Citation Key

for more information see: http://open.umich.edu/wiki/CitationPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

Public Domain – Government: Works that are produced by the U.S. Government. (17 USC § 105)

Public Domain – Expired: Works that are no longer protected due to an expired copyright term.

Public Domain – Self Dedicated: Works that a copyright holder has dedicated to the public domain.

Creative Commons – Zero Waiver

Creative Commons – Attribution License

Creative Commons – Attribution Share Alike License

Creative Commons – Attribution Noncommercial License

Creative Commons – Attribution Noncommercial Share Alike License

GNU – Free Documentation License

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

Public Domain – Ineligible: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

Fair Use: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.

Pathogenesis and Treatment of Fibromyalgia

Daniel J. Clauw M.D.

Professor of Anesthesiology and Medicine (Rheumatology)
Associate Dean for Clinical and Translational Research
The University of Michigan

Fall 2008
M2 Musculoskeletal

University of Michigan
Medical School

Mechanistic Characterization of Pain

Peripheral (nociceptive)

- Primarily due to inflammation or mechanical damage in periphery
- NSAID, opioid responsive
- Responds to procedures
- Behavioral factors minor
- Examples
  - Osteoarthritis
  - Rheumatoid arthritis
  - Cancer pain

Neuropathic

- Damage or entrapment of peripheral nerves
- Responds to both peripheral and central pharmacological therapy

Central (non-nociceptive)

- Primarily due to a central disturbance in pain processing
- Tricyclic, neuroactive compounds most effective
- Behavioral factors more prominent
- Examples
  - Fibromyalgia
  - Irritable bowel syndrome
  - Tension headache
  - Idiopathic low back pain

Paradigm Shift in Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Psychologic and behavioral factors nearly always present and negative

PD-INEL Source Undetermined

- Chronic widespread pain
- Tenderness in ≥11 of 18 tender points
- Final common pathway
- Part of a larger continuum
- Many somatic symptoms, diffuse tenderness
- Psychologic and behavioral factors play roles in some individuals


PD-INEL Source Undetermined

Overlap Between Fibromyalgia and Related Syndromes

Fibromyalgia

- 2%-4% of population
- Defined by widespread pain and tenderness

Chronic Fatigue Syndrome (CFS)

- 1% of population
- Fatigue and 4 of 8 “minor criteria”

Regional Pain Syndromes

- eg, irritable bowel [IBS]
- Painful bladder / interstitial cystitis [PBS/IC]
- TMD
- Tension HA
- Vulvodynia

Psychiatric Disorders

- Major depression
- OCD
- Bipolar
- PTSD
- GAD
- Panic attack

Somatoform Disorders

- 4% of population
- multiple unexplained symptoms — no “organic” findings

LBP = low back pain; TMD = temporomandibular disorders.
Clauw and Chrousos. *Neuroimmunomodulation*. 1997;4:134-53.

Shared features

- Characterized by multiple somatic symptoms and high rates of comorbidities with other related syndromes
- 1.5 – 2X more common in females
- Strong familial/genetic underpinnings
- Triggered or exacerbated by “stressors”
- Pain and/or sensory amplification most reproducible pathophysiological feature
- Dysautonomia, neuroendocrine dysfunction, and neurogenic inflammation also commonly noted, but of unclear physiological significance

"Stressors" Capable of Triggering These Illnesses (Supported by Case-Control Studies[1,2])

- Early life stressors[3]
  - Children born in 1958 who had experienced a motor traffic accident or who were institutionalized were 1.5 – 2X more likely to have CWP 42 years later
- Peripheral pain syndromes (e.g. RA, SLE, osteoarthritis)[4]
- Physical trauma (automobile accidents)[5]
- Certain catastrophic events (war but not natural disasters)[6]
- Infections
- Psychological stress/distress

Sources: 1. Clauw and Chrousos. Neuroimmunomodulation. 1997;4:134-53. 2. McLean and Clauw. Med Hypotheses. 2004;63:653-8.
3. Jones et al. ACR Meeting. 2007. 4. Clauw et al. JCR. 1997.
5. McBeth. ACR Meeting. 2006. 6. Clauw et al. J Occup Environ Med. 2003;45:1040-8.

Genetics of Fibromyalgia

- Familial predisposition[1]
  - Most recent work by Arnold, et al suggests >8 odds ratio (OR) for first-degree relatives, and much less familial aggregation (OR 2) with major mood disorders
  - Much stronger with bipolarity, obsessive compulsive disorder
- Genes that may be involved
  - 5-HT2A receptor polymorphism T/T phenotype[2]
  - Serotonin transporter[3]
  - Dopamine D4 receptor exon III repeat polymorphism[4]
  - COMT (catecholamine o-methyl transferase)[5]

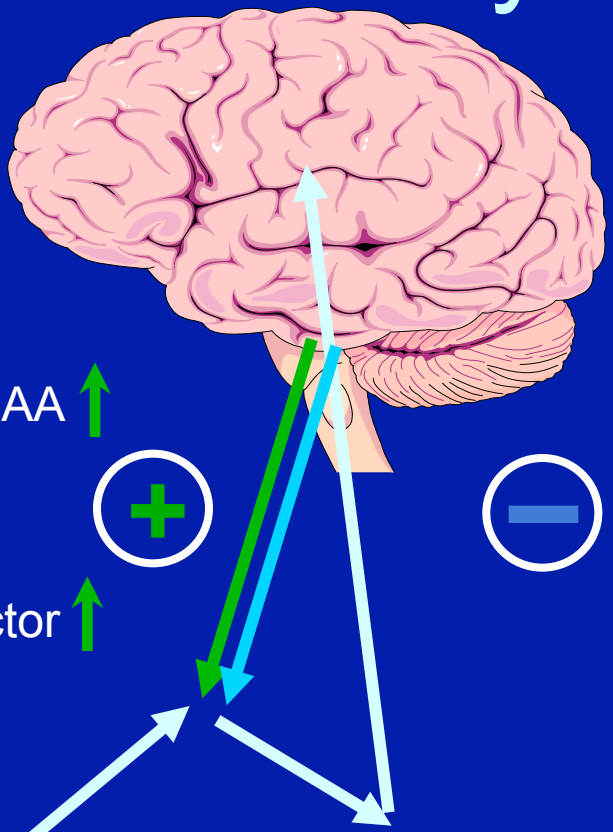
Sources: 1. Arnold et al. *Arthritis Rheum*. 2004;50:944-52. 2. Bondy et al. *Neurobiol Dis*. 1999;6:433-9.
3. Offenbaecher et al. *Arthritis Rheum*. 1999;42:2482-8. 4. Buskila et al. *Mol Psychiatry*. 2004;9:730-1.
5. Gürsoy et al. *Rheumatol Int*. 2003;23:104-7.

Conditions Characterized by Widespread Secondary Hyperalgesia / Allodynia

- Fibromyalgia
- Temperomandibular disorder[1,2]
- Headache (tension > migraine)[3,4]
- Idiopathic low back pain[5,6]
- Vulvodynia/vulvar vestibulitis[7]
- Whiplash associated disorder[8]
- IBS[9,10]

Sources: 1. Maixner et al. Pain. 1995;63:341-51. 2. Kashima et al. Cranio. 1999;17:241-246.
3. Langemark et al. Arch Neurol. 1993;50:1061-4. 4. Buchgreitz et al. Pain. 2006;123:19-27.
5. Giesecke et al. Arthritis Rheum. 2004;50:613-23. 6. Giesbrecht and Battie. Phys Ther. 2005;85:1085-92.
7. Giesecke et al. Obstet Gynecol. 2004;104:126-33. 8. Lemming et al. Clin J Pain. 2005;21:412-21.
9. Whitehead at al. Gastroenterology. 1990;98:336-40. 10. Mertz et al. Gastroenterology. 1995;109:40-52.

