PMH for recovery from EBV infection 1 month ago, admitted for intractable RLQ pain and observation, completely negative medical work up to include GI studies, with the finding of an increased stool burden and lymphadenitis with a negative work-up from ID. After clean out, pain remains.

Otherwise healthy 9 Y.O. boy comes into your practice after hairline fracturing his left foot with worsening pain after 2 weeks in a soft cast. The x-ray shows healing bone, exam is benign except that his left foot is colder, is painful to the touch, and shiny. Opiates do not help him.

“This does not hurt much, we will not even have any blood loss.”

PAIN.. Bah HUMBUG!

Oct. 16, 1846

John Collins Warren/ William T. Morton

In the past , the treatment, particularly, of postoperative pain has been given low priority.

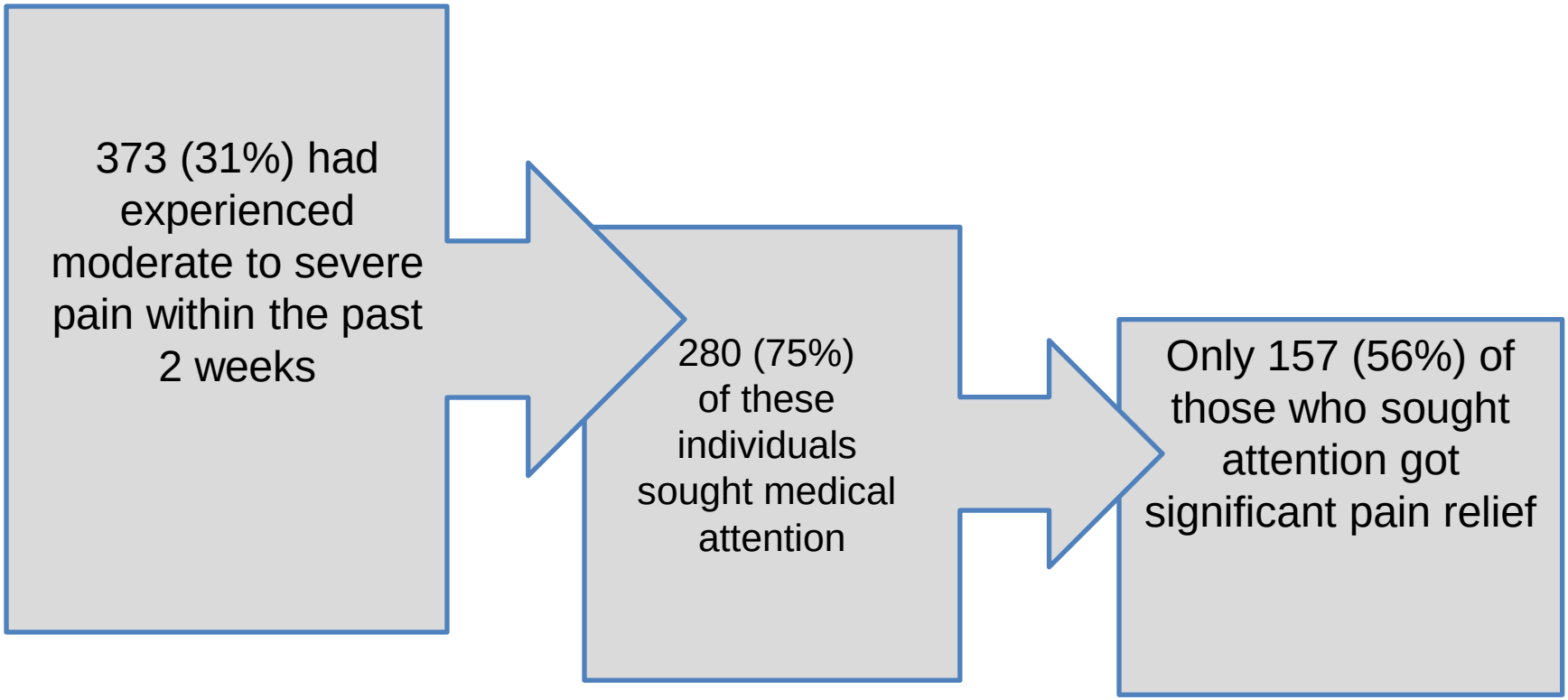
Pain was considered a requisite part of the operative “experience”.

Pain control in neonates and small children was not standard of practice until the 1980’s.

To date pediatric pain remains still grossly under treated on the whole.

Under treatment of Pain

Nationwide random survey conducted 2005 (1204 respondents)



Shi Q et al. J Pain 2007, 8;624-636

Why do patients with pain go under treated?

- I don 't know how to treat it
- Fear of drug side effects
- Fear of addiction
- I don't have enough experience with these types of patients
- I don't know who to ask for help with managing patients with pain

Under Treatment, Why?

- Lack of knowledge
- Non priority triage
- Clinical disinterest
- Fear of drug side effects
- Fear of addiction
- Institutional barriers preventing implementing new technologies
- Lack of knowledge of tools available
- Lack of colleagues skilled in specialized pain management techniques

Complex Pain: Why is pain sometimes so difficult to treat?

- Acute pain: Nociceptive Pain
- Chronic pain syndromes
- Neuropathic pain
- Non-neuropathic Pain?
- Neuroplastic pain
- Psychosocial factors
- Personal Bias

→ Cause ≠ Effect?

Pain Mechanisms: Definition

Pain is defined by the International Association for the Study of Pain as:

“an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

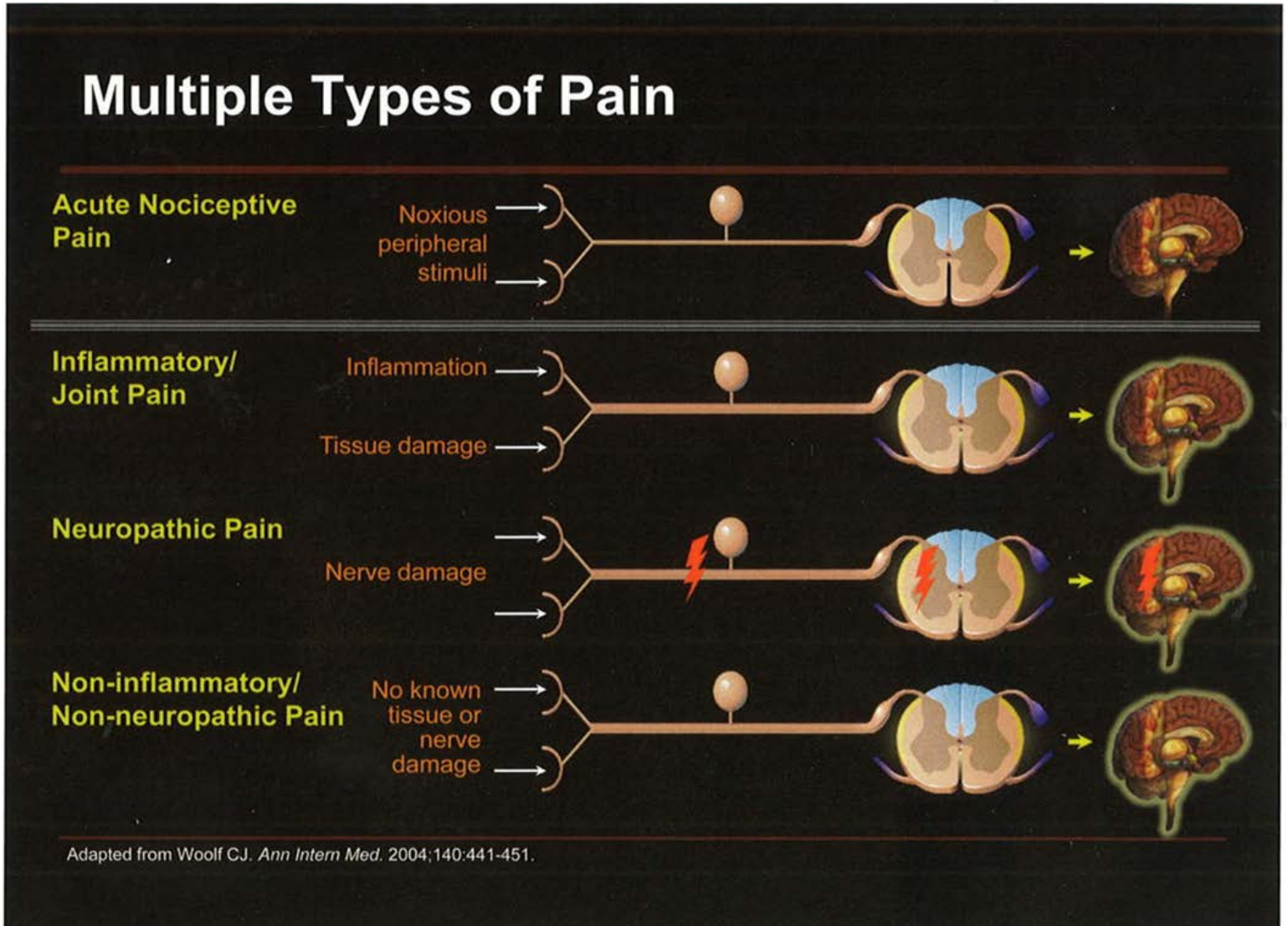
http://www.iasppain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm#Pain. Retrieved 3/6/2013

Types of pain:
Acute, Chronic, and Both?

