

# Treatment options in fibromyalgia

M. Fitzcharles



# Disclosure

Consultant, speaker, advisory board

- Pfizer, Jennsen-Ortho, Purdue, Valeant, Boerhinger-Ingelheim, Lilly
- Health Canada
- FDA - USA

# Fibromyalgia does exist.....

- *American College Rheumatology (ACR)*
  - diffuse widespread pain
  - *11/18 tender points (to stay or not to stay)*
- 2% population
- a spectrum of severity
  - > 90% are women
  - no fibrosis, no muscle abnormality

# Not just a problem of pain.....

- Pain
- Sleep disturbance
- Fatigue
- Mood disorder
  - Anxiety and depression
- Other somatic symptoms
- Function and activity
- Goals

# Fibromyalgia is not a diagnosis of exclusion

- A good history and physical exam
- Laboratory tests
  - CBC, ESR, CK, TSH, Ca and PO<sub>4</sub>
  - Any other testing directed by clinical evaluation
- Do not over investigate
- Do not refer repeatedly to multiples of specialists

Ensure the diagnosis is correct

# What can mimic FM?

- **Endocrine**
  - ↓ thyroid, ↑parathyroid, ↓ vitamin D
- **Neurological**
  - MS, myasthenia gravis, neuropathy
- **MSK disease**
  - early inflammatory arthritis, SLE, myositis, PMR, hypermobility
- **Psychiatric**
  - Depression, borderline personality, drug seeking, somatization
- **Drugs**
  - statins, aromatase inhibitors

Lady Agnew of Lochnaw

1892

A bout of influenza

Never recovered

Pain

Delicate

Air of ennui

6 sittings for Sargent

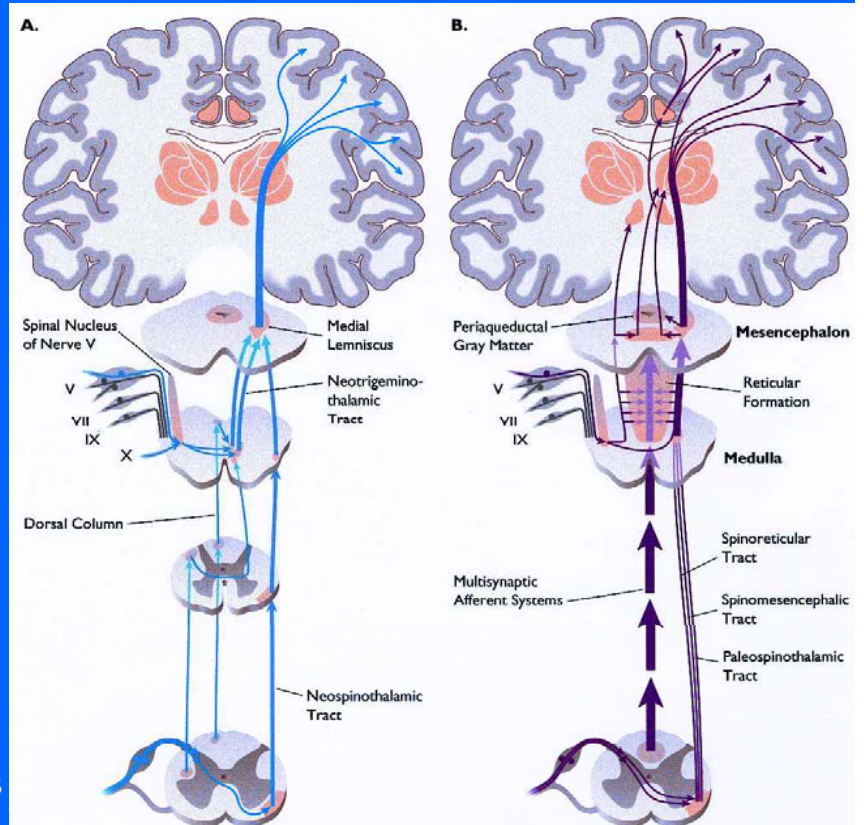


# Are FM patients similar worldwide?

- Pregabalin trial, 800 patients
- Europe, Asia, Central/south America, Canada, Australia
  - Pain 6.6-6.9
  - Sleep 5.8-6.3
  - FIQ 60-66
  - Fatigue, anx/dep
- Fairly similar scores across countries
- Highest scores in Central and S America

