

Presentation 6 – Daniel Clauw

Treatment of Fibromyalgia and Other Chronic Multisymptom Illnesses

Daniel J. Clauw, MD

Professor of Medicine, Division of Rheumatology
Director, Chronic Pain and Fatigue Research Center
Assistant Dean for Clinical and Translational Research
The University of Michigan Medical Center

Summary

- ◆ **Peripheral (nociceptive)**
 - Primarily due to *inflammation* or mechanical damage in periphery
 - NSAID, opioid responsive
 - Responds to procedures
 - Behavioral factors minor
 - Examples
 - ◆ OA
 - ◆ Acute pain models (e.g. third molar, post-surgery)
 - ◆ RA
 - ◆ Cancer pain
- ◆ **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
 - ◆ Interstitial cystitis / vulvodynia, non-cardiac chest pain / etc.

The Physiological / Psychobehavioral Continuum

Population	Primary Care	Tertiary Care
Definition factors (e.g., tender points, behavioral components)		

Physiologic factors

- ◆ Abnormal sensory processing
- ◆ Autonomic and HPA axis dysfunction
- ◆ Peripheral factors

Psychobehavioral factors

- ◆ General “distress”
- ◆ Psychiatric comorbidities
- ◆ Maladaptive illness behavior
- ◆ Secondary gain issues

HPA = hypothalamic-pituitary-adrenal.

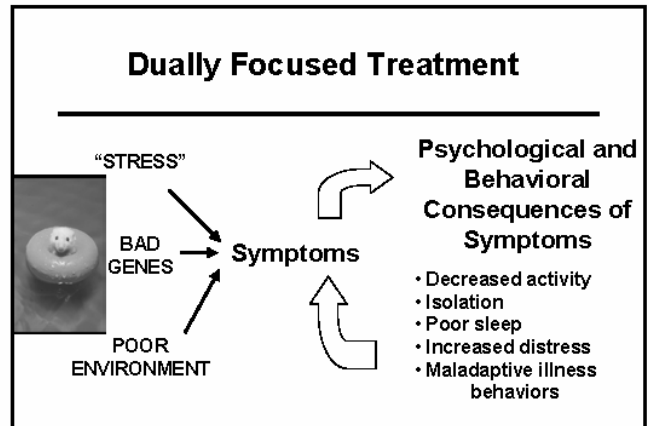
Sub-grouping FM patients

- ◆ 97 FM patients (85 female) were administered a battery of self-report questionnaires and subjected to evoked pain testing.
- ◆ The study variables were chosen a priori to reflect
 - a) measures of hyperalgesia that were less influenced by distress than tenderpoints (e.g. dolorimeter and supra-threshold random pressure testing);
 - b) affect (i.e. CES-D (depression), STPI (trait anxiety))
 - c) cognitive/evaluative factors (i.e. catastrophizing and control subscales of the Coping Strategies Questionnaire).
- ◆ Clustering of patients into subgroups

Geescke et. al.
Arthritis Rheum 2003

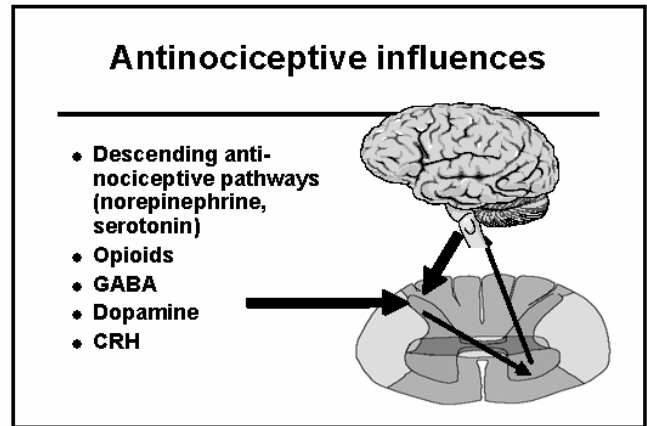
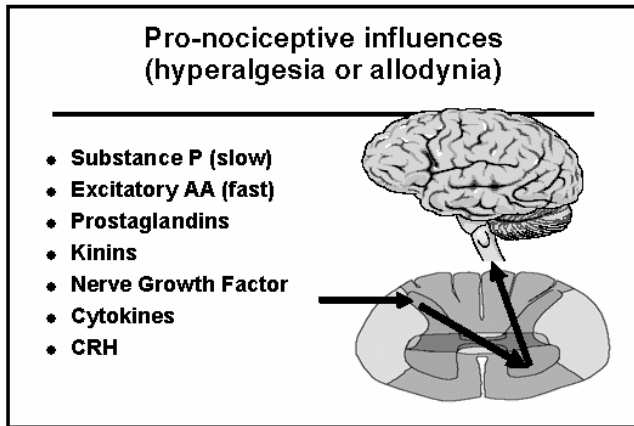
Subgroups of FM patients