Children's National Medical Center

Neuropathic Pain	Mixed Pain	Nociceptive Pain
• Peripheral neuropathies (diabetes, HIV)	• Migraine and chronic daily headache	• Mechanical low back pain
• Postherpetic neuralgia	• Fibromyalgia	• Rheumatoid arthritis
• Trigeminal neuralgia	• Phantom limb pain	• Osteoarthritis
• Central post-stroke pain	• Complex regional pain syndrome	• Chronic inflammatory conditions
• Spinal cord injury	• Multiple sclerosis	• Somatoform pain disorder
• Neuropathic low back pain	• Low back pain	• Postoperative pain
	• Myofascial pain syndrome	• Sickle cell crisis
	• Skeletal muscle pain	• Sports/exercise injury

Pain Mechanisms: Types of Pain



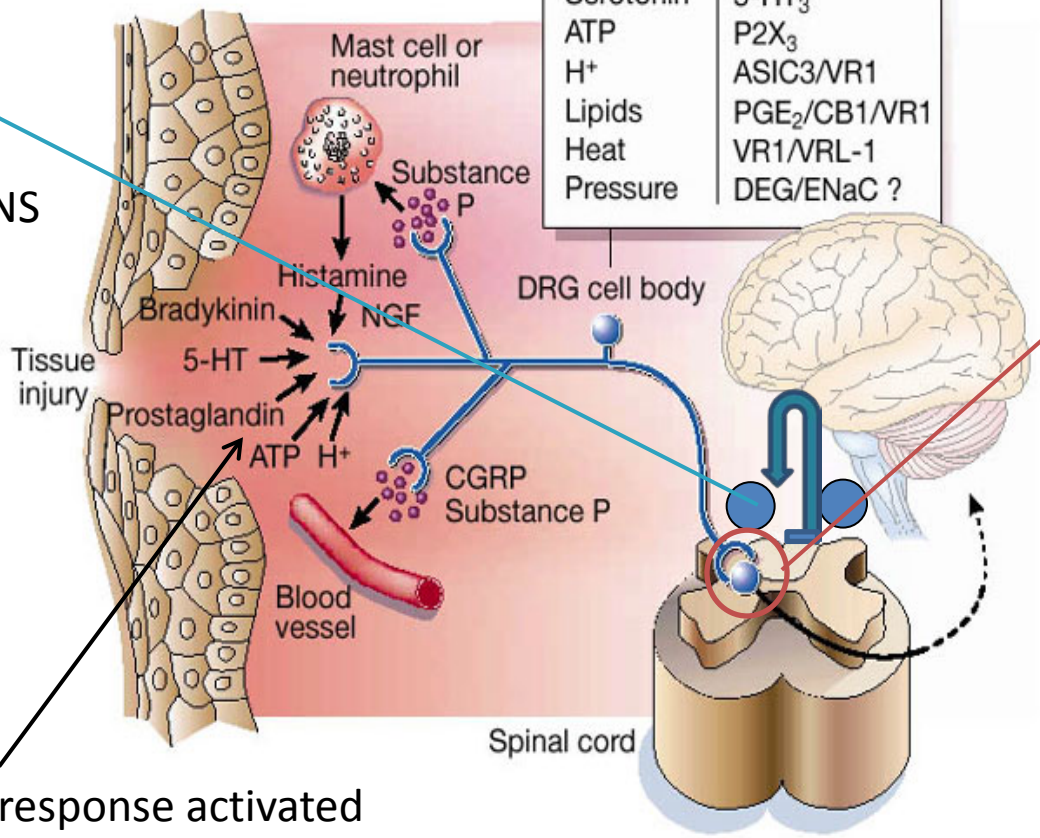
Nociception

Autonomic
NS CHAIN

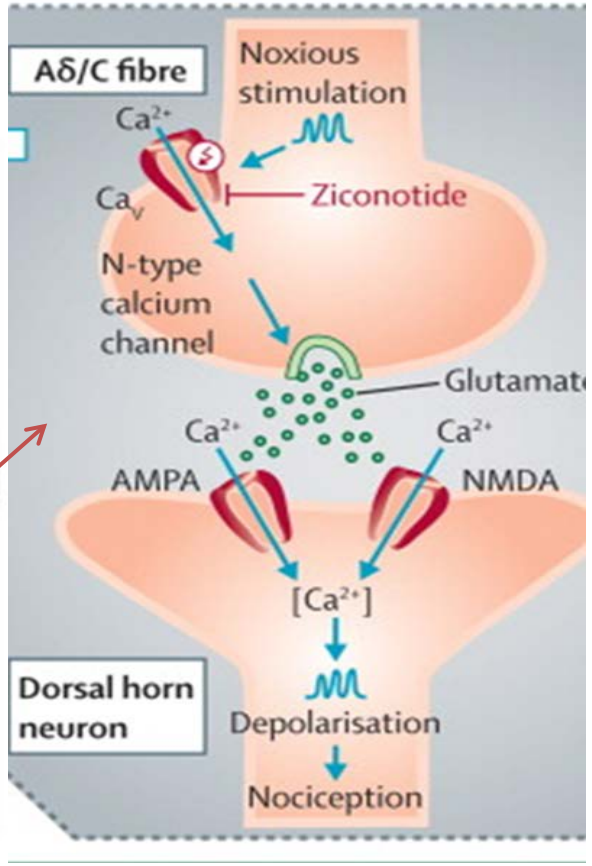
Sympathetic NS
activated

Immune response activated

Stimulus	Representative receptor
NGF	TrkA
Bradykinin	BK_2
Serotonin	$5\text{-}HT_3$
ATP	$P2X_3$
H^+	ASIC3/VR1
Lipids	PGE_2/CB1/VR1
Heat	VR1/VRL-1
Pressure	DEG/ENaC ?



Dorsal Horn Schematic



Neuropathic pain syndromes

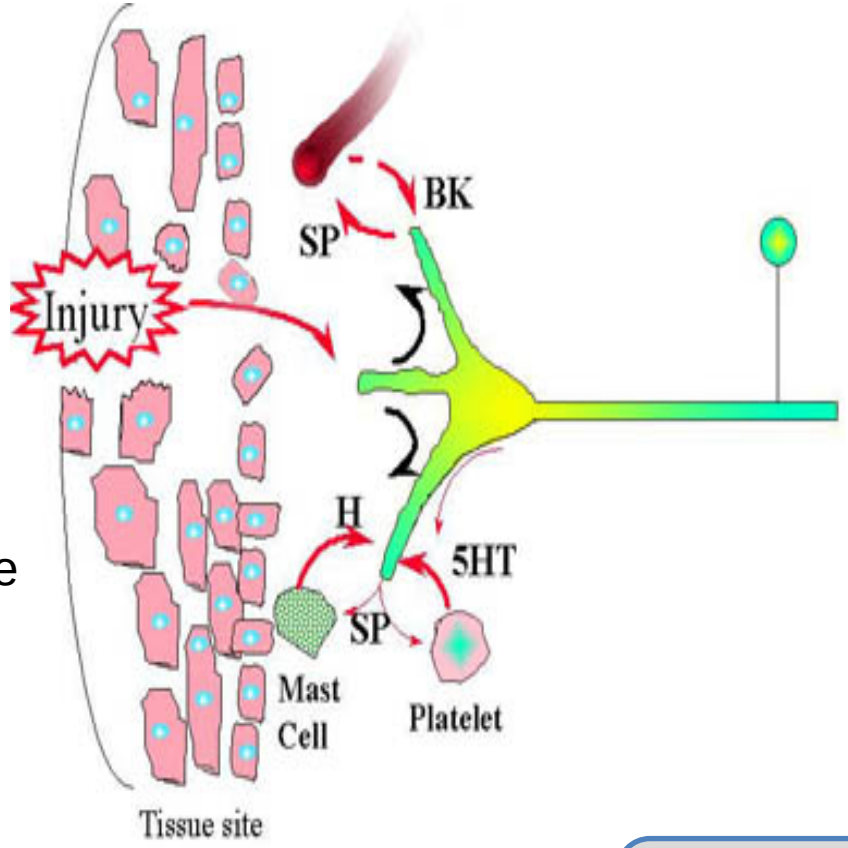
Neuropathic pain syndromes are caused by lesions or diseases of the parts of the nervous system that normally signal pain

Peripheral Sensitization

-Inadequately treated acute pain

-chronic inflammatory states

-Activation of the sympathetic NS



Stimulus	Representative receptor
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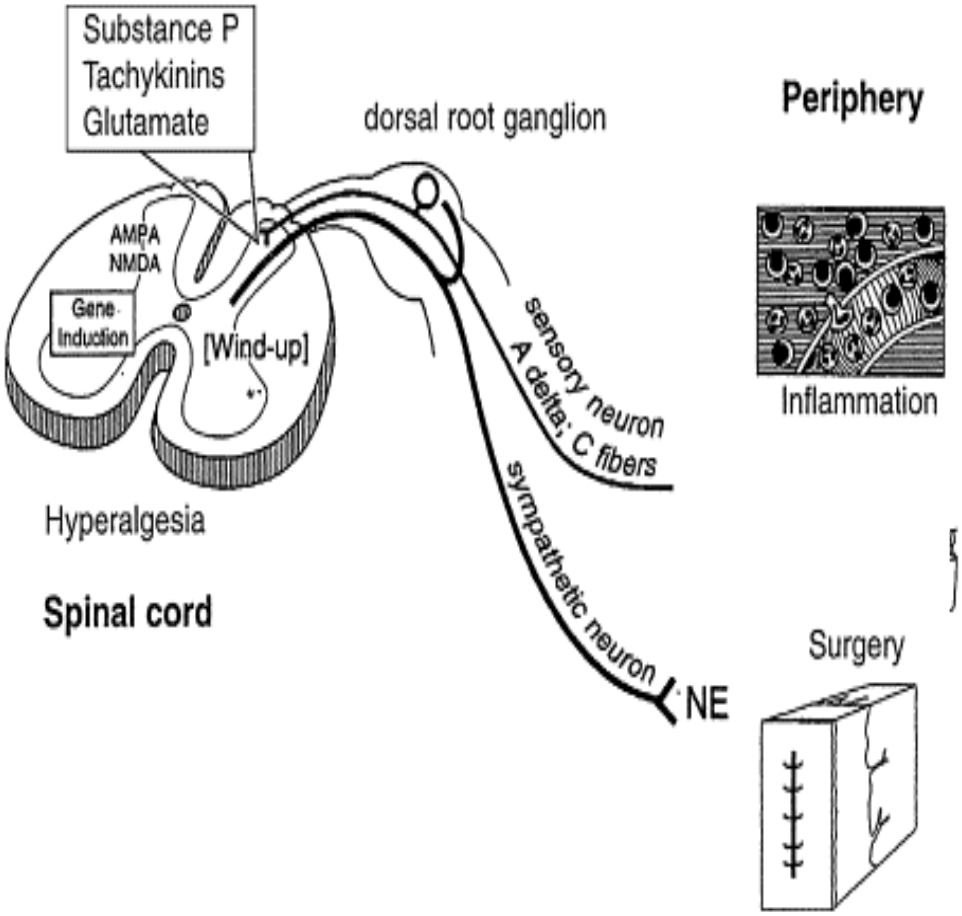
Heat	VR1/VRL-1
Pressure	DEG/ENaC ?