Supraspinal Influences on Pain and Sensory Processing

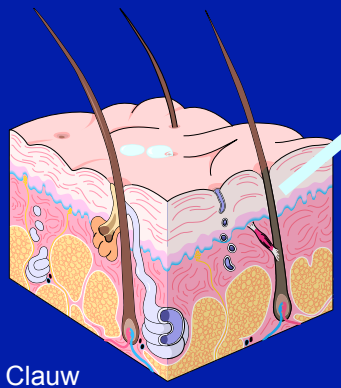


Facilitation

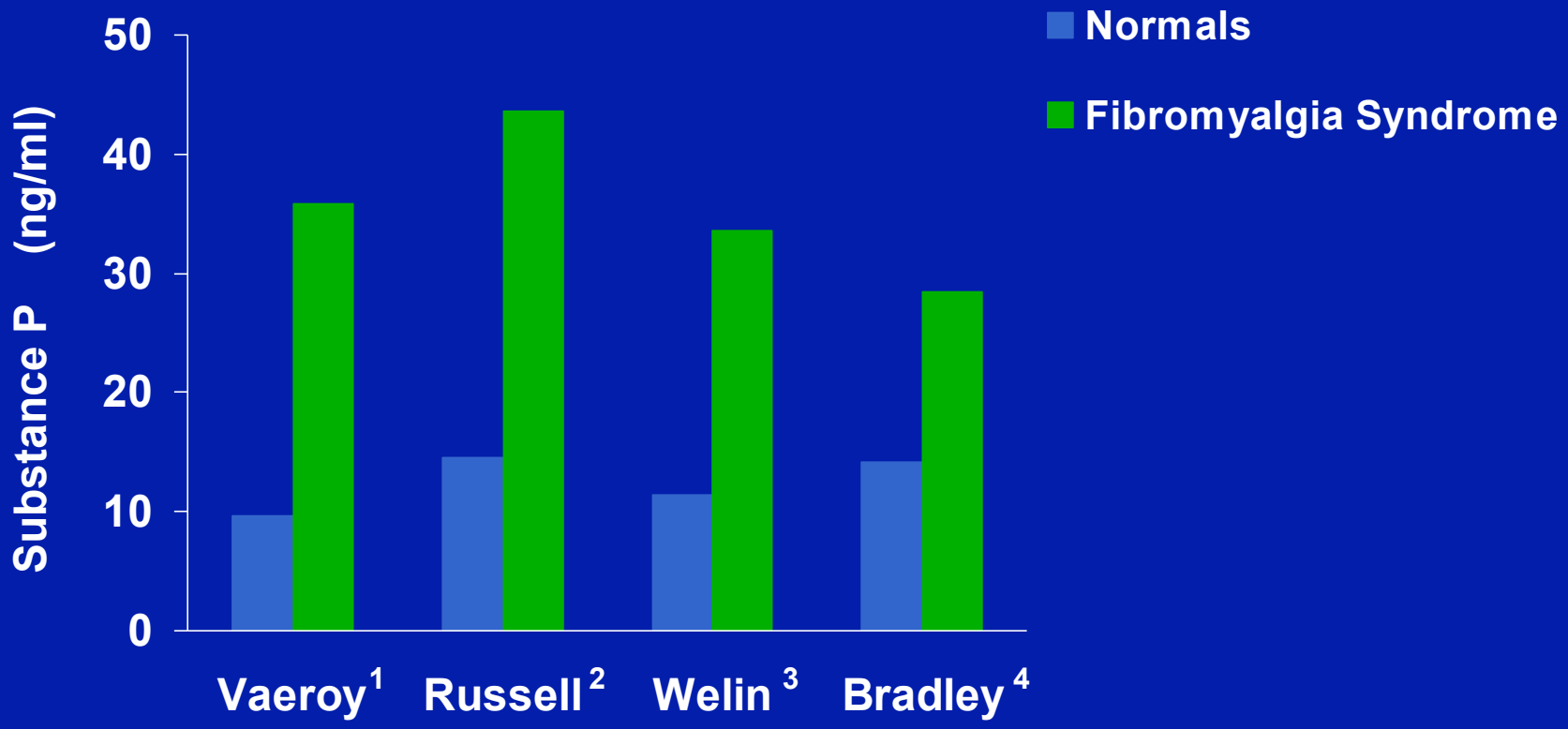
- Substance P ↑
- Glutamate and EAA ↑
- Serotonin ($5HT_{2a, 3a}$)
- Nerve growth factor ↑
- CCK

Inhibition

- Descending anti-nociceptive pathways
  - ↓ Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine
  - ↑ Opioids
- GABA
- Cannabanoids
- Adenosine

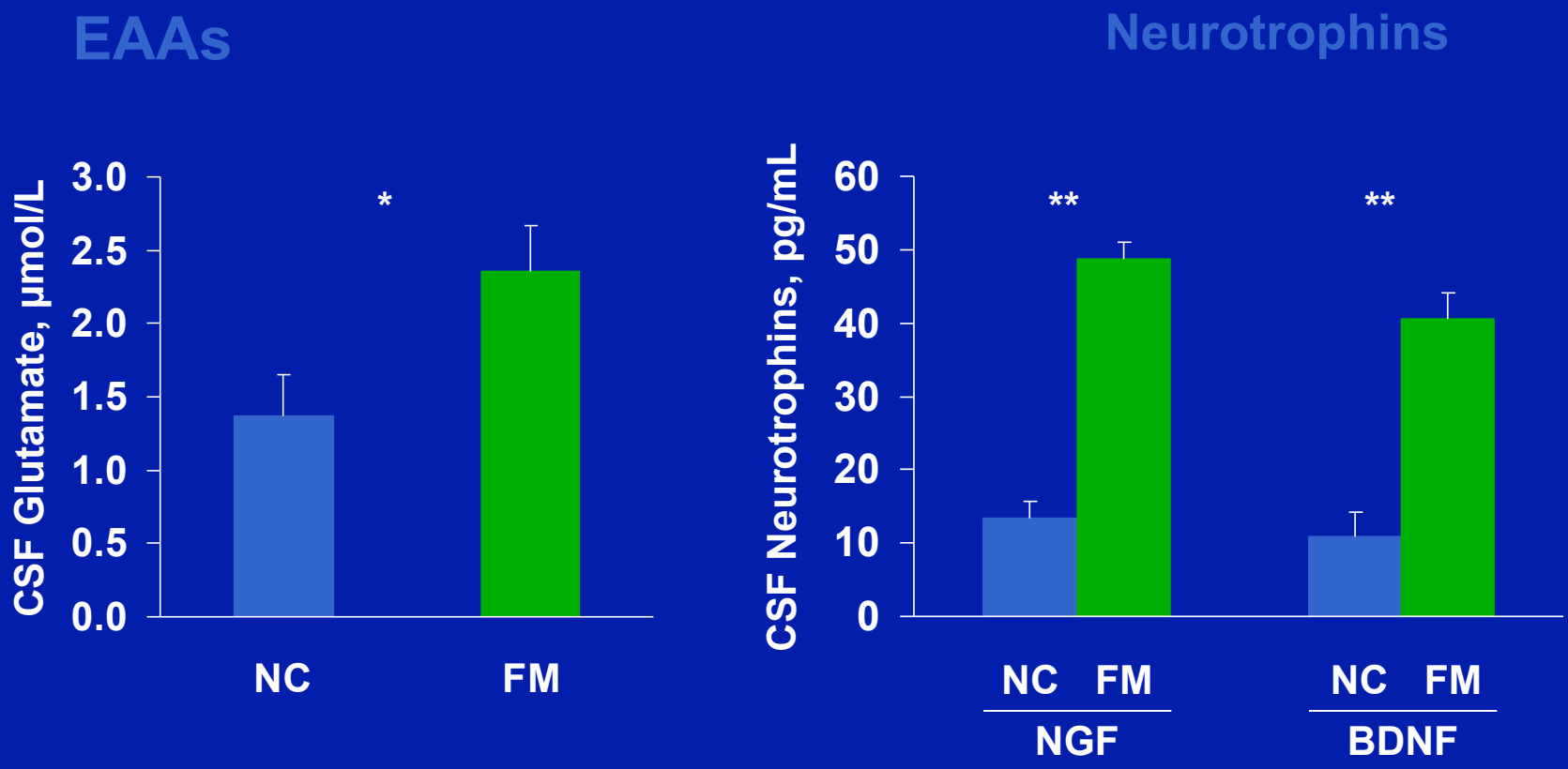


Fibromyalgia Cerebrospinal Fluid Substance P



1. Vaeroy et al. *Pain*. 1988;32:21-6. 2. Russell et al. *Arthritis Rheum*. 1994;37:1593-601.
3. Liu et al. *Peptides*. 2000;21:853-60. 4. Bradley and Alarcon. *Arthritis Rheum*. 1999;42:2731-2.