# The science – areas being explored.....

- Fired up nervous system - sensitization
- Brain abnormality
  - grey matter volume brain
  - Hypervigilance
  - HPA axis
- defective inhibition



# The culprit molecules

- Glutamate, substance P
- Serotonin, norepinephrine, dopamine
- Endogenous opioids, cannabinoids

No objective clinical measure to  
confirm diagnosis or measure  
response to treatment

# Focus treatments

Address all components of suffering.....

- Pain
- Sleep disturbance
- Fatigue
- Mood disorder
  - Anxiety and depression
- Activity
- Goals

- No gold standard of treatment
- Balance efficacy and side effect profile
- Patient adherence to treatments
- Clinical practice vs the study setting
- Is an agent continued over time

# Agents Recently Approved for fibromyalgia

- Pregabalin (Lyrica)
  - $\alpha$ -2 $\delta$  ligand
  - FDA approved -June 2007
  - Health Canada approved -March 2009
- Duloxetine (Cymbalta)
  - Dual reuptake inhibitor
  - FDA approved - June 2008
  - Not approved by Health Canada
- Milnacipran (Savella)
  - Dual reuptake inhibitor
  - FDA approved - Jan 2009
  - Not approved by Health Canada



- Do not overmedicalize patient
- Locus of control shifted to patient
- Patient must have goals
- Patient must be active participant in treatment

# Recent review of treatments

*Good evidence for:*

TCA's, SSRI, analgesics, anticonvulsants  
exercise

multidisciplinary treatment, CBT, relaxation  
massage, acupuncture

!!!!!!!

# Usual treatments in FM

## Patient “help thyself”

Avoid making the patient a passive receptacle of medical magic

## Non pharmacologic treatments

coping, adjusting goals, a normal exercise program, CBT, relaxation, acupuncture, biofeedback

## Pharmacologic

analgesics, NSAIDS, anticonvulsants, opioids, TCA, antidepressants, muscle relaxants

Goldenberg DL, et al. *JAMA*. 2004

Clauw DJ, et al. *Best Pract Res Clin Rheumatol*. 2003

Arnold LM, et al. *Arthritis Rheum*. 2007

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Do guidelines truly guide us?

# What questions to ask about guidelines?

- Were they under umbrella of some official body
- Who made up the group of “experts”
- What conflicts of interest were declared
- How were they financed

# Guidelines an example...FM

- 3 sets of guidelines
- 3 erudite groups
  - American Pain Society, EULAR, German
- The committee members
  - how chosen, background
  - Financing

# FM guidelines: the process...

- What studies were included... RCT, meta-analyses, lower quality studies
- What outcome was studied
- Were study outcomes meta-analysed
- How much expert opinion (Delphi)
- What if a modality is commonly used but never studied
- Level of evidence, recommendation can vary even within same study

# FM guidelines.....

## APS

- Exercise, CBT, **Amitriptyline**, cyclobenzaprine, multimodal

## EULAR

- **Amitriptyline**, tramadol, anticonvulsant, SSRI, SNRI

## German

- Exercise, CBT, education, acupuncture, **amitriptyline**, multimodal

*How many patients continue to use amitriptyline in f/u?*

# Tailor Treatments to Individual Patient

- Pain
- Sleep disturbance
- Fatigue
- Mood disorder
  - Anxiety and depression
- Activity
- Patient goals