Substance P SP

Continued nerve stimulation results in hyperexcitability in periphery as well

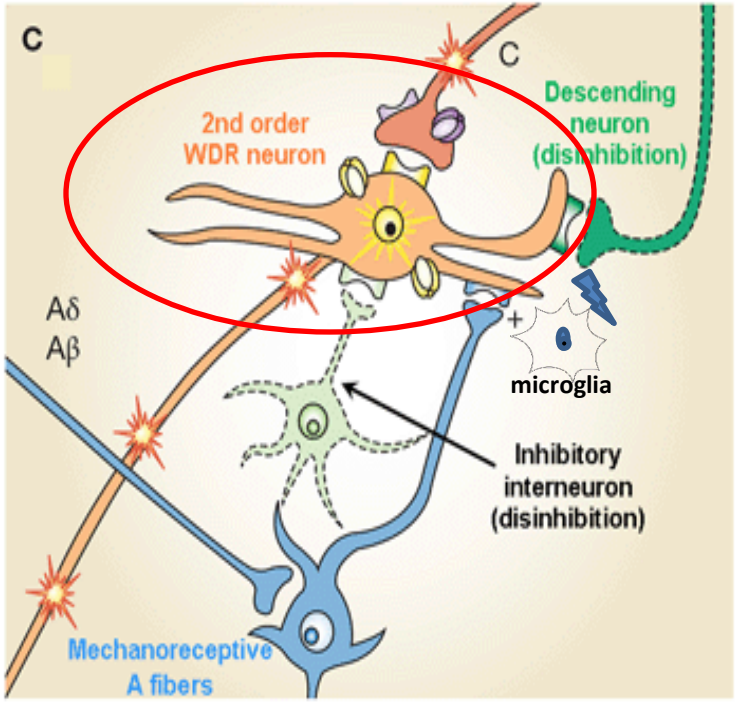
Wind-up

- Sympathetic tone increase/adrenaline
- Repetitive noxious stimulation
  ? inflammation?
- Central spinal mechanism
- Activates NMDA receptors
- Calcium entry results in synthesis of Nitric Oxide(NO)
- NO affects nociceptive terminals and enhances the release of neuropeptides (ex. Substance P [SP])
- Expands receptive fields and activates wide dynamic neurons by non-nociceptive impulses
- Results in central sensitization and hyperalgesia



Pain Mechanisms: Central Sensitization

Central Sensitization I



Sodium channel

Calcium channel ($\alpha_2\delta$ subunit)

Opioid receptor

Glutamate receptor

NE/5-HT receptor

GABA receptor

AMPA/KA receptor

Modified from Baron R. *Nat Clin Pract Neurol*. 2006;2:95-106.

Medscape

WDR(wide dynamic range) 2nd order neuron spread of the hyper-excitability to other segments

Glutamic acid
(pre-synaptic N-gated calcium channels)

↓

Post synaptic NMDA Rz

↓ NO synthase

NO

Can occur as a result of wind-up and result in hyperalgesia

Wind-up

Immune cells and wind up

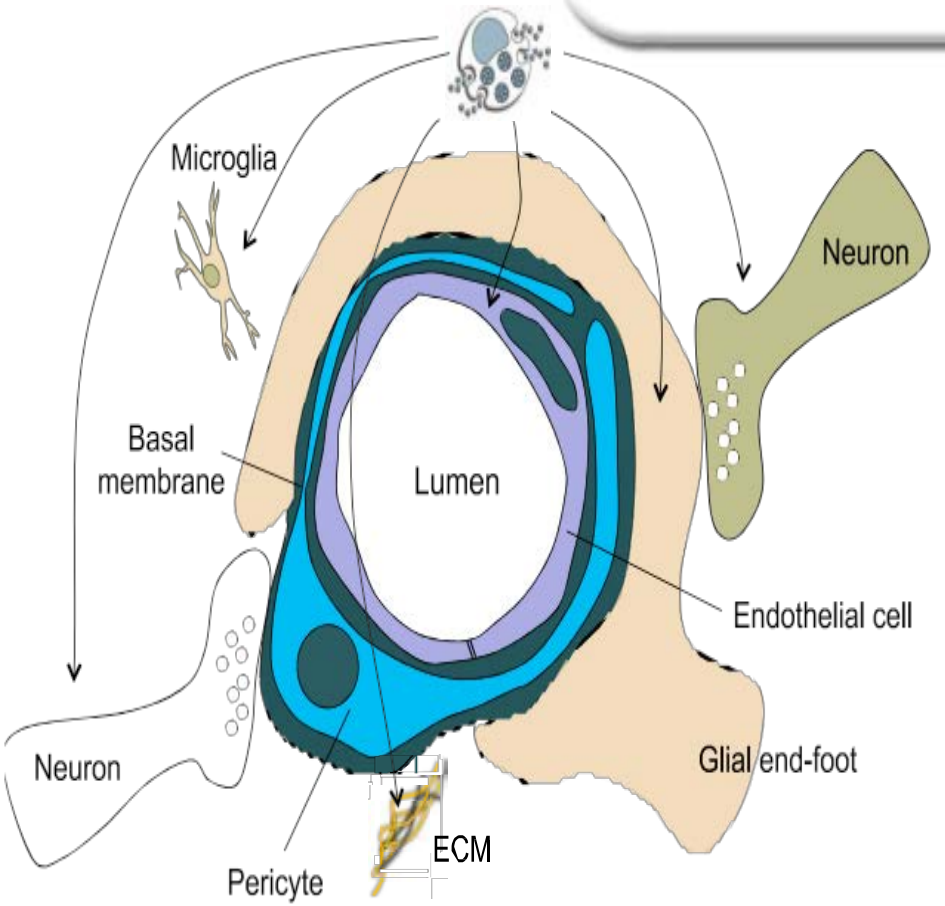
Mast Cell

Neuroinflammation: appear to rely on interaction between glia, immune cells and neurons

Systemic inflammation signals brain to a change in metabolism and behavior, to include expression of pro-inflammatory phenotype by microglia

Inflammation or nerve injury can cause NO production=IL-1beta= could bind to glial cells and induce NMDA Rz=painful signal facilitation

- Results in central sensitization and hyperalgesia



Schematic illustration of the cellular elements of the neurovascular unit comprising an intracerebral arteriole or apillary. ECM, extracellular matrix.

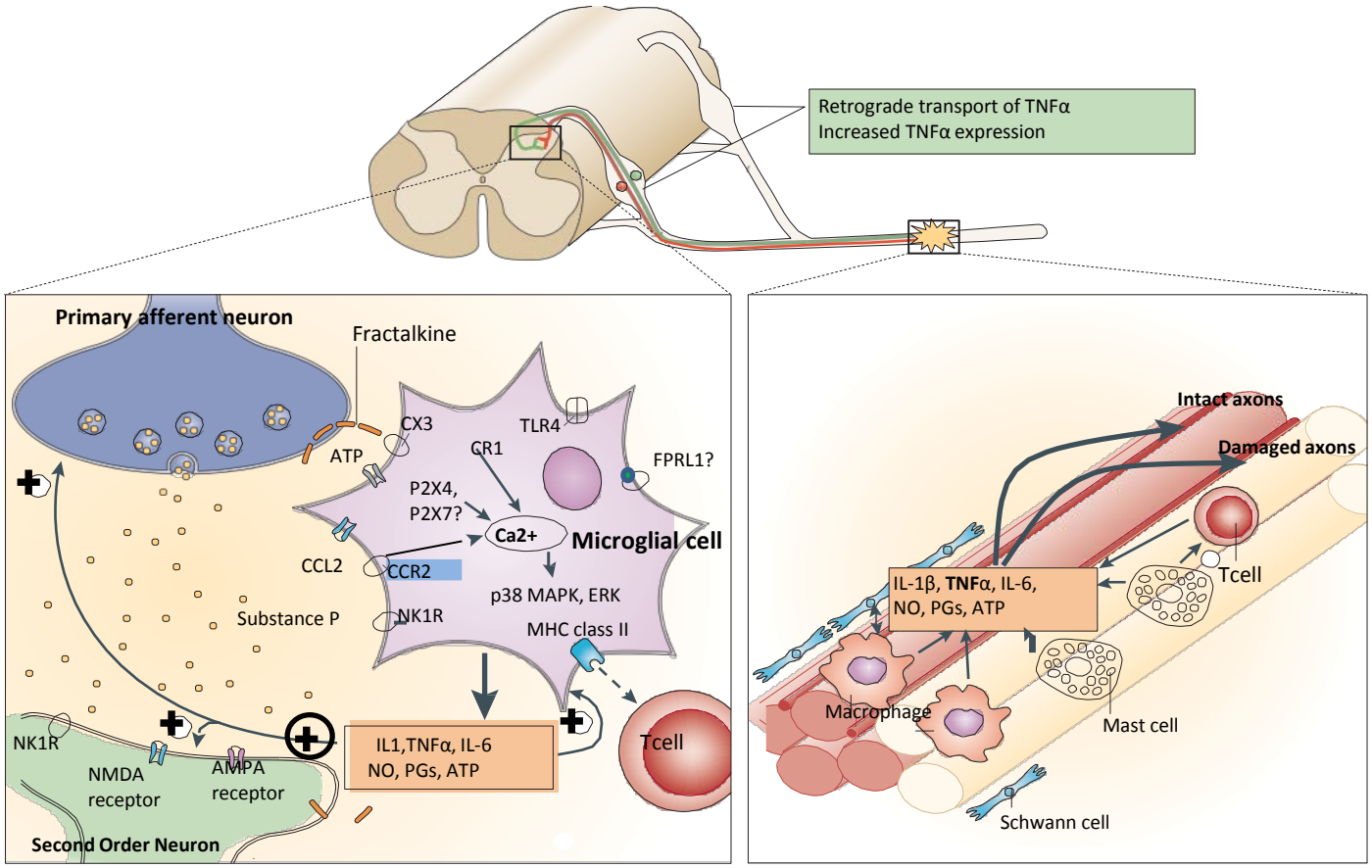
Skaper et al. 2012 FASAB J

Marchand et. al. 2005 Nature Reviews/Neuroscience

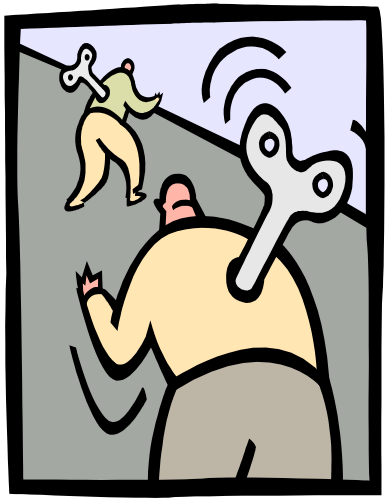
Wind-up

Neuroinflammation: appear to rely on interaction between glia, immune cells and neurons

Immune mediators modulate pain processing and signaling.
This can be adaptive or maladaptive to the function of the organism.