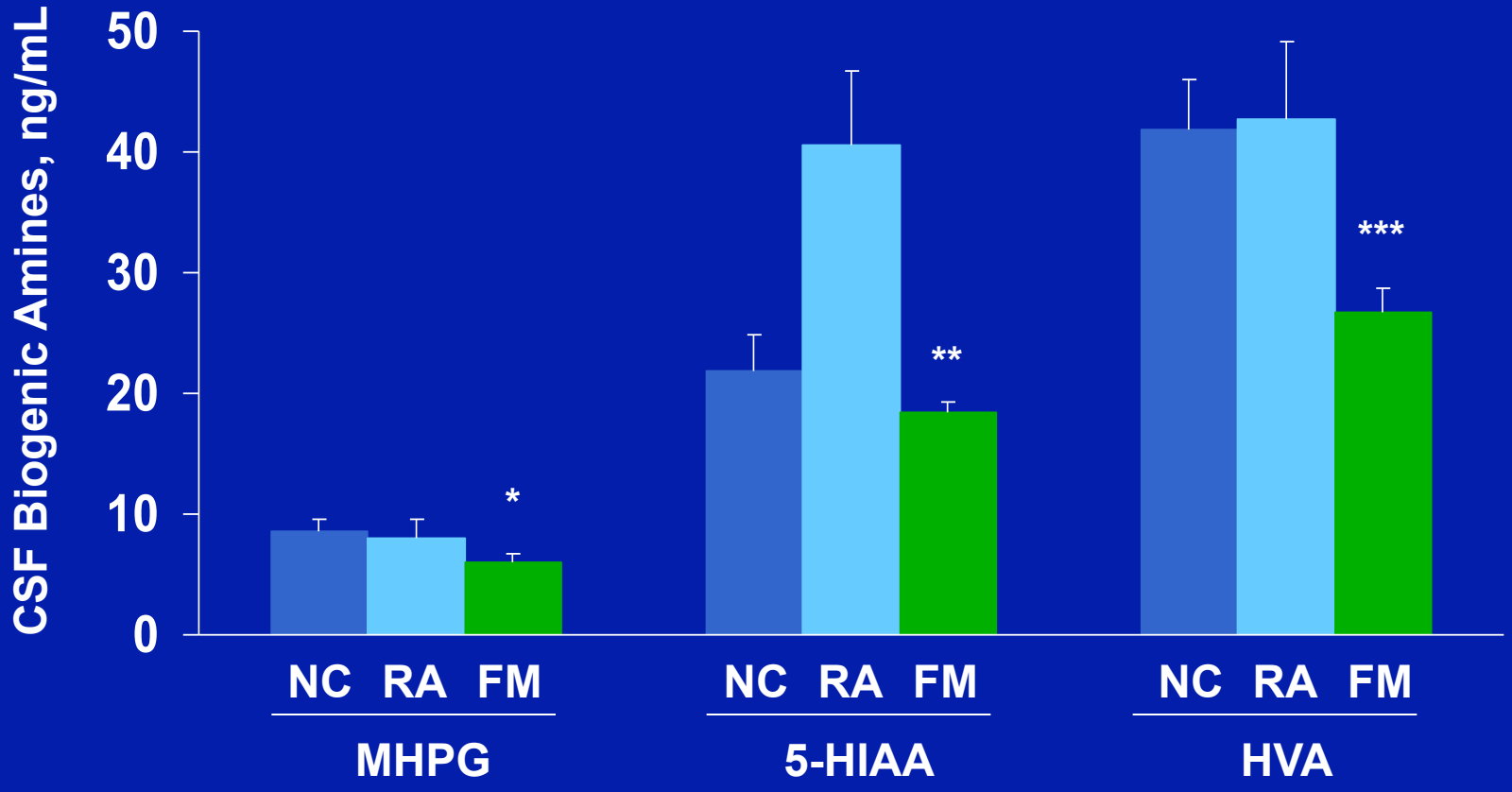
Increased Spinal Fluid Levels Of Glutamate and Neurotrophins



*P<0.003; **P<0.001.
BDNF, brain-derived neurotrophic factor; EAA, excitatory amino acid; NGF, nerve growth factor.
N=20 patients with fibromyalgia and 20 control subjects.

Sarchielli et al. *J Pain*. 2007;8:737-45.

Decreased Spinal Fluid Levels Of Biogenic Monoamines



*P=0.028; **P=0.057; ***P=0.005 vs nonfibromyalgia controls.
5-HIAA, 5-hydroxyindole acetic acid; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenethylene glycol.
N=17 patients with fibromyalgia, 5 patients with rheumatoid arthritis, and 7 control subjects.
Russell et al. *Arthritis Rheum*. 1992;35:550-6.

"Pain Matrix" – Pain is Processed in at Least Three Domains in CNS

- Sensory: where it is and how much it hurts
  - Primary and secondary somatosensory cortices
  - Thalamus
  - Posterior insula
- Affective: emotional valence of pain
  - Anterior cingulate cortex
  - Anterior insula
  - Amygdala
- Cognitive: similar to affective plus prefrontal regions

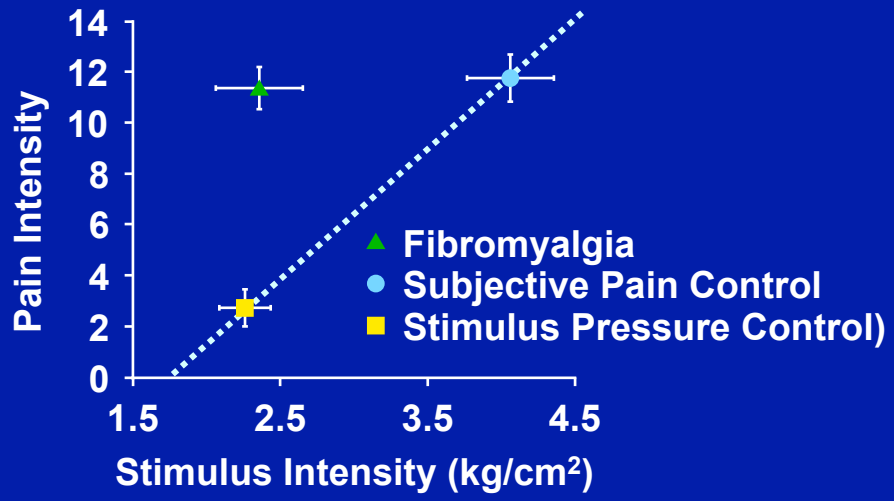
Source:
Melzack and Wall. *Science*. 1965;150:971-9.
Casey. *Headache*. 1969;8:141-53.

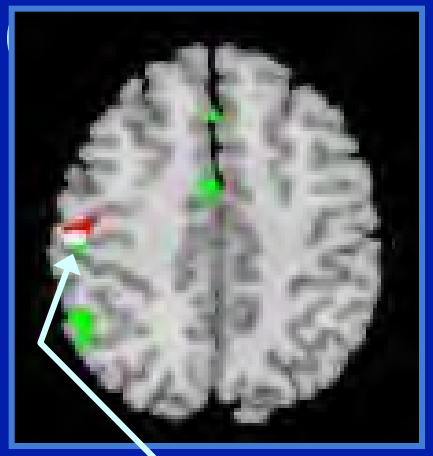
fMRI of Evoked Pressure Pain in Fibromyalgia and Related Conditions

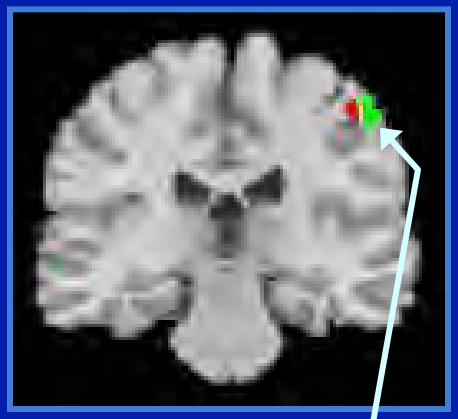
- Is there objective evidence of augmented pain processing in fibromyalgia?[1]
- Role of depression in pain processing in FM[2]
- Role of cognitive factors in pain processing in FM
  - Locus of control
  - Catastrophizing[3]
- fMRI changes of augmented central processing of pain also seen in idiopathic low back pain[4]

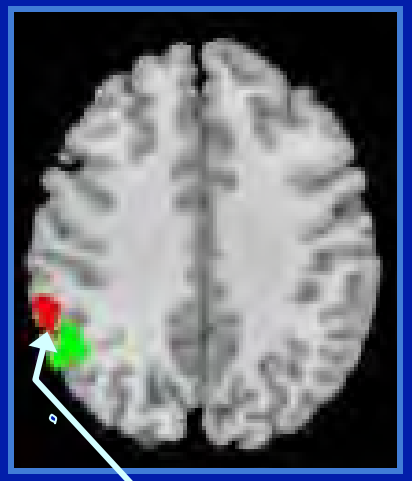
Sources:
1. Gracely et al. *Arthritis Rheum*. 2002;46:1333-43. 2. Giesecke et al. *Arthritis Rheum*. 2003;48:2916-22.
3. Gracely et al. *Brain*. 2004;127:835-43. 4. Giesecke et al. *Arthritis Rheum*. 2004;50:613-23.

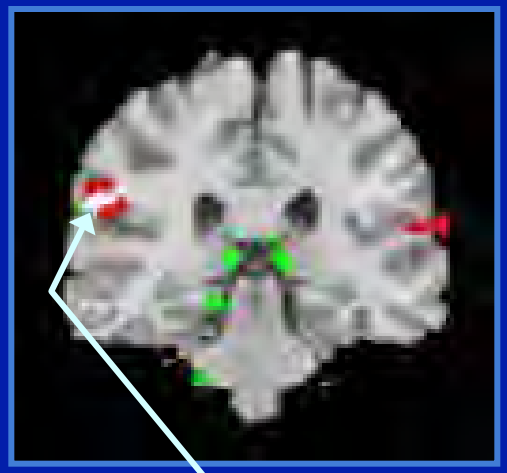
Stimuli and Responses During Pain S

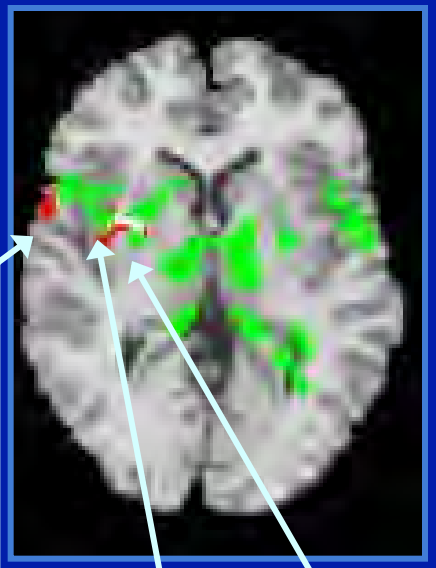


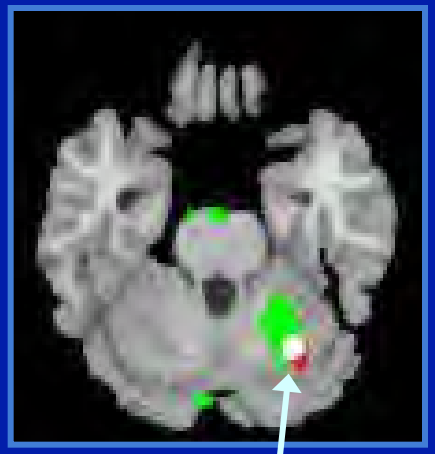












STG=superior temporal gyri; SI=primary somatosensory cortex; SII=secondary somatosensory cortex; IPL=inferior parietal lobule.