Group 1 (n=50) •Low depression/anxiety •Not very tender •Low catastrophizing •Moderate control over pain	Psychological factors <i>neutral</i>
Group 2 (n=31) •Tender •High depression/anxiety •Very high catastrophizing •No control over pain	Psychological factors <i>worsening symptoms</i>
Group 3 (n=16) •Extremely tender •Low depression/anxiety •Very low catastrophizing •High control over pain	Psychological factors <i>improving symptoms</i>



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- Education
 - Pharmacologic
 - Aerobic exercise
 - Alternative therapies
 - Cognitive behavioral therapy

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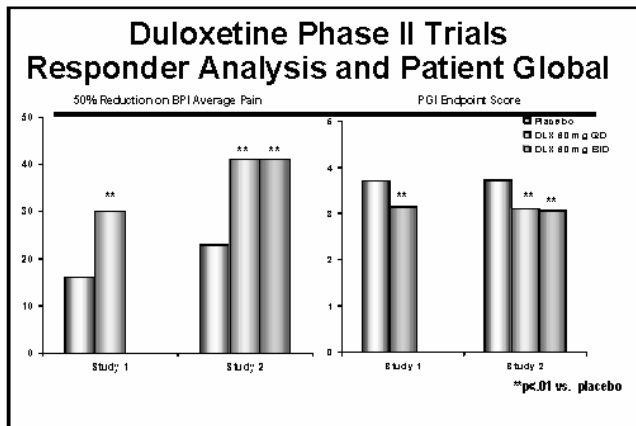
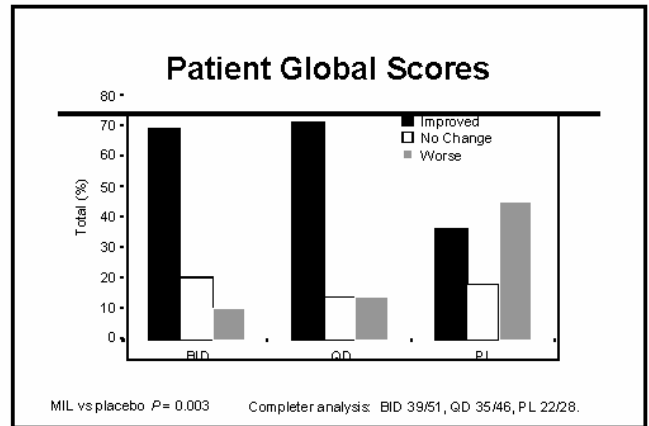
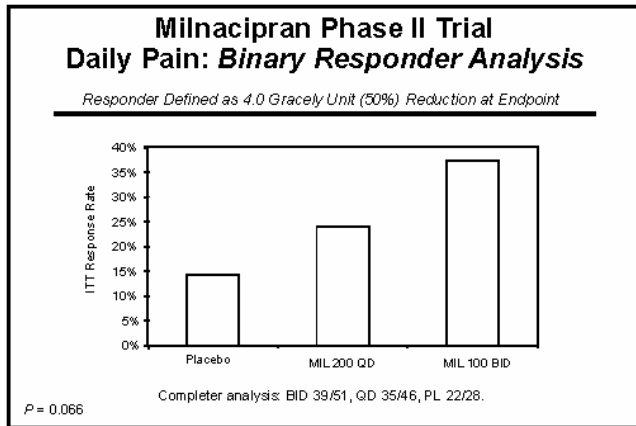
Pharmacologic Therapy Supported by RCT in FM