Nature Reviews/Neuroscience2005 Volume 6 p. 527



Recapitulation

Nerve damage or Repeated Excitability
Chronic Neuroinflammation

(C fiber hyperactivity)

Chronic Neuroinflammation

WDR(wide dynamic range) 2nd order neuron

Increase of excitability

spread of the hyper-excitability to other segments

Glutamic acid **(pre-synaptic N-gated calcium channels)**

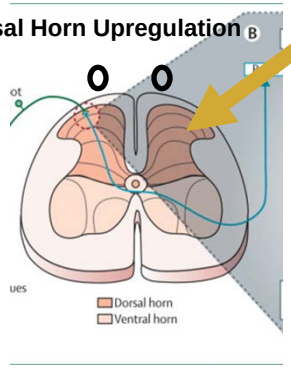
Neuropeptide Substance P

Post synaptic NMDA Rz

Increase in response to noxious stimulus**Hyperalgesia**
Algesic response to non-painful stimuli
Allodynia

Increase in neuronal receptive field

Dorsal Horn Upregulation



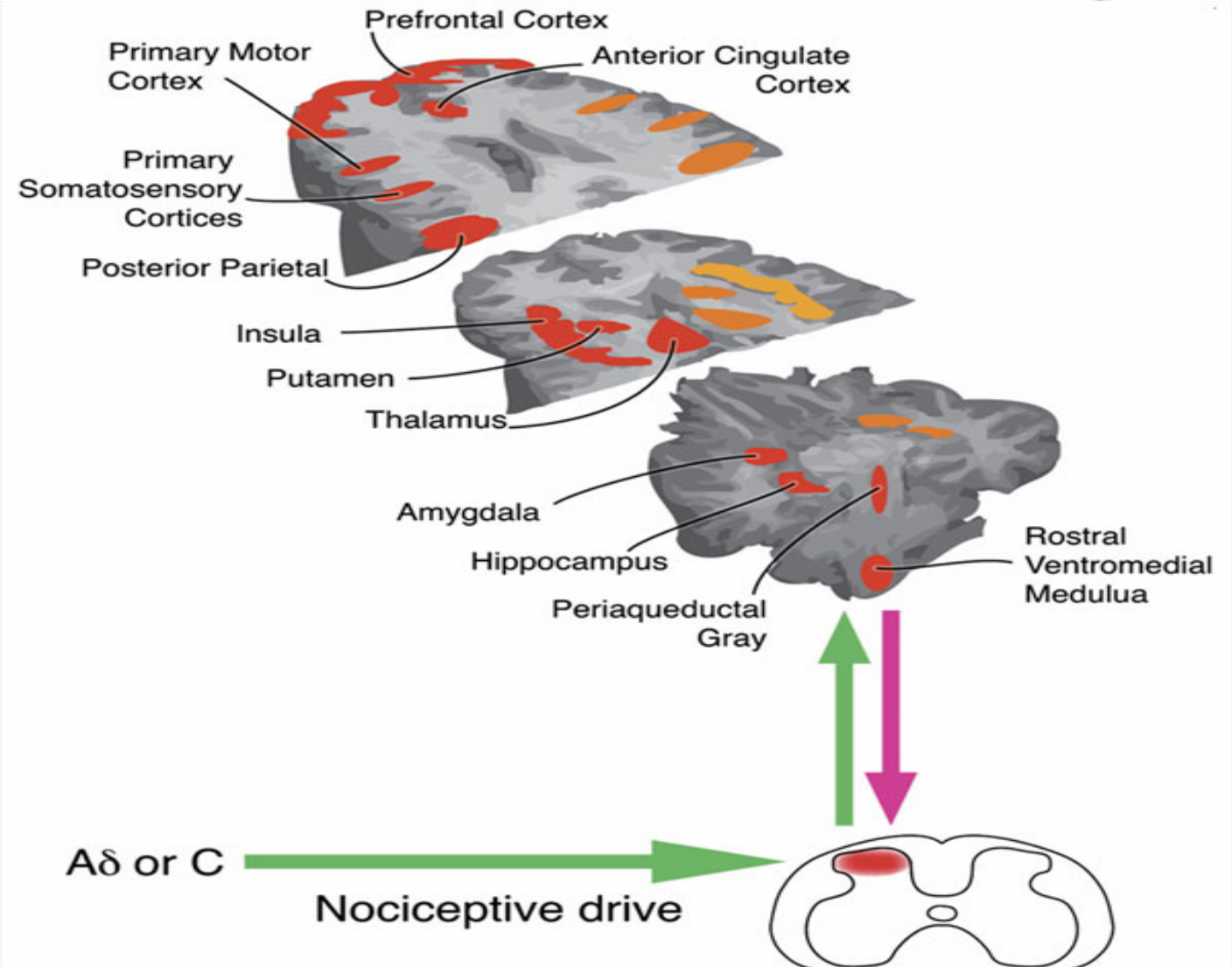
NO synthase

Nitric Oxide

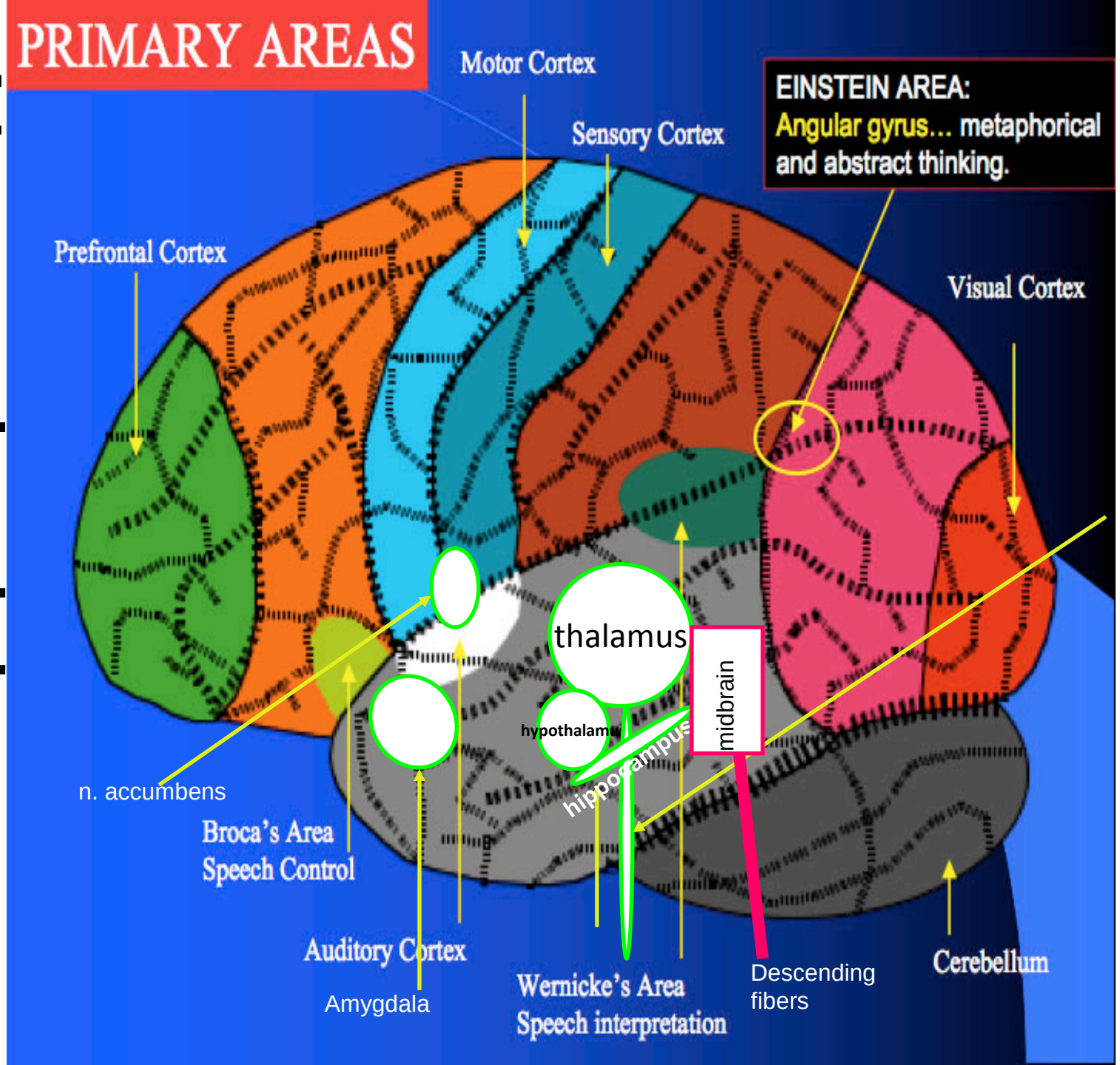
Enhanced expression of the pre-synaptic voltage-gated N-calcium channels