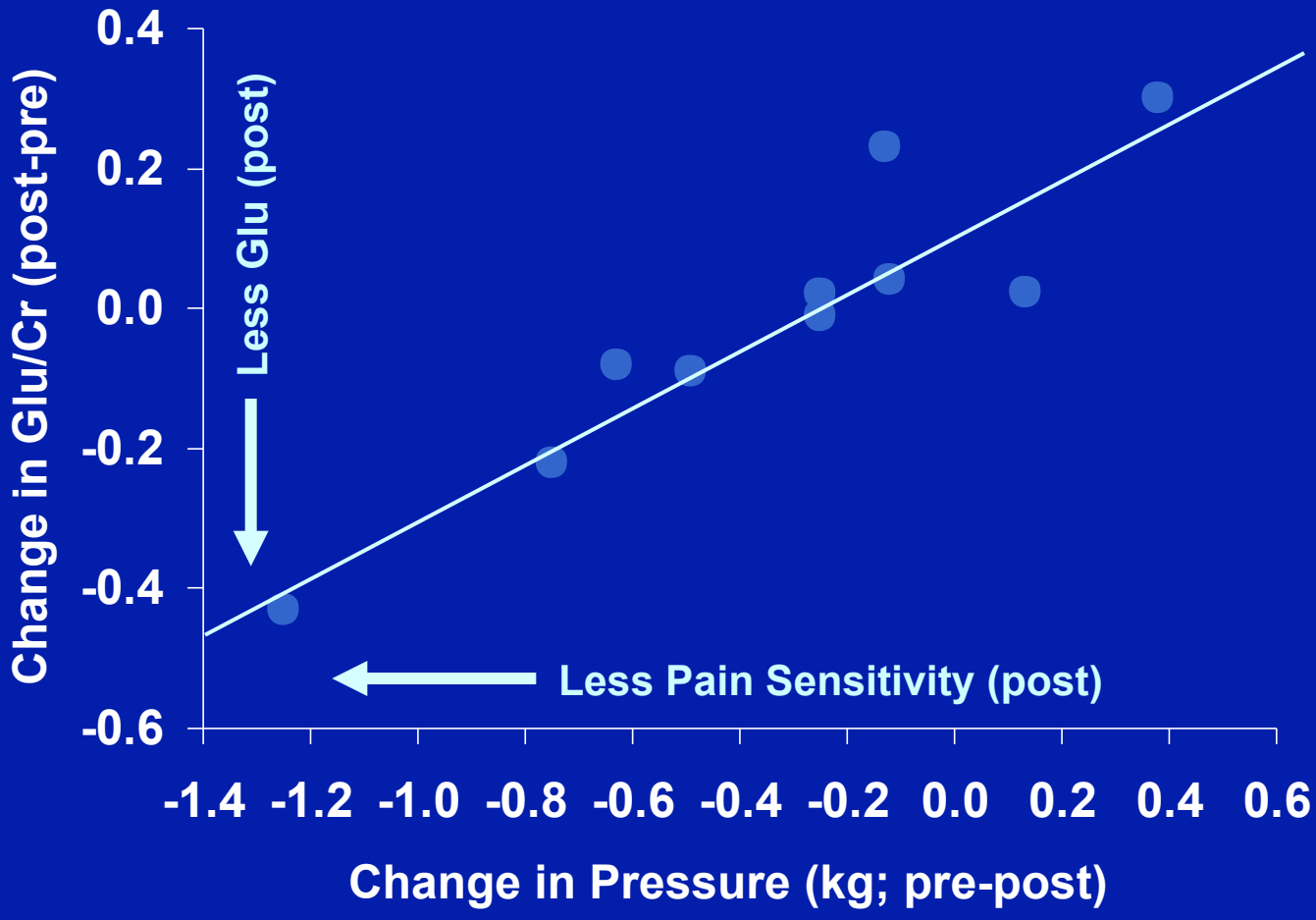
Gracely et al. *Arthritis Rheum*. 2002;46:1333-43.

Specific Underlying Mechanisms in Fibromyalgia

- Global problem with sensory processing (i.e. interoception)
  - FM patients equally sensitive to loudness of auditory tones[1]
  - Insular hyper-reactivity consistently seen[2-4]
  - H-MRS studies of glutamate levels in posterior insula[5]

Sources:
1. Geisser et al. *J Pain*. 2008;9:417-22. 2. Gracely et al. *Arthritis Rheum*. 2002;46:1333-43.
3. Giesecke et al. *Arthritis Rheum*. 2004;50:613-23. 4. Cook et al. *J Rheumatol*. 2004;31:364-78.
5. Harris et al. *Arthritis Rheum*. 2008;58:903-7.

Reduction in Glu is Associated with Reduced Experimental Pressure Pain in FM



r=-0.95; P<0.001.

Harris et al. *Arthritis Rheum*. 2008;58:903-7.

Specific Underlying Mechanisms in Fibromyalgia

- Decreased descending analgesic activity
  - Absent or attenuated DNIC in FM and IBS[1-3]
  - Brainstem activations with conditioning stimulus seen in controls but not in FM patients[4]

Source:
1. Kosek and Hansson. *Pain*. 1997;70:41-51. 2. Julien et al. *Pain*. 2005;114:295-302.
3. Wilder-Smith and Robert-Yap. *World J. Gastroenterol*. 2007;13:3699-704. 4. Gracely et al. *Arthritis Rheum*. 2006 (abstract).

There is a Deficiency of Descending Analgesic Activity in FM:[1,2] Which one?

Opioids

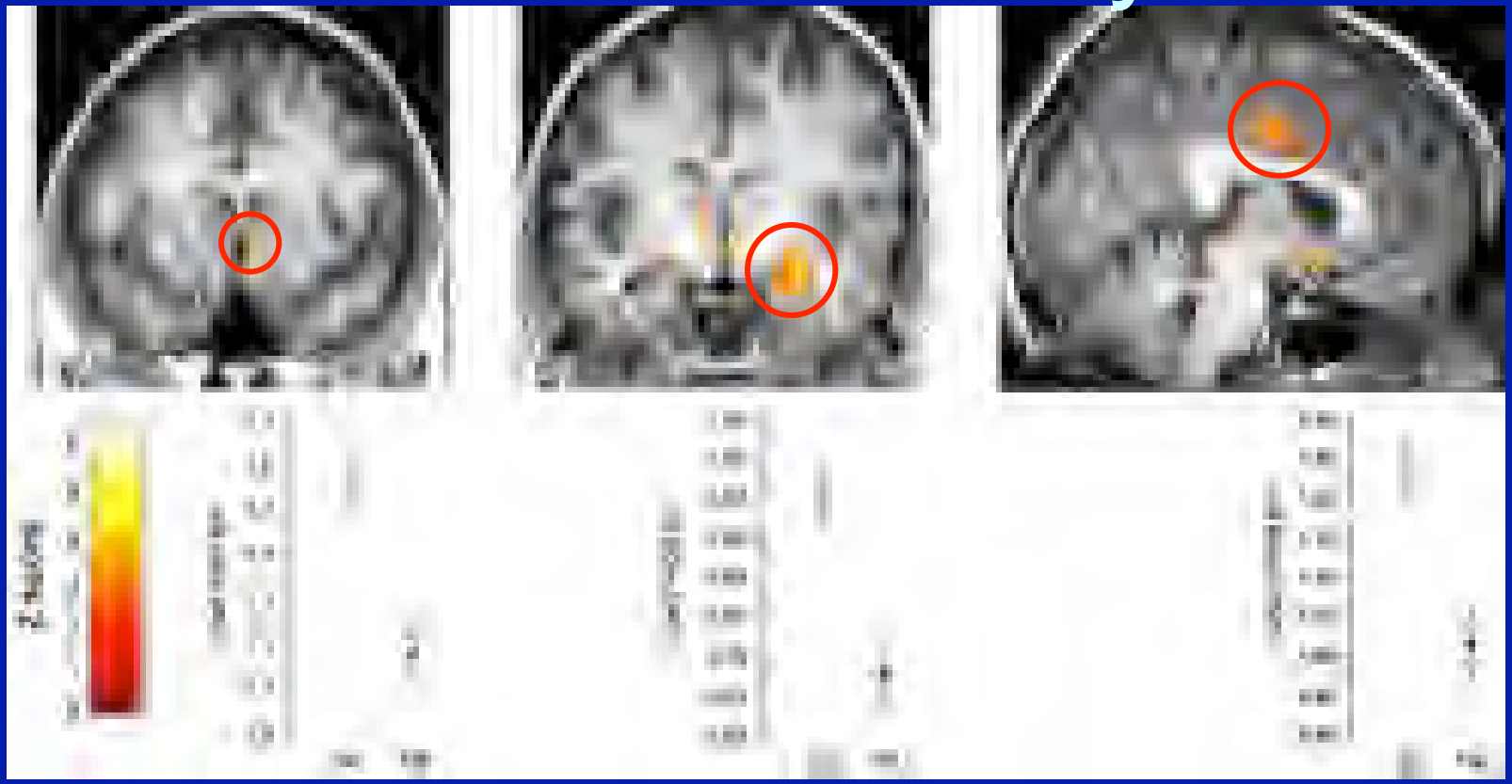
- Normal or high levels of CSF enkephalins[3]
- Never been administered in RCT but most feel that opioids are ineffective or marginally effective
- Harris recently used PET to show decreased mu opioid receptor binding in FM[4]