- Ideal treatment will address a number of symptoms
- Is there an anchor treatment?
- Most patients will likely need a mélange
- Limited studies on combinations

# Usual management of FM

## Nonpharma and pharma Combinations

- Analgesics
- Anticonvulsants
- Antidepressants
  - Stimulants
  - Dopaminergic, Na channel blockers, anxiolytics

# The close to gold standard: amitriptyline

- Systematic Review 10 RCTs
- study quality - moderate to high
- Only 25 mg/day better than placebo for:
  - pain
  - sleep
  - fatigue
  - overall patient and investigator impression
- TP – no change
- benefit 6–8 weeks
- no effect at 12 weeks

## TCAs may not be the ideal agent

- Tolerability
  - Sleepiness, dry mouth, weight gain
  - Risk of cardiac toxicity
    - Caution in patients with cardiac problems
    - Caution when tertiary amines (ie, amitriptyline, imipramine) used in elderly patients.
- What is the continuation rate??

# The pain

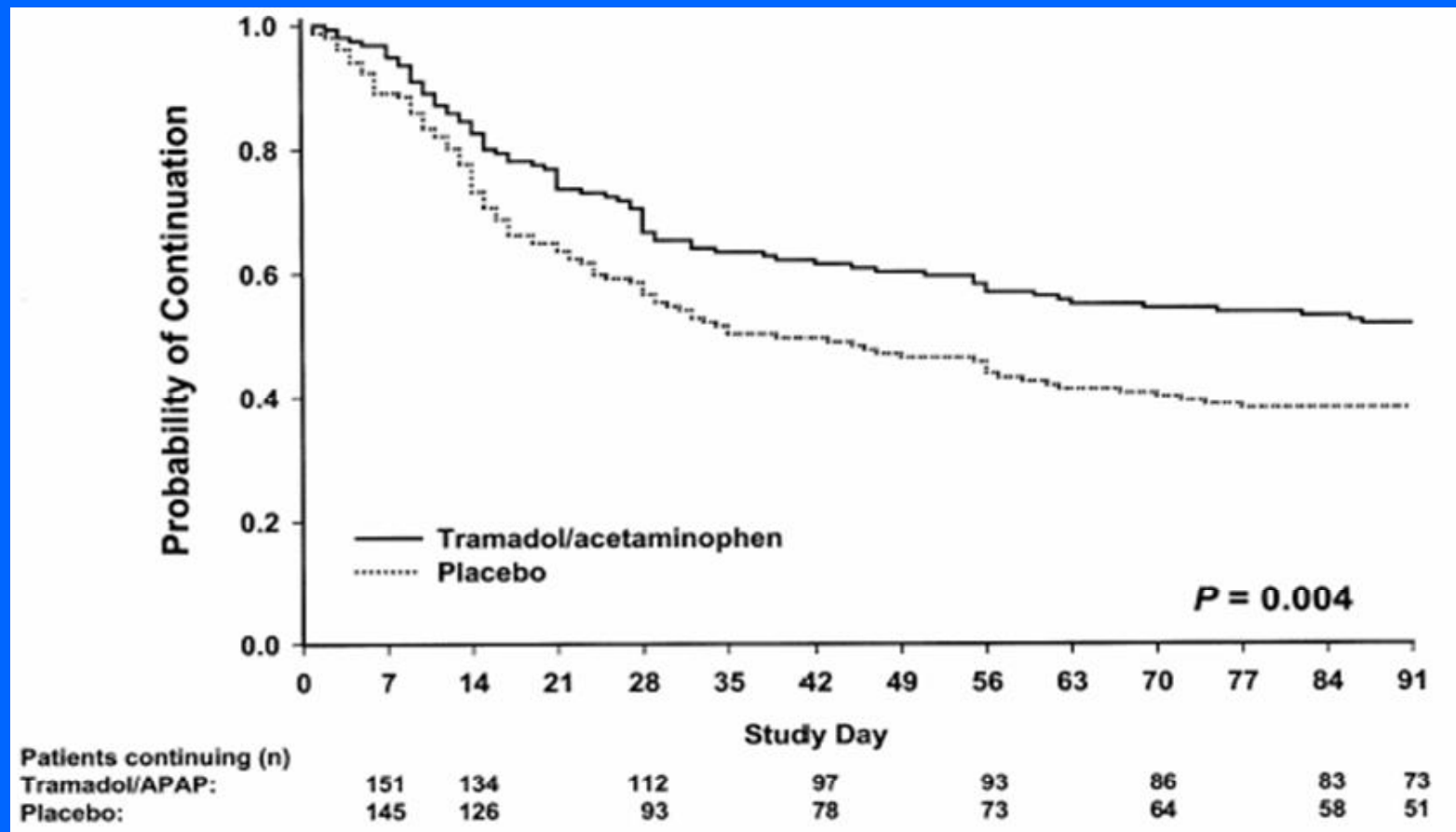
- Analgesics
  - Simple
  - Opioid
  - ? Cannabinoids
- Antiepileptics
- Antidepressants
  - norepinephrine
  - dopamine
  - ? serotonin
- Nsaids – not consistent