Central and peripheral Sensitization & Wind up

The brain and its ability to change pathways with receiving and sending signals



Neuroplasticity



Receiving pain signal

Pain Modulation

Reticular Formation And Locus Coeruleus

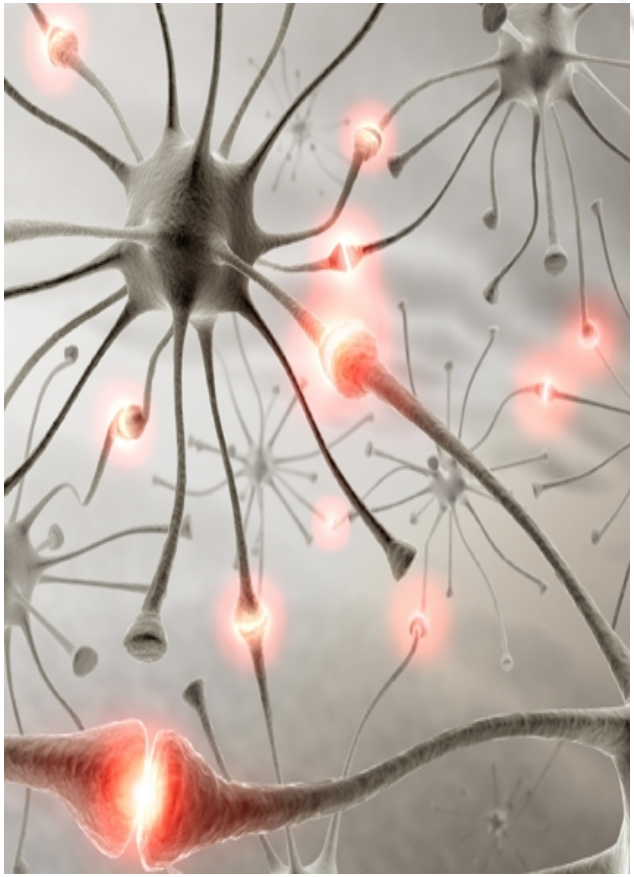
Neuroplasticity: Adaptive

- Can be influenced by environment, behavior, and emotion
- Can modify the neural representation of pain through new neuronal pathways
- Example: Following meditation: Improvement on the effects of chronic pain on corticol reorganization and grey matter
  - Pain decreases corticol somatotopic organization
  - Pain reduces the volume of grey matter in the prefrontal cortex and right thalamus

Baron, Ralph (2006). "Mechanisms of Disease: neuropathic pain—a clinical perspective". ***Nature Clinical Practice Neurology*** **2**
Staud, Roland; et. al (2007). "Brain activity related to temporal summation of C-fiber evoked pain". *Pain* (1-2 ed.) 129 (1–2): 130–142
Wang, Zaijie J; et.al (2010)"Neurobiological Mechanisms of pain in SCD". Hematology pp 403-408.
Lazar, S. et al. (2005). "Meditation experience is associated with increased cortical thickness". *NeuroReport* **16** (17): 1893–97
Schwartz, A. (2009). http://www.mentalhelp.net/poc/view_doc.php?type=doc&id=29804
Davidson, Richard; &Lutz, Antoine (2008). "Buddha's Brain: Neuroplasticity and Meditation. IEEE Signal Processing magazine. 171-174

Neuroplasticity: Maladaptive

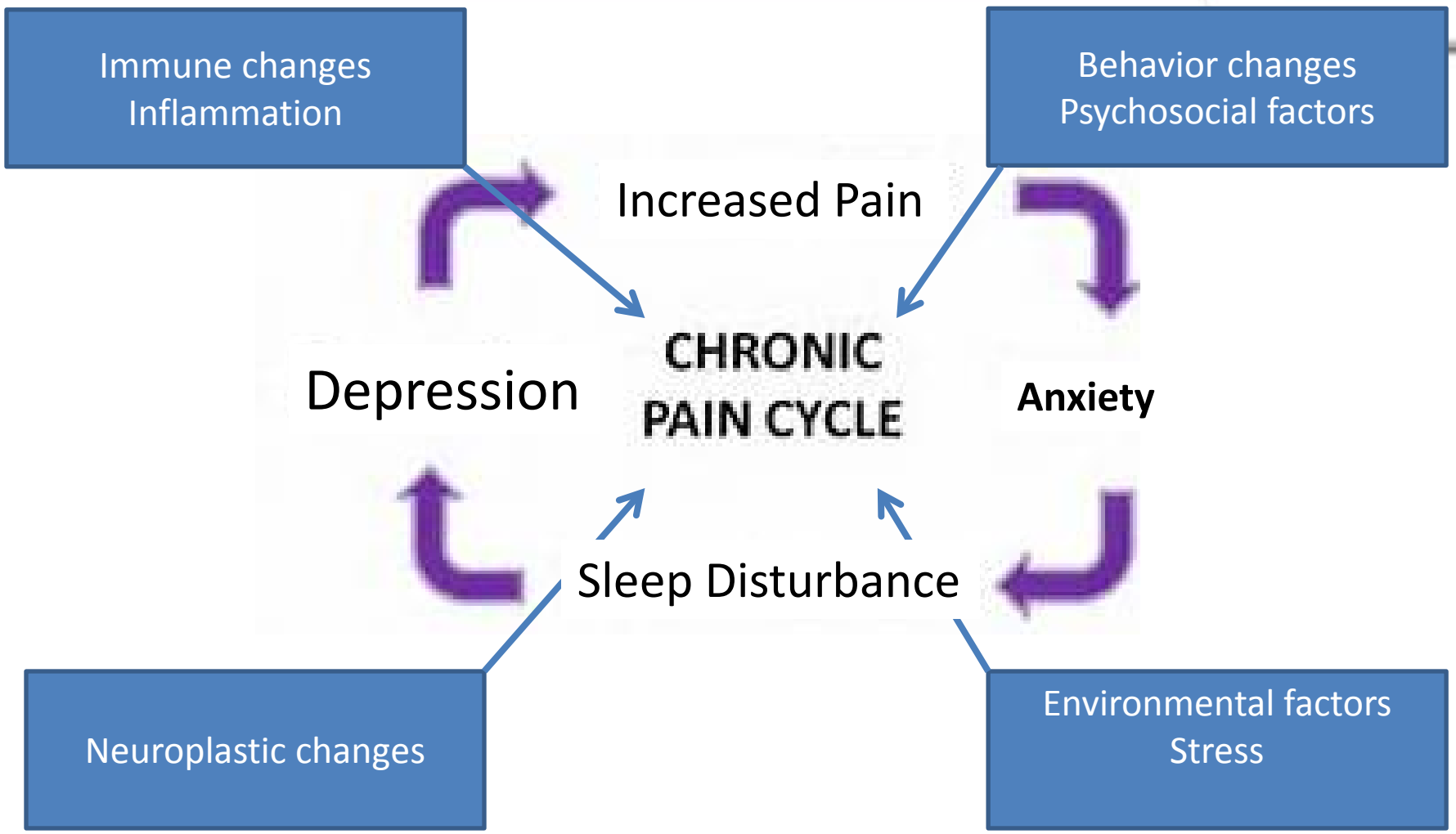
- Decreases the body's inhibitory system
- Nervous system changes in the neuronal structure
- Creates short-term and long-term changes in the nervous system
- Pain becomes more intense and wide-spread



Activing B-adrenergic Rz during stress may enhance inflammation in the CNS through increasing expression of IL-1 Beta

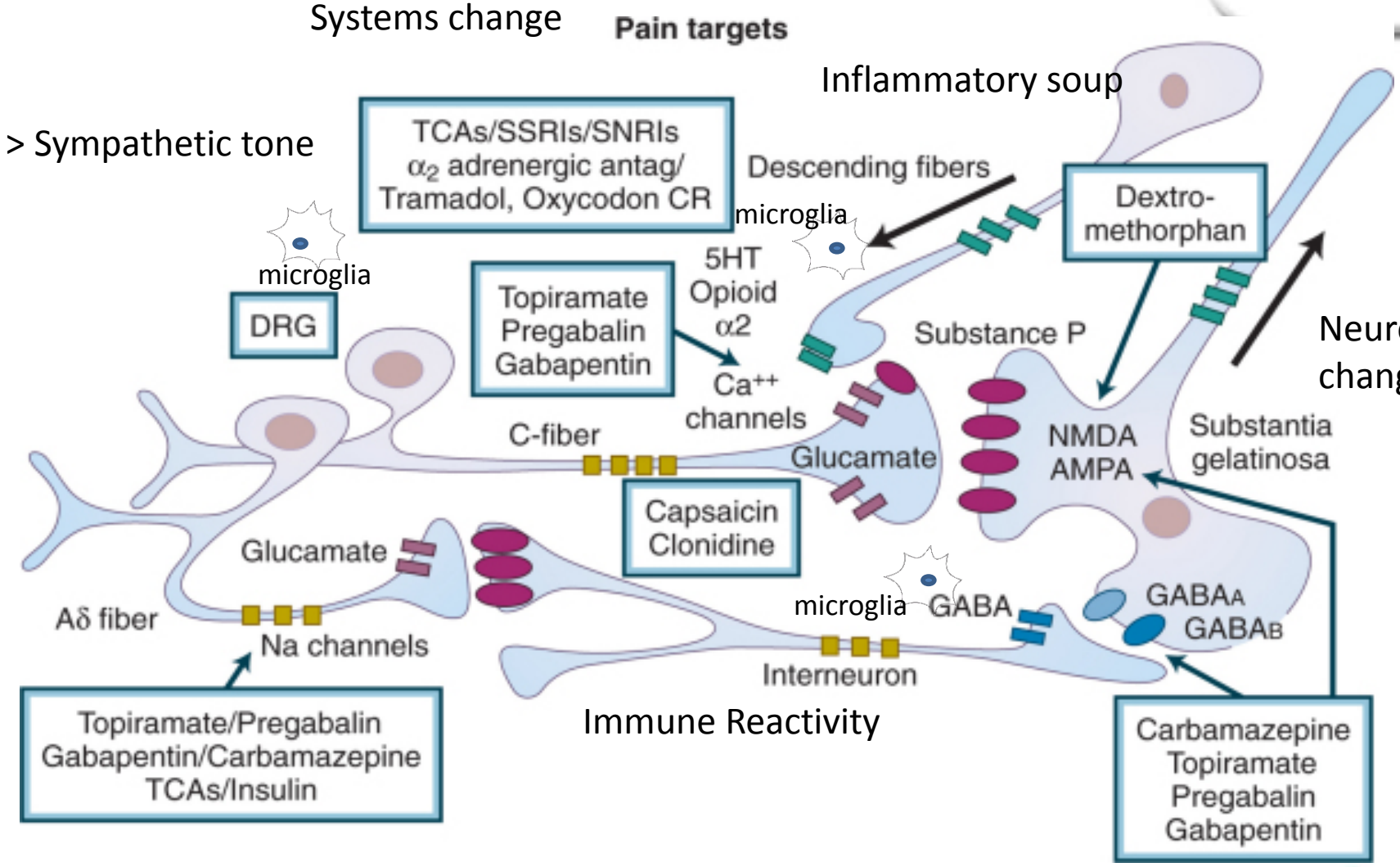
Scholz, J. (2002). Nat Neuroscience. Suppl 5; 1062-1067

Systems change



Fabulous, now what?.