Noradrenergic/Serotonergic

- Low levels of biogenic monoamines in CSF in FM[5]
- Nearly any class of drug that raises both serotonin and norepinephrine has demonstrated efficacy in FM

Sources:
1. Kosek and Hansson. *Pain*. 1997;70:41-51. 2. Julien et al. *Pain*. 2005;114:295-302.
3. Baraniuk et al. *BMC Musculoskelet Disord*. 2004;5:48. 4. Harris et al. *J Neurosci*. 2007;27:10000-6.
5. Russell et al. *Arthritis Rheum*. 1992;35:550-6.

FM Patients Have Reduced MOR Availability



	L NAcc	lAMY	L dCC
Z	4.12	4.21	3.39
P-Value*	<0.05	< 0.05	<0.05
%D BP	33.1(7.1)	31.1(7.0)	21.5(6.4)

*corrected

Harris et al. *J Neurosci*. 2007;27:10000-6.

Is Chronic Pain a Neurodegenerative Disease?

- Apkarian[1] was first to show that chronic pain may be a neurodegenerative disease, showing
  - Decreased gray matter density in DLPFC and thalamus
  - Related to length of pain
- More recently seen in other pain states including
  - Headache (insula and ACC)[2]
  - IBS (insula and ACC)[3]
  - Fibromyalgia[4] (multiple regions)
  - PTSD[5] (insula)

Sources:
1. Apkarian et al. *J Neurosci*. 2004;24:10410-5. 2. Schmidt-Wilcke et al. *Pain*. 2007;132 Suppl 1:S109-16.
3. Davis et al. *Neurology*. 2008;70:153-4. 4. Kuchinad et al. *J Neurosci*. 2007;27:4004-7.
5. Chen et al. *Psychiatry Res*. 2006;146:65-72.

The Biopsychosocial Continuum

Population **Primary Care** **Tertiary Care**

Neurobiological

- Abnormal sensory processing
- Autonomic dysfunction
- HPA dysfunction
- Psychiatric disorders
- ? Peripheral nociceptive input

Psychosocial factors

- General “distress”
- Psychiatric comorbidities
- Cognitive factors
- Maladaptive illness behaviors
- Secondary gain issues

Source: Aaron et al. *Arthritis Rheum*. 1996;39:436-45.

FM: From Mechanism to Treatment

- This is primarily a neural disease and "central" factors play a critical role
- This is a polygenic disorder
- There is a deficiency of noradrenergic-serotonergic activity and/or excess levels of excitatory neurotransmitters
- Lack of sleep or exercise increase pain and other somatic sx, even in normals
- How FM patients think about their pain (cognitions) may directly influence pain levels
- Treatments aimed at the periphery (i.e., drugs, injections) are not very efficacious
- There will be subgroups of FM needing different treatments
- Drugs that raise norepinephrine and serotonin, or lower levels of excitatory neurotransmitters, will be efficacious in some
- Exercise, "sleep hygiene," and other behavioral interventions are effective therapies for biological reasons
- Cognitive therapies are effective in FM and have a biological substrate

So How Do I Really Diagnose Fibromyalgia? The History – I

- Pain
  - Current and lifetime history of widespread pain
  - The more widespread, the more likely it is fibromyalgia
  - “I hurt all over”
  - Pain felt in any area of musculoskeletal and non-musculoskeletal regions
  - Often “unpredictable”, worsened by stress
  - Often accompanied by stiffness, non-dermatomal paresthesias

So How Do I Really Diagnose Fibromyalgia? The History – II

- Other somatic symptoms
  - Fatigue
    - Not made better by rest or exercise
  - Memory difficulties
    - Difficulty with memory and concentration
  - Insomnia and sleep disturbances
  - Co-morbid syndromes
    - Irritable bowel
    - Interstitial cystitis
    - Headache
    - TMJ/TMD

So How Do I Really Diagnose Fibromyalgia?

Family History

- Family history of other pain syndromes

Social History

- Symptoms often triggered or exacerbated by "stressors"

Past Medical History

- Regional somatic and visceral pain syndromes
- Psychiatric disorders

Physical Exam

- Normal except for diffuse tenderness
- Tenderness not just confined to the joints

Diagnostic Work-up

- Intensity of evaluation depends largely on history
  - If symptoms acute or sub-acute extensive evaluation necessary
  - If symptoms have lasted for many years and history is classic virtually no work-up is necessary
- Laboratory evaluation at some point in illness
  - ESR, CRP
  - CBC and chemistry profile
  - TSH, Vitamin D
  - Avoid serological studies e.g. ANA, RF

Treatment of Fibromyalgia and Other Central Pain Syndromes

Education

Pharmacological Therapy

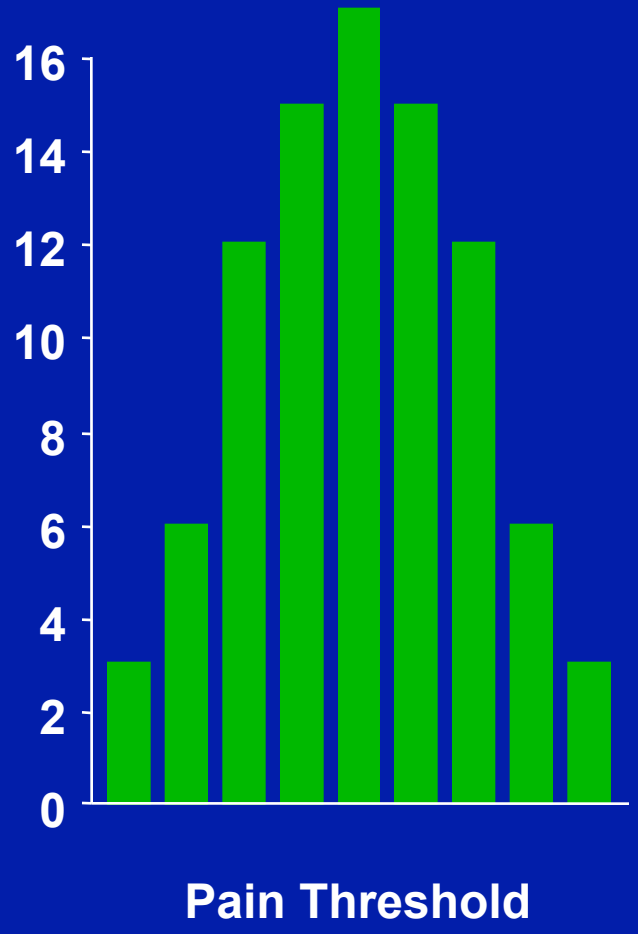
Aerobic Exercise

Cognitive Behavioral Therapy (CBT)

Summary

Increased

- Neurotransmitters
  - Serotonin
  - Norepinephrine
  - Opioids
- Exercise
- Sleep



Decreased

- Neurotransmitters
  - Glutamate
  - Substance P
  - Nerve growth factor
- Cognitions
  - Catastrophizing
  - External locus of control

Pharmacological Therapies

Strong Evidence	▪ Dual reuptake inhibitors such as
	  ▪ Tricyclic compounds (amitriptyline, cyclobenzaprine)
	  ▪ SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?)
	▪ Anticonvulsants (e.g., pregabalin, gabapentin)

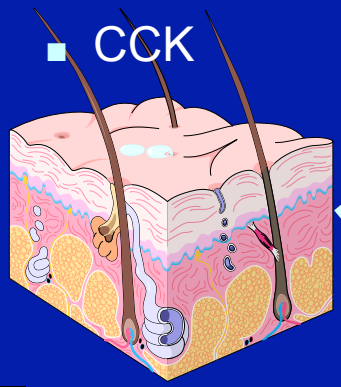
Modest Evidence	▪ Tramadol ▪ Selective serotonin reuptake inhibitors (SSRIs) ▪ Gamma hydroxybutyrate ▪ Dopamine agonists
Weak Evidence	▪ Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)
No Evidence	▪ Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin

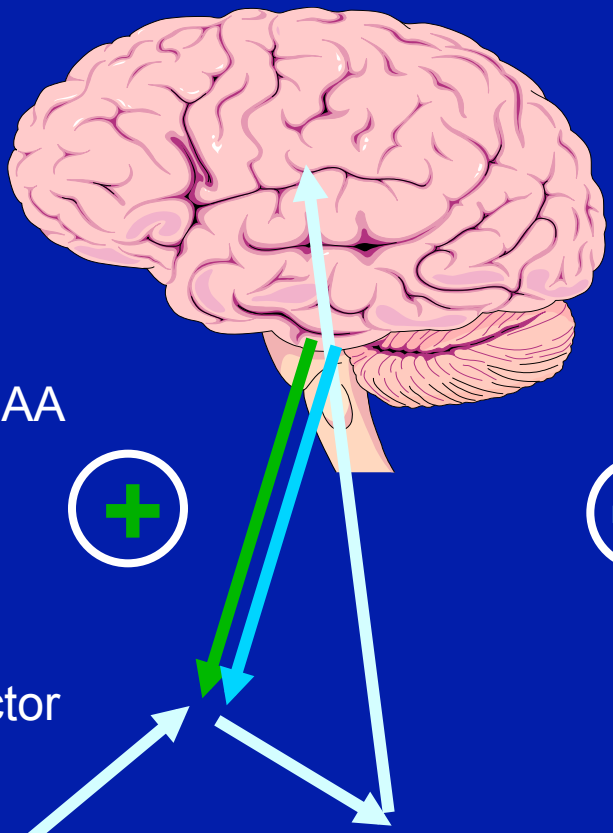
Modified from Goldenberg et al. *JAMA*. 2004;292:2388-95.