- Low doses of tricyclic drugs (e.g. amitriptyline, cyclobenzaprine) best studied
 - tolerance increased by starting at low dose (≤ 10 /mg), giving several hours before bedtime, increasing slowly
- SSRIs, NSAIDs ineffective or less effective
- Mixed noradrenergic / serotonergic agents
 - Atkinson et. al. Pain 1999: Maprotiline > Paroxetine > Placebo for non-depressed LBP
- Symptom-based therapy
 - Tramadol
 - Gabapentin

NSAIDs = nonsteroidal antiinflammatory drugs; RCT = randomized controlled trials; SSRI – selective serotonin reuptake inhibitors.

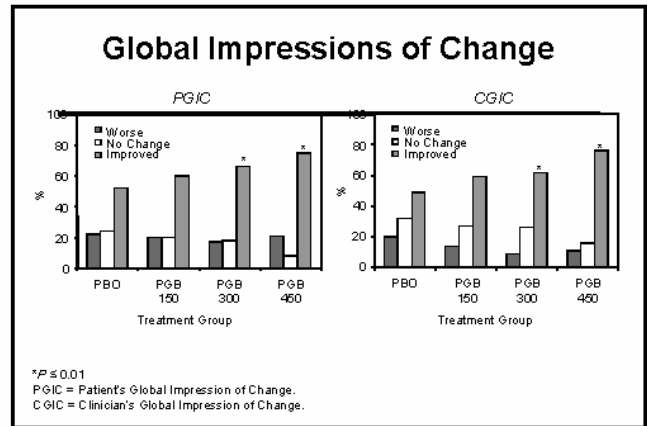
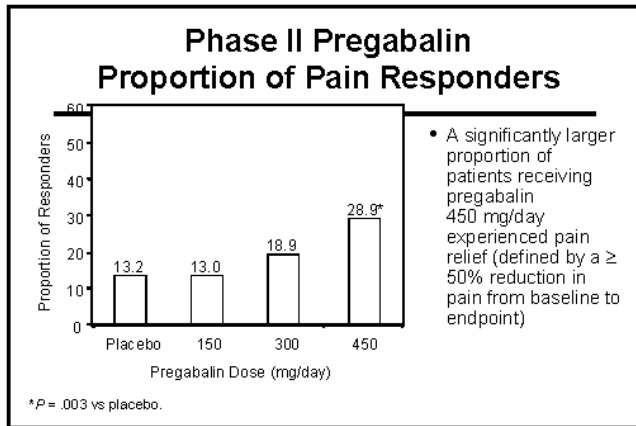
Relative Serotonin and Norepinephrine Re-uptake Amongst Antidepressants

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



Pregabalin

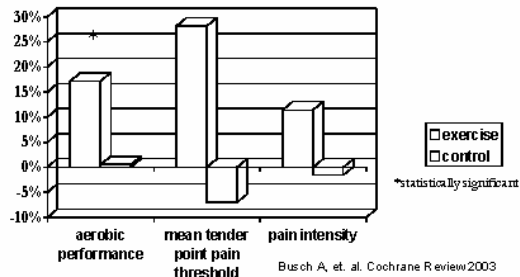
- Binds to $\alpha_2\delta$ subunit of voltage-gated calcium channels of neurons
- Reduces calcium influx at nerve terminals and therefore inhibits release of neurotransmitters
 - Glutamate, noradrenaline, substance P



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- ### Exercise
- Aerobic 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

Improvements in aerobic exercise vs non-exercise controls (combined data 4 studies)



Exercise Tolerability

- High intensity (heart rate > 150) aerobic exercise is poorly tolerated with high drop-out rates over time
- Moderate intensity programs (50 to 70% of age-adjusted maximal heart rate) can be well tolerated
- Exercise should start at just below the capacity of the participant and gradually increase in duration to goal of 30 min of moderate intensity aerobic exercise

Gowans SE et. al Curr Opin Rheumatol. 2004

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Complementary and Alternative Therapies

- Some evidence supporting
 - Acupuncture
 - Physical modalities
 - Myofascial release therapy
 - Trigger point injections (dry needling may be as effective)
 - Chiropractic manipulation
 - Biofeedback