It is really quite simple.



Complex and Ongoing pain does not have a single pill, psychological, functional answer, rather multiple targets and multi-modal therapy.

Multi-modal Approach

- Complementary and alternative/integrative therapies
- Behavioral therapy
- Pharmacological therapies
- Physical therapy
- Support, Education and coordination
- Function will be better prior to a change in pain perception

Eccleston, C., Palermo, T., Williams, A., Lewandowski, A., & Morley, S. (2009) Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database.

When Complex Pain is the diagnosis

1. Pain can be the diagnosis. Start families understanding that pain can be the stand alone pathology of the nervous system.

2. Reassure them that this pain is real and there is a pain physiology, but to treat pain as the pathology, treatment modalities for pain move away from what is causing the pain, and that there is a shift to treating pain from all angles and treat the whole person.

3.Reassure and listen to families and patients. Being heard for them is important. Explain that even if there are no pathological test results, their child will be taken care of from the complex pain perspective.
-We treat complex pain with multiple modalities, but consider further work-up to rule out pathology, keeping in mind shifting the focus from a single pill or psychological answer to multimodal therapies.

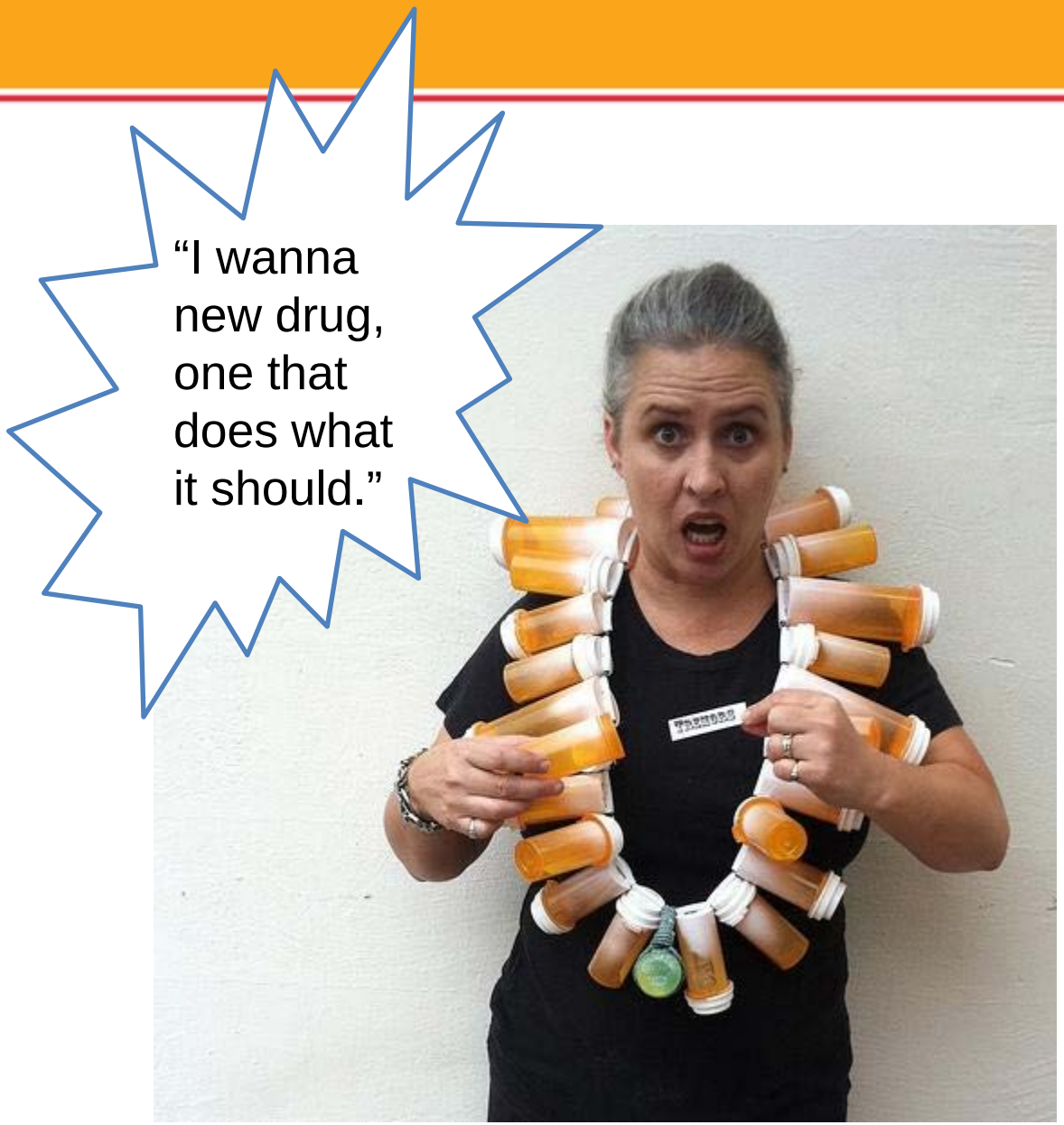
4. When pain becomes the suspected pathology, the hospital can be the worst place for a patient once the initial crisis is somewhat abated, and the work-up negative.

5. Start multi-modal approach A.S.A.P., set reasonable goals with patients and families and help families re-set expectations

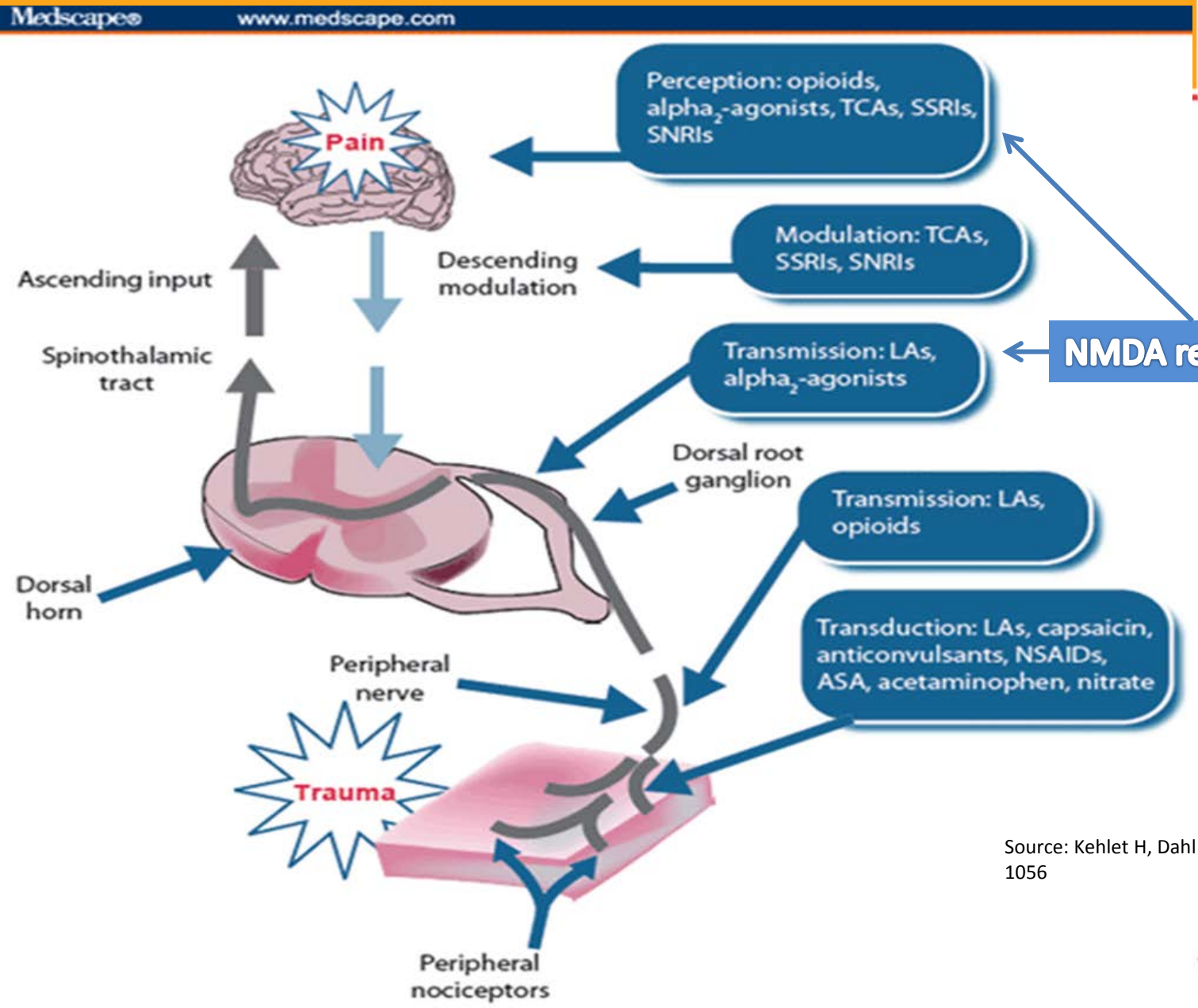
When to refer to complex outpatient pain medicine

- Once you think that pain is disproportionate to disease process, or pain is not improving on acute pain regimens.
- Often referral criteria say 6 weeks to 3 months of ongoing pain. If pain is disproportionate or unresponsive to treatment, early consultation with a complex pain medicine specialist is warranted and advised.