Supraspinal Influences on Pain Processing

Facilitation

- Substance P
- Glutamate and EAA
- Serotonin ($5HT_{2a, 3a}$)
- Neurotensin
- Nerve growth factor
- CCK





Inhibition

- Descending anti-nociceptive pathways
  - Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine
  - Opioids
- GABA
- Cannabanoids
- Adenosine

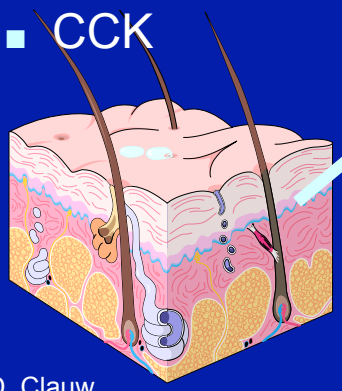
Source Undetermined (All Images)

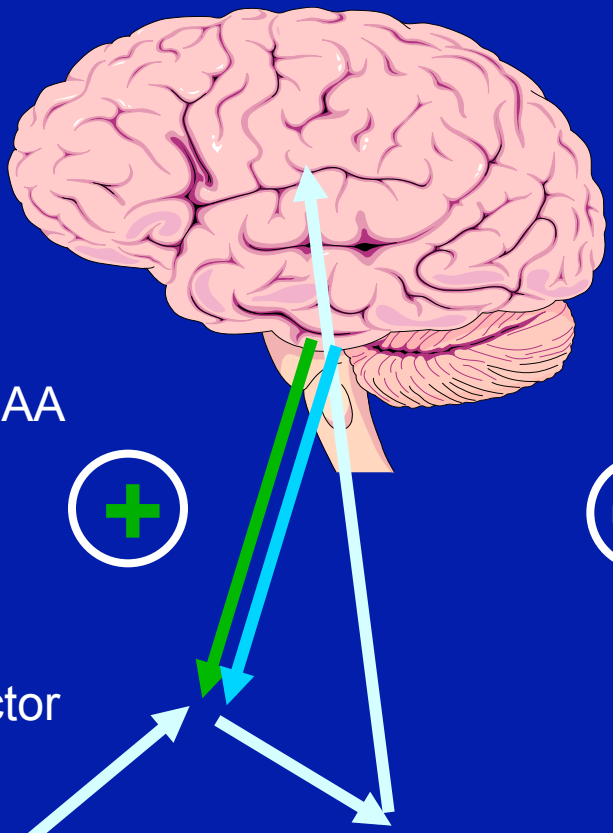
D. Clauw

Likely MOA of Dual-Reuptake Inhibitors

Facilitation

- Substance P
- Glutamate and EAA
- Serotonin ($5HT_{2a, 3a}$)
- Neurotensin
- Nerve growth factor
- CCK





Inhibition

- Descending anti-nociceptive pathways
  - **Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine**
  - Opioids
- GABA
- Cannabanoids
- Adenosine

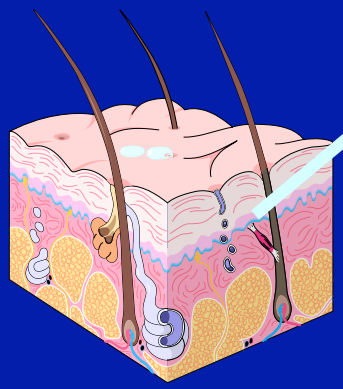
Source Undetermined (All Images)

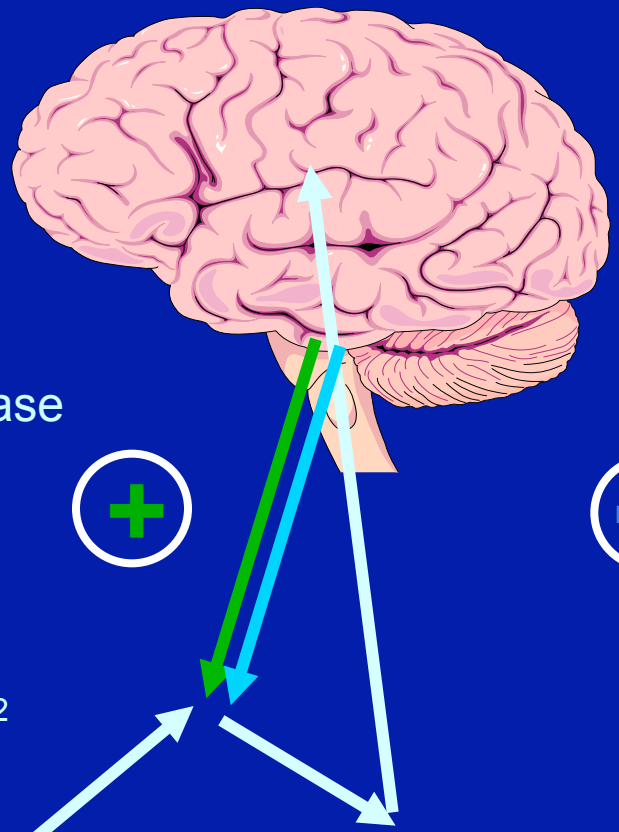
D. Clauw

Possible MOA of Pregabalin/ Gabapentin

Facilitation

- Substance P
  - Decrease SP release in inflammatory states[1]
- Glutamate and EAA
  - Inhibit SP-induced glutamate release[2]





Inhibition

- Descending anti-nociceptive pathways
  - Norepinephrine-serotonin ($5HT_{1a,b}$), dopamine
  - Opioids
- GABA
- Cannabanoids
- Adenosine

Sources: 1. Fehrenbacher et al. *Pain*. 2003;105:133-41. 2. Maneuf et al. *Pain*. 2001;93:191-6.

There is a Deficiency of Descending Analgesic Activity in FM:[1,2] Which one?

Opioids

- Normal or high levels of CSF enkephalins[3]
- Never been administered in RCT but most feel that opioids are ineffective or marginally effective
- Harris recently used PET to show decreased mu opioid receptor binding in FM[4]

Noradrenergic/Serotonergic

- Low levels of biogenic monoamines in CSF in FM[5]
- Nearly any class of drug that raises both serotonin and norepinephrine has demonstrated efficacy in FM

Sources:
1. Kosek and Hansson. *Pain*. 1997;70:41-51. 2. Julien et al. *Pain*. 2005;114:295-302.
3. Baraniuk et al. *BMC Musculoskelet Disord*. 2004;5:48. 4. Harris et al. *J Neurosci*. 2007;27:10000-6.
5. Russell et al. *Arthritis Rheum*. 1992;35:550-6.