# The pain

- Analgesics – used by most
    - Acetaminophen
    - Tramadol
    - Opioid
    - ? Cannabinoids
  - Anticonvulsants
    - Pregabalin,
    - gabapentin,
    - topiramate
  - Antidepressants
    - norepinephrine
    - dopamine
    - ? serotonin
  - Nsaids – not consistent
- Analgesics
    - Compliance with 4gm
    - Mod effective
    - No studies
    - Better for sleep
  - Anticonvulsants
    - ?anchor for pain, sleep, anxiety
    - 1800mg/day
    - CNS, GI effects
  - Antidepressants
    - For fatigue
    - wellbeing
    - Not so good for pain
  - All the concerns

# Tramadol/Acetaminophen in Fibromyalgia

Cumulative rate of discontinuation for any reason



Bennett RM, et al. *Am J Med.* 2003;114(7):537-545.

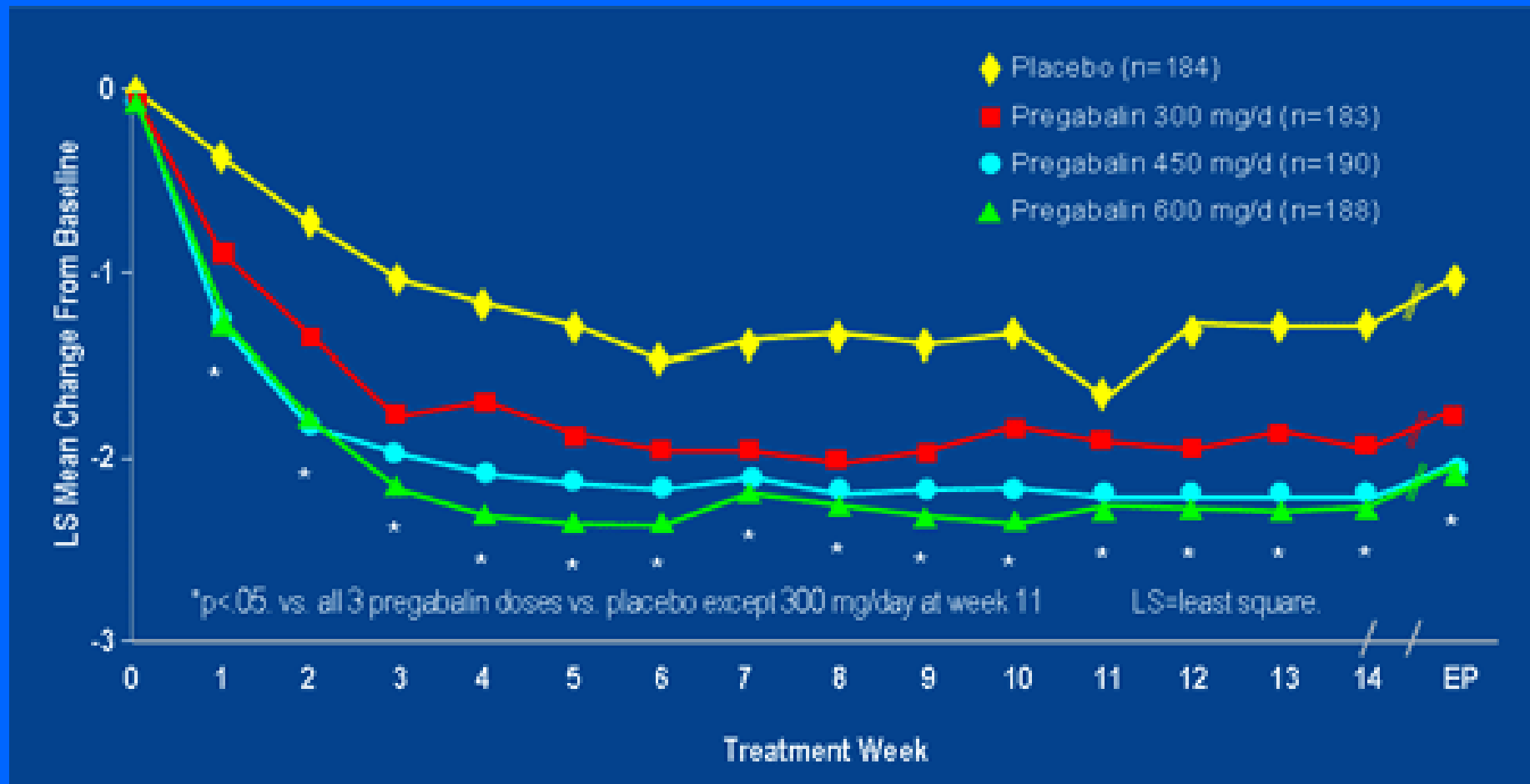
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## Pregabalin.....

- Binds to  $\alpha 2$ - $\delta$  subunit of voltage-gated calcium channels
  - Reduces  $\text{Ca}^{2+}$  influx during depolarization
  - Binding required for analgesic, anxiolytic, and anticonvulsant activity
- Effective in trials of epilepsy, neuropathic pain, fibromyalgia and generalized anxiety