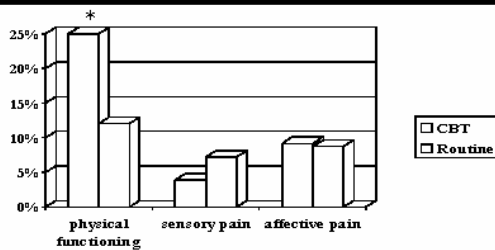
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Cognitive behavioral therapy

- 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 dependant on therapist and program

Improvements noted, CBT vs standard care over 12 months (n=122)



OR 2.9, p<0.05

Williams DA, et al. J Rheum 2002

Veterans Affairs Cooperative Study (CSP #470) CSP #470

- Multi-center trial carried out at 18 VAMC and Department of Defense military hospitals
- Hypothesis – The proportion of patients who had a clinically important difference in self-report physical function would be better with either exercise or CBT than those receiving usual care, and the combination of the therapies would be more effective than either single therapy

Inclusion criteria

- To be eligible veterans had have been deployed to the Gulf War between August 1990 and August 1991, and to endorse ≥ 2 of the following symptoms:
 - fatigue limiting usual activity
 - pain in ≥ 2 body regions
 - neurocognitive symptoms
- These symptoms had to begin after August 1990, last for more than six months, and be present at the time of screening.

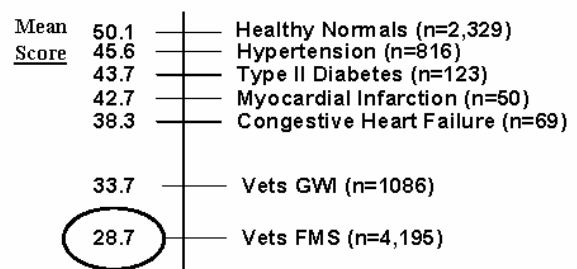
Subjects / Methods

- 1092 veterans who satisfied the eligibility criteria and gave written informed consent were randomized to one of four treatment arms: 1) CBT alone, 2) exercise alone, 3) CBT + exercise, or 4) usual care.
- Both CBT and exercise were delivered in groups of three to eight participants.
- CBT Treatment sessions were 60-90 minutes long and met weekly for 12 weeks.
- Exercise prescriptions focusing on low impact exercise were individualized for each participant after they performed a submaximal cycle ergometer exercise test at baseline. Veterans in the exercise group were asked to exercise once/wk in the presence of the exercise therapist, and 2 - 3X / wk independently during the 12-week treatment phase.

Results – Demographics of Participants

- 85% male
- Mean age 40.7
- 81% presented with all three cardinal symptoms of GWVI at the time of screening
- The mean duration of symptoms was 6.7 years
- Based on the Prime MD:
 - 45% percent of veterans had either a major depressive disorder or dysthymia,
 - 35% had an anxiety disorder
 - 43% had posttraumatic stress disorder
- 24% percent of veterans had a pending disability claim and 42% were receiving disability payments.

PCS (SF-36)



Kazis, (1999; P.C.); Ware, Kosinski, Keller, 1995

Response to Treatment

- There was a modest difference in the proportion of veterans who reported an improvement in physical function at one year among the treatment groups:
 - 11.5% for usual care
 - 11.7% for exercise
 - 18.4% for CBT
 - 18.5% for CBT + exercise
- More significant improvements in fatigue, cognitive symptoms, distress, and mental health functioning were observed with exercise alone, and with exercise plus CBT compared to usual care.
- CBT alone had a statistically significant effect on cognitive symptoms and in mental health functioning.

Recommended Approach

- For patients that need or want medications start with low doses of tricyclics; start low, go slow
- If patient tolerates and but symptoms persist:
 - Add mixed reuptake inhibitor (e.g. venlafaxine, duloxetine) or SSRI
 - For additional analgesic effect add gabapentin, tramadol, tizanidine
- If patient doesn't tolerate TCA use zolpidem, zaleplon, trazadone
- Aggressively introduce non-pharmacological therapies, consider tapering pharmacologic therapies