Relative Activity on Serotonin and Norepinephrine Reuptake Among Antidepressants

Serotonin	Mixed	Norepinephrine	
Citalopram	Venlafaxine	Amitriptyline	Maprotiline
Fluvoxamine	Duloxetine	Milnacipran	Desipramine
Sertraline		Imipramine	Nortriptyline
Paroxetine			Reboxetine
Fluoxetine			

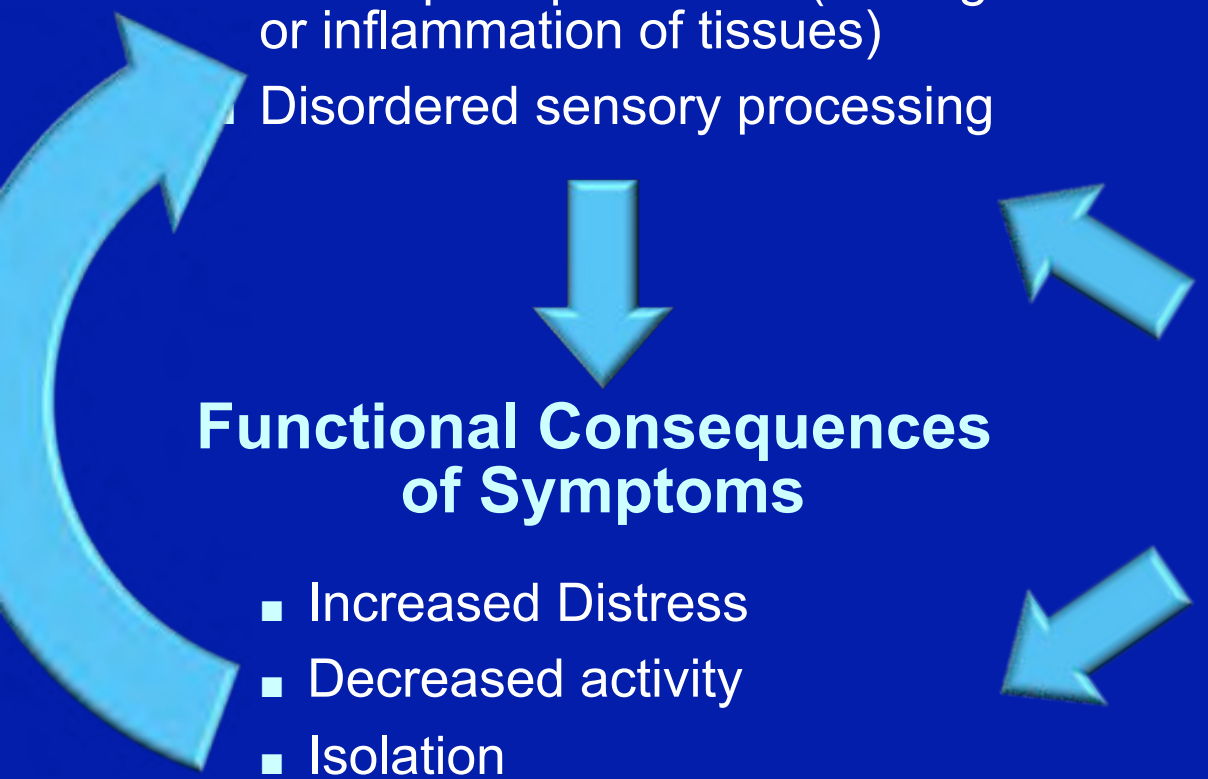
Antidepressant **Analgesic/Antidepressant**

Fishbain et al. *Pain Med*. 2000;1:310-6.

Nonpharmacological Therapies

Strong Evidence	■ Education ■ Aerobic exercise ■ Cognitive behavior therapy
Modest Evidence	■ Strength training ■ Hypnotherapy, biofeedback, balneotherapy
Weak Evidence	■ Acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound
No Evidence	■ Tender (trigger) point injections, flexibility exercise

Goldenberg et al. *JAMA*. 2004;292:2388-95.



Symptoms of Pain, Fatigue, etc.

- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing

Functional Consequences of Symptoms

- Increased Distress
- Decreased activity
- Isolation
- Poor sleep
- Maladaptive illness behaviors

Dually Focused Treatment

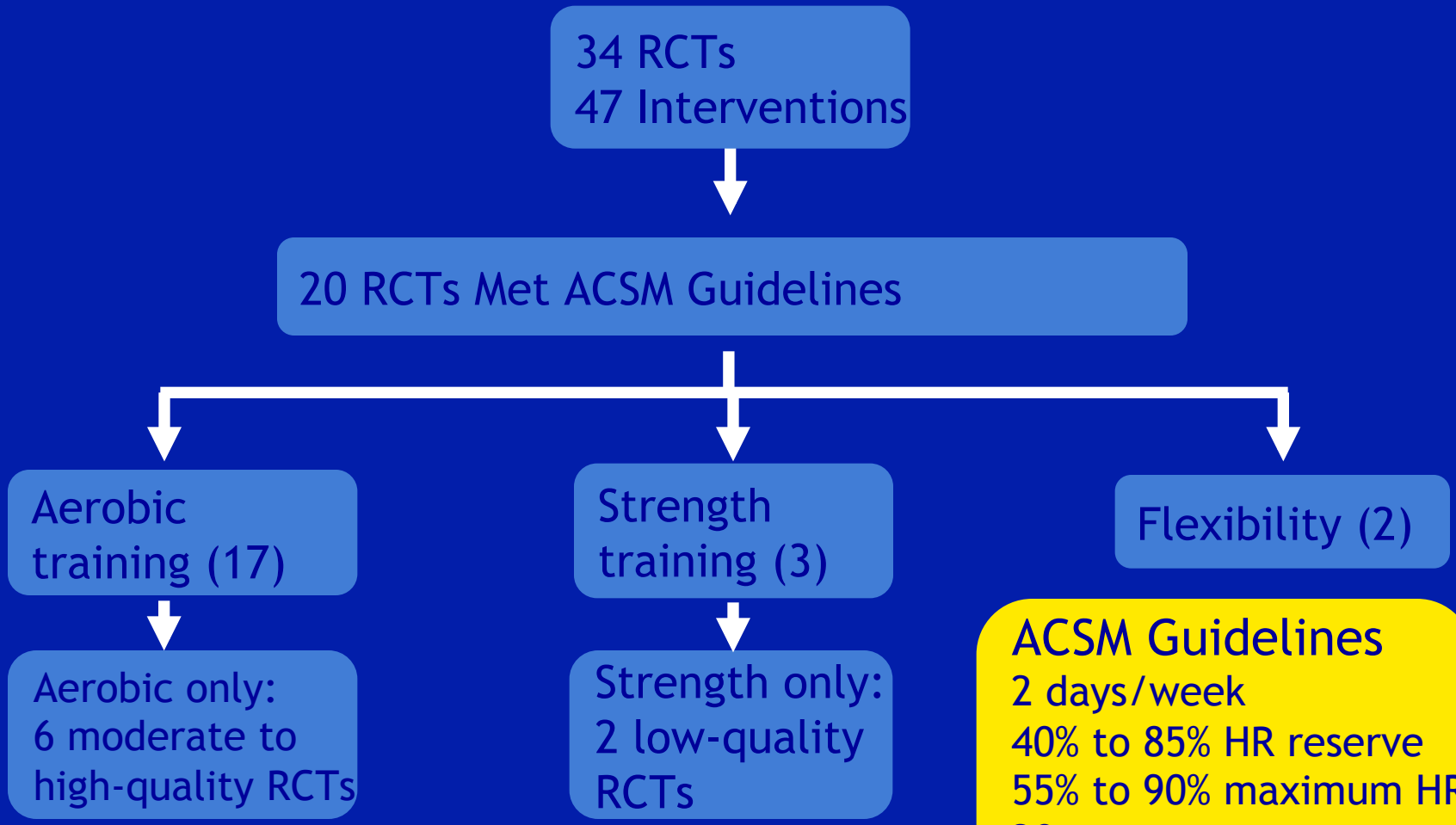
- Pharmacological therapies to improve **symptoms**
- Nonpharmacological therapies to address **dysfunction**

Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.

Exercise

- Aerobic exercise nearly universally beneficial; tolerance, compliance, adherence are biggest issues
- To maximize benefits
  - Begin several months after pharmacologic therapy
  - Begin with low-impact exercises; avoid strength training until late
  - Both physician and patient should consider this as a “drug”
- Less evidence supporting strengthening, stretching

Exercise for Treating Fibromyalgia: Cochrane Review



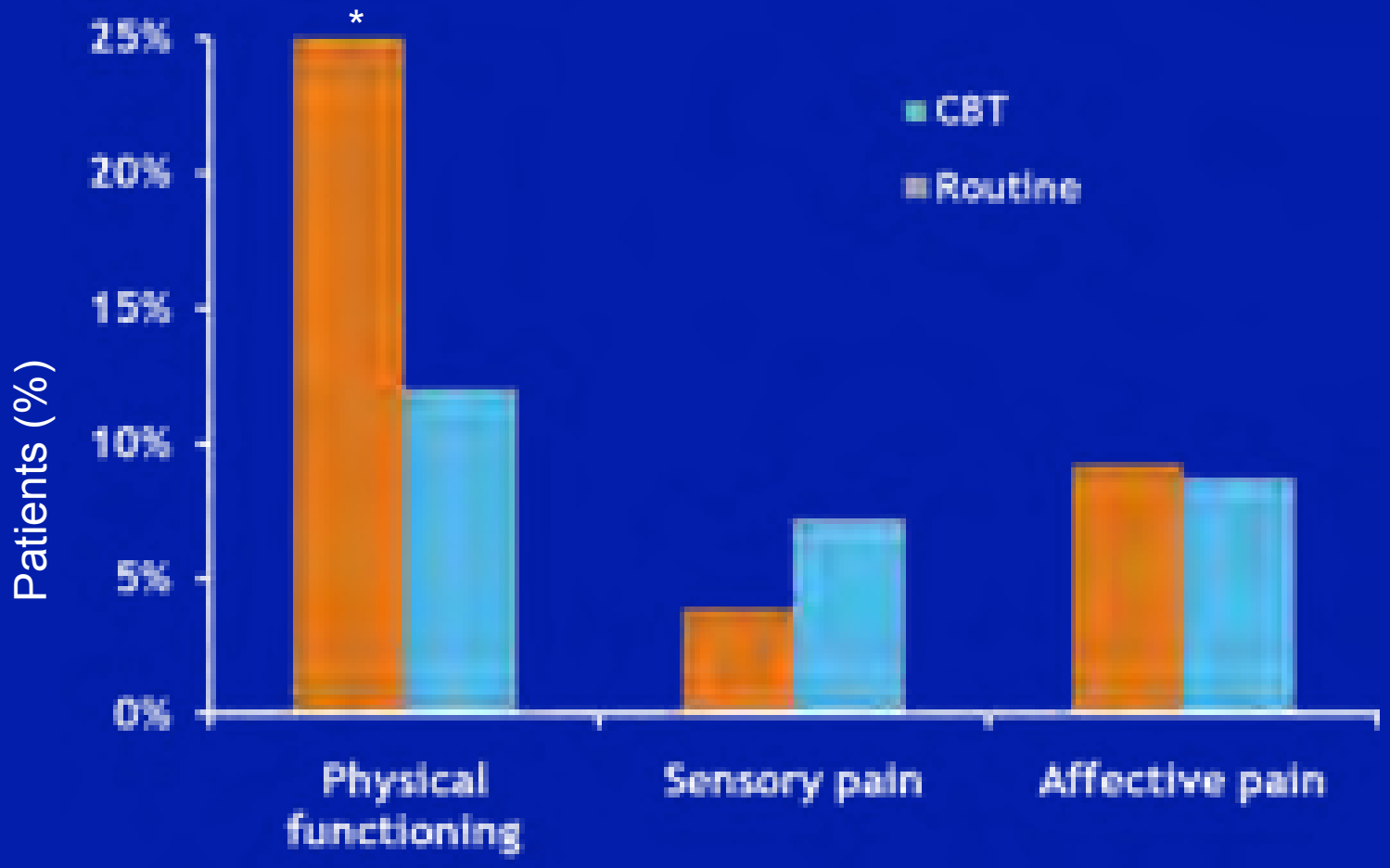
ACSM=American College of Sports Medicine; HR=heart rate.