Fabulous, now what?.



Pain Mechanisms: Transduction to Perception



Source: Kehlet H, Dahl JB. Anesth Analg. 1993;77:1048-1056

Treatment: Pharmacology

- Acetaminophen
- Ibuprofen
- Ketorolac
- Acetaminophen with codeine
- Tramadol

- Oxycodone
- Oxycodone with acetaminophen
- Morphine
- Hydromorphone
- Fentanyl
- Methadone

(Remember methyl naltrexone for the gut)

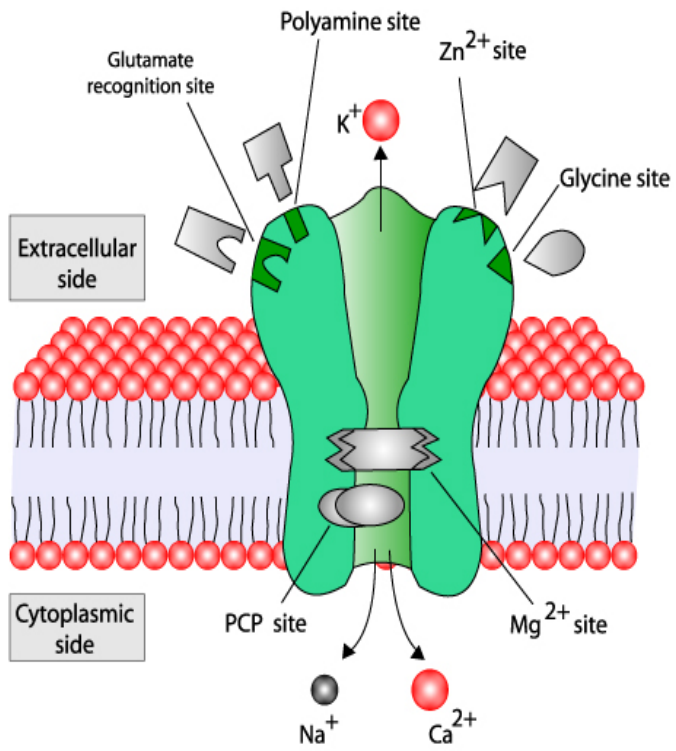
Treatment: Pharmacology

- Benzodiazepine
- Gabapentin
- Pregabalin
- Sodium Channel Blockers
- NSRI-Norepi Selective Re-uptake Inhibitors
- Tricyclics
- Ketamine (ULD)
- Memantine
- Clonidine
- Dexmedetomidine

ULD Ketamine

- NMDA antagonist
- May interact with opiate receptors in brain and spinal cord
- Advantages
  - Can prevent or reduce central sensitization
  - Neuropathic pain treatment
  - Acute post-operative pain in chronic pain patients
  - No respiratory depression, bradycardia, or hypotention
  - Some cases of opioid sparing effect
- Disadvantages
  - No long-term studies in pediatrics
  - Dissociative reaction
  - Tachcardia/hypertention

Schematic representation of the NMDA (N - Methyl D- Aspartate) receptor complex



Anesth Analg 2003;97:1730–9

Pain Medicine Volume 14, Issue 6, pages 925–934, June 2013

AnaesthesiaUK

www.dechildrens.com

New evidence for Immunomodulation in certain types of chronic complex pain

Evidence of Small Nerve Fiber neuropathy In Unexplained, Juvenile Onset, Widespread Pain Syndromes

Neuro-endocrine-immune interactions

-Role of corticosteroids
-Role of IVIG

Oaklander and Klein Pediatrics Volume 131, number 4, April 2013 pp.e1091-e1100

Complementary and Alternative/Integrative (CAM)

- Acupuncture/acupressure
- Massage
- Stress management
- Coping skills training
- Cognitive restructuring
- Relaxation therapy
- Thermal biofeedback
- Positive reinforcement

- Hypnosis
- Group therapy
- Imagery
- Education
- Heat/ice
- Immobilization
- Music
- Comfort hold/items
- Distraction

Behavioral Therapy

Pain is real, feelings, behavior, stress and emotion modulate pain intensity, but do not cause pain. Patients do not “just” need to see a psychologist.

- Cognitive behavioral therapy (CBT) is used in Chronic Pain Treatment
- Biofeedback-assisted relaxation resulted in reduction of pain frequency
- Hypnosis
- Meditation

NOTE:(hospital environment makes any psychological approach difficult)

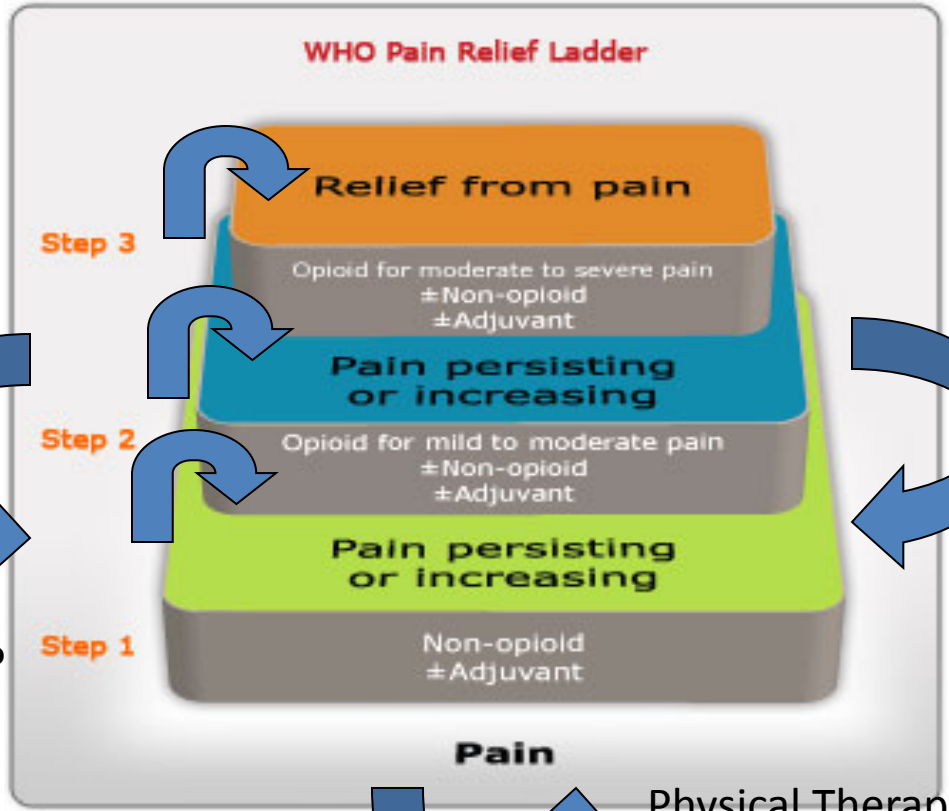
Myrvik, et al, 2012. Single-session biofeedback-assisted relaxation training in children with sickle cell disease. J Pediatr Hematol Oncol, 34(5); 340-343
Thomas, V. (2000). Cognitive behavioural therapy in pain management for sickle cell disease. Int J Palliat Nurs. 6(9); 434-442.
Chronic Pain: An Integrated Biobehavioral Approach: Herta Flor, PhD, Dennis C. Turk, PhD, 2011
“Pain in Children” McGrath

Managing the pain in real time
Re-set goals and expectations

Education about complex pain 1st

Increased Function, normalcy, and quality of life.

CAM and Integrative therapies



2.Psychological Support, coping strategies

- Benzodiazepine
- Gabapentin
- Pregabalin
- Sodium Channel Blockers
- NSRI-Norepi Selective Re-uptak Inhibitors
- Tricyclics
- Ketamine (ULD)
- Memantine
- Clonidine
- Dexmedetomidine

Immune modulation?

Physical Therapy and Occupational therapy

RECAP: What can you do?

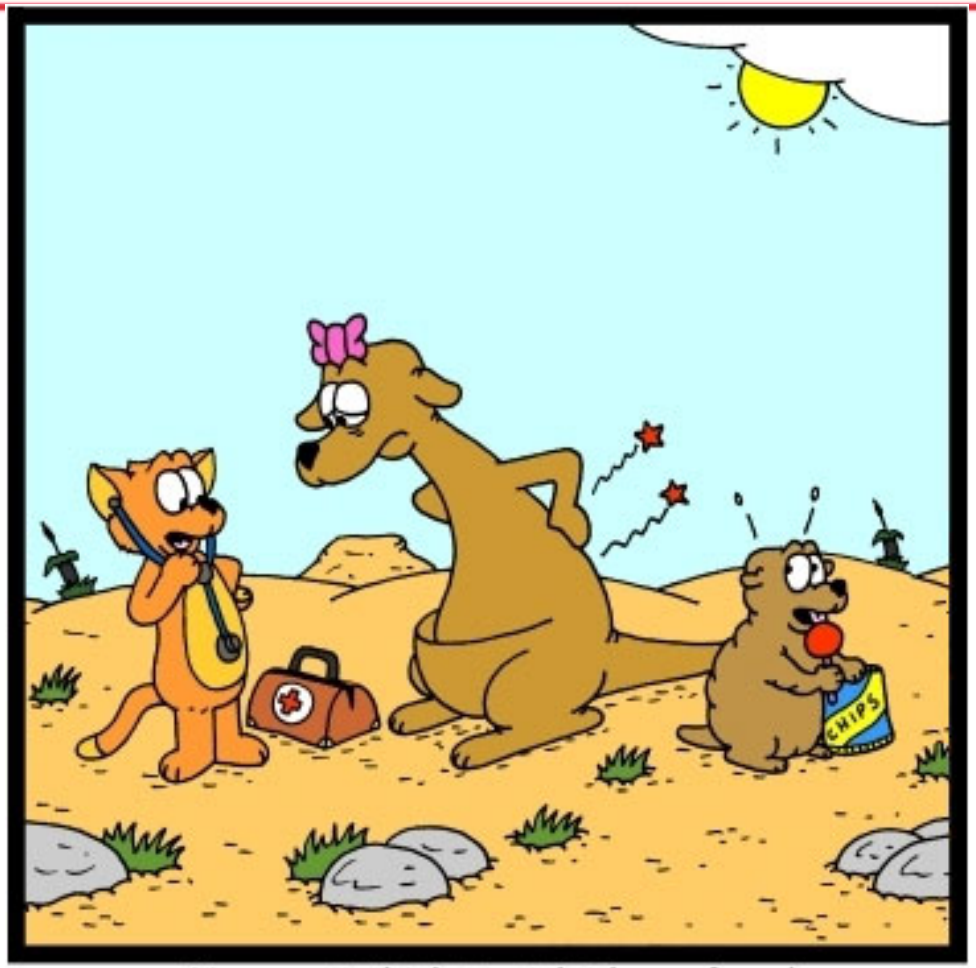
1. Recognize pain disproportionate or unresponsive to treatment
2. Start multi-modal treatment, educate and listen to families, shift treatment and thought focus from a single uni-treatment modality to treating the whole patient. Re-set expectations.
3. Decide on a pharmacology regimen in a stepwise fashion.
4. Refer early to an outpatient complex pain medicine provider for consultation
5. Do not expect patients to leave the hospital or your practice With 0/10 pain or let personal bias drive treatment

Food for Thought

Otherwise healthy 16 Y.O. female PMH for recovery from EBV infection 1 month ago, admitted for intractable RLQ pain and observation, completely negative medical work up to include GI studies, with the finding of an increased stool burden and lymphadenitis with a negative work-up from ID. After clean out, pain remains.