- High trial doses not used in clinical practice

# Pregabalin: Pain Scores from Daily Diary



# The sleep disturbance

- Sleep hygiene
- TCA
  - S/E – wt gain, too sleepy



# Sleep..what is the problem?

- OSA
- Restless legs
  - pramipexole
  - Carbidopa-levodopa
- Sleep architecture
  - Pregabalin
  - Chlorpromazine
  - Quetiapine
  - Trazadone
  - Sodiun oxybate
- Benzodiazepines
- Cannabinoids
- Sleep study
- Restless legs
  - 4.5mg, compulsive states
  - Cheap, no study
- Sleep architecture
  - ? Transitory effect
  - 100mg slow wave sleep
  - 100mg periodic leg movements
  - 100mg, no FM study
  - For catalepsy, ?abuse
- ↓ architecture, cognition, addiction
- tolerability

# Cannabinoids .....

- Endocannabinoids physiological functions<sup>1</sup>:
  - Pain modulation
  - Appetite control
  - Motor coordination
  - Memory processes and neuroprotection
- Cannabinoids effectiveness for neuropathic pain<sup>2</sup>
- Nabilone synthetic THC analog
  - Canada approved for chemotherapy assoc nausea & vomiting

1. Staud R, Koo EB. *Nat Clin Pract Rheumatol*. 2008; 4(7): 348-349.

2. Ashton JC, Milligan ED