Busch AJ et al. *Cochrane Database Syst Rev*. 2007;(4):CD003786.

Cognitive Behavioral Therapy

- A program designed to teach patients techniques to reduce their symptoms, to increase coping strategies, and to identify and eliminate maladaptive illness behaviors
- Shown to be effective for nearly any chronic medical illness
- Not all CBT is created equally; very dependent on content, therapist and program

Improvements Noted in CBT vs Standard Care Over 12 Months (n=122)



*Clinically significant. OR 2.9, *P*<.05.

Williams DA et al. *J Rheumatol*. 2002;29:1280-1286.

Recommended Approach

- Education
- Identify and treat "peripheral" pain generators
- For patients who need or want medications, start with low doses of mixed tricyclic antidepressants (amitriptyline, cyclobenzaprine); start low, go slow
- If patient has depression, memory problems, fatigue as most prominent symptoms
  - Add mixed reuptake inhibitor (eg, duloxetine, milnacipran, venlafaxine)
    or SSRI (may need high doses)
- If patient has sleep disturbance as most prominent symptom
  - Use pregabalin or gabapentin first, give higher % of dose at night

Source: Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.

Recommended Approach - II

- If no response, consider use of dopamine agonist, sodium oxybate
- For additional analgesic effect, add tramadol, tizanidine, opioids
- For sleep, if patient doesn't tolerate TCA, use zolpidem, zaleplon, trazodone
- Aggressively introduce non-pharmacological therapies

Source: Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.

Conclusions

- Fibromyalgia has strong neurobiological underpinnings
- This is a polygenic disorder characterized by pain and sensory amplification
- There is evidence of increased levels of pro-nociceptive neurotransmitters (e.g. Subtance P, glutamate) and decreased levels of anti-nociceptive neurotransmittters (e.g. serotonin, norepinephrine)
- The condition can be easily diagnosed in clinical practice based primarily on the patient history

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 4: Daniel Clauw

Slide 5: Source Undetermined; Source Undetermined

Slide 6: Daniel Clauw

Slide 8: 1. Clauw and Chrousos. Neuroimmunomodulation. 1997;4:134-53. 2. McLean and Clauw. Med Hypotheses. 2004;63:653-8. 3. Jones et al. ACR Meeting. 2007. 4. Clauw et al. JCR. 1997. 5. McBeth. ACR Meeting. 2006. 6. Clauw et al. J Occup Environ Med. 2003;45:1040-8.

Slide 9: 1. Arnold et al. *Arthritis Rheum*. 2004;50:944-52. 2. Bondy et al. *Neurobiol Dis*. 1999;6:433-9. 3. Offenbaecher et al. *Arthritis Rheum*. 1999;42:2482-8. 4. Buskila et al. *Mol Psychiatry*. 2004;9:730-1. 5. Gürsoy et al. *Rheumatol Int*. 2003;23:104-7.

Slide 10: 1. Maixner et al. Pain. 1995;63:341-51. 2. Kashima et al. Cranio. 1999;17:241-246. 3. Langemark et al. Arch Neurol. 1993;50:1061-4. 4. Buchgreitz et al. Pain. 2006;123:19-27. 5. Giesecke et al. Arthritis Rheum. 2004;50:613-23. 6. Giesbrecht and Battie. Phys Ther. 2005;85:1085-92. 7. Giesecke et al. Obstet Gynecol. 2004;104:126-33. 8. Lemming et al. Clin J Pain. 2005;21:412-21. 9. Whitehead at al. Gastroenterology. 1990;98:336-40. 10. Mertz et al. Gastroenterology. 1995;109:40-52.

Slide 11: Daniel Clauw; Source Undetermined (All Images)

Slide 12: Daniel Clauw

Slide 13: Daniel Clauw

Slide 14: Daniel Clauw

Slide 15: Melzack and Wall. *Science*. 1965;150:971-9. Casey. *Headache*. 1969;8:141-53.

Slide 16: 1. Gracely et al. *Arthritis Rheum*. 2002;46:1333-43. 2. Giesecke et al. *Arthritis Rheum*. 2003;48:2916-22. 3. Gracely et al. *Brain*. 2004;127:835-43. 4. Giesecke et al. *Arthritis Rheum*. 2004;50:613-23.

Slide 17: Gracely et al. *Arthritis Rheum*. 2002;46:1333-43.

Slide 18: 1. Geisser et al. *J Pain*. 2008;9:417-22. 2. Gracely et al. *Arthritis Rheum*. 2002;46:1333-43. 3. Giesecke et al. *Arthritis Rheum*. 2004;50:613-23. 4. Cook et al. *J Rheumatol*. 2004;31:364-78. 5. Harris et al. *Arthritis Rheum*. 2008;58:903-7.

Slide 19: Harris et al. *Arthritis Rheum*. 2008;58:903-7.

Slide 20: 1. Kosek and Hansson. *Pain*. 1997;70:41-51. 2. Julien et al. *Pain*. 2005;114:295-302. 3. Wilder-Smith and Robert-Yap. *World J. Gastroenterol*. 2007;13:3699-704. 4. Gracely et al. *Arthritis Rheum*. 2006 (abstract).

Slide 21: 1. Kosek and Hansson. *Pain*. 1997;70:41-51. 2. Julien et al. *Pain*. 2005;114:295-302.3. Baraniuk et al. *BMC Musculoskelet Disord.* 2004;5:48. 4. Harris et al. *J Neurosci*. 2007;27:10000-6. 5. Russell et al. *Arthritis Rheum*. 1992;35:550-6.

Slide 22 : Harris et al. *J Neurosci*. 2007;27:10000-6.

Slide 23: 1. Apkarian et al. *J Neurosci*. 2004;24:10410-5. 2. Schmidt-Wilcke et al. *Pain*. 2007;132 Suppl 1:S109-16. 3. Davis et al. *Neurology*. 2008;70:153-4. 4. Kuchinad et al. *J Neurosci*. 2007;27:4004-7. 5. Chen et al. *Psychiatry Res*. 2006;146:65-72.

Slide 24: Aaron et al. *Arthritis Rheum*. 1996;39:436-45.

Slide 28: Daniel Clauw

Slide 30: Daniel Clauw

Slide 31: Daniel Clauw

Slide 32: Modified from Goldenberg et al. *JAMA*. 2004;292:2388-95.

Slide 33: Daniel Clauw; Source Undetermined (All Images)

Slide 34: Daniel Clauw; Source Undetermined (All Images)

Slide 35: Daniel Clauw; Source Undetermined (All Images)

Slide 36: 1. Kosek and Hansson. *Pain*. 1997;70:41-51. 2. Julien et al. *Pain*. 2005;114:295-302. 3. Baraniuk et al. *BMC Musculoskelet Disord*. 2004;5:48. 4. Harris et al. *J Neurosci*. 2007;27:10000-6. 5. Russell et al. *Arthritis Rheum*. 1992;35:550-6.

Slide 37: Fishbain et al. *Pain Med*. 2000;1:310-6.

Slide 38: Goldenberg et al. *JAMA*. 2004;292:2388-95.

Slide 39: Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.

Slide 41: Busch AJ et al. *Cochrane Database Syst Rev*. 2007;(4):CD003786.

Slide 43: Williams DA et al. *J Rheumatol*. 2002;29:1280-1286.

Slide 44: Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.

Slide 45: Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.