Otherwise healthy 9 Y.O. boy develops comes into your practice after hairline fracturing his left foot with worsening pain after 2 weeks in a soft cast. The x-ray shows healing bone, exam is benign except that his left foot is colder, is painful to the touch, and shiny. Opiates do not help him.

????



Hmmm, I think I might have found
the cause of your backache Ma'am...

Children's
National Medical Center

Neuroplasticity and Stress

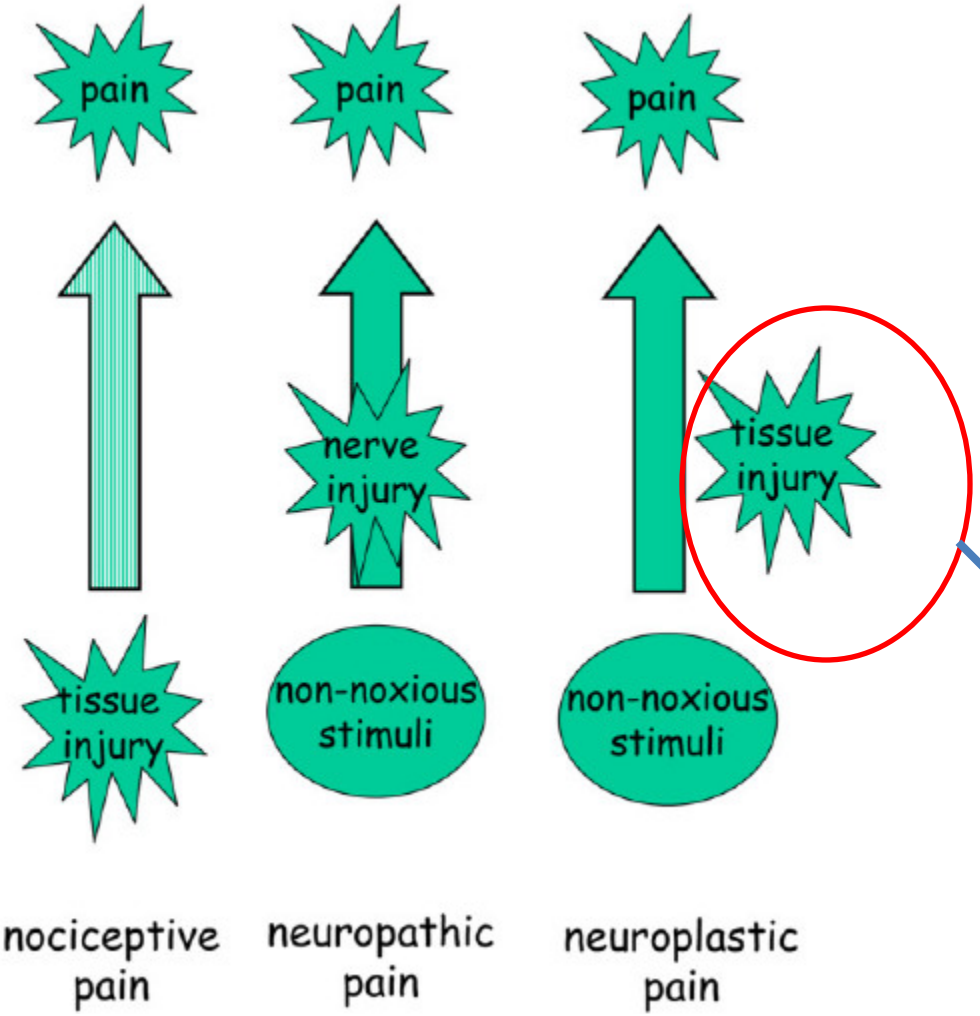
Tynan R. J. et al. 2010 in Brain Behavior and Immun. Chronic stress alters density and morphology of microglia in a subset of stress responsive brain regions.

McNamee et. al. 2010, Neuropharmacology B-receptors induce expression of IL-1Beta in rat cortex

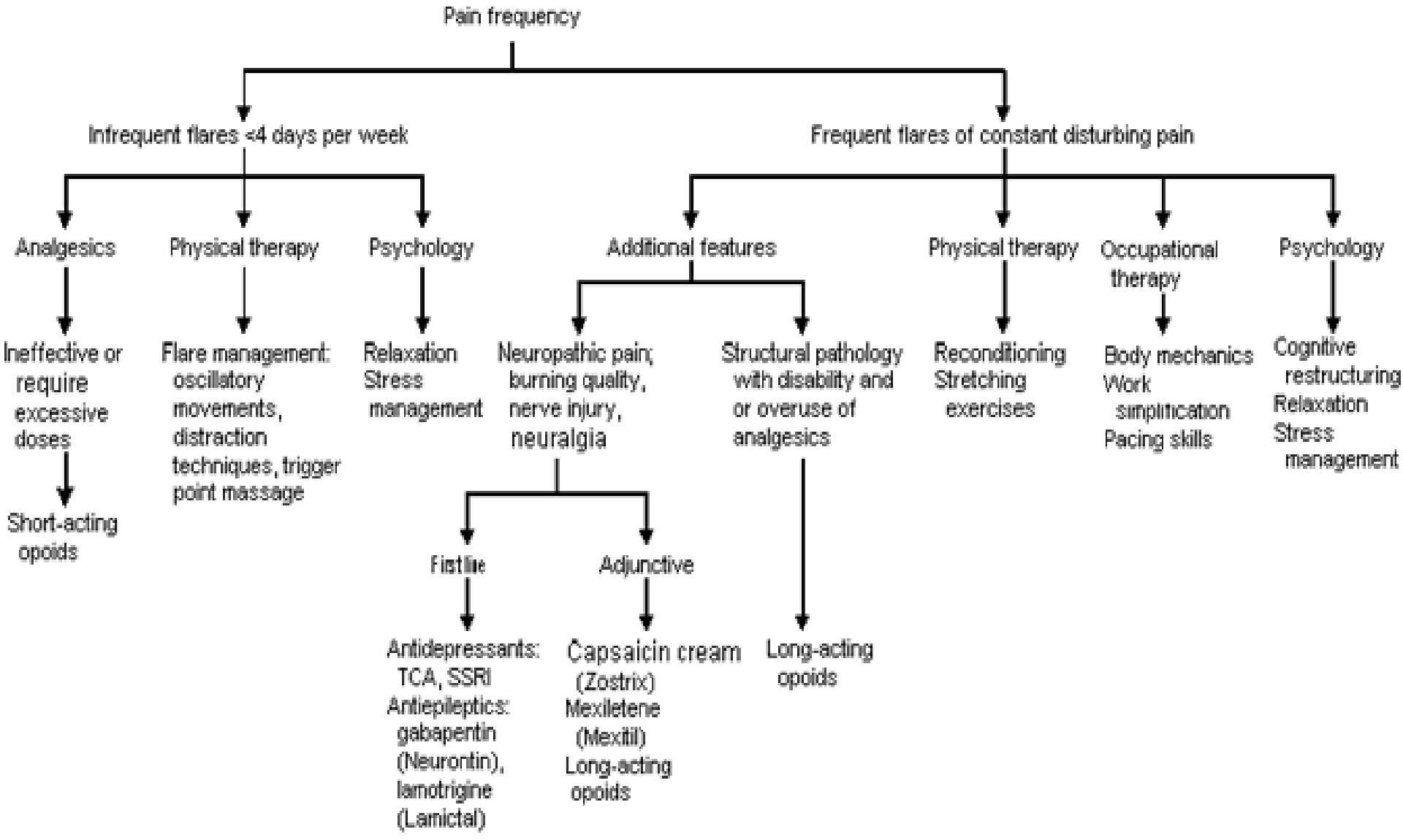
Cole et. al. in 2010 ID gene –social environmental interaction at the Human IL-6 locus

Wohleb et. al. 2011 in J. of Neuroscience put a story together for us regarding B-adrenergic receptor antagonism preventing anxiety-like behavior and microglial reactivity induced by repeated social defeat.

Review Types of Pain



Systems change
Immune changes
neuroplasticity


Pain frequency
Infrequent flares <4 days per week
Frequent flares of constant disturbing pain
Analgesics
Physical therapy
Psychology
Additional features
Physical therapy
Occupational therapy
Psychology
Ineffective or require excessive doses
Short-acting opoids
Flare management: oscillatory movements, distraction techniques, trigger point massage
Relaxation
Stress management
Neuropathic pain; burning quality, nerve injury, neuralgia
Structural pathology with disability and or overuse of analgesics
Reconditioning
Stretching exercises
Body mechanics
Work simplification
Pacing skills
Cognitive restructuring
Relaxation
Stress management
First line
Adjunctive
Antidepressants: TCA, SSRI
Antiepileptics: gabapentin (Neurontin), lamotrigine (Lamictal)
Capsaicin cream (Zostrix)
Mexiletene (Mexitil)
Long-acting opoids
Long-acting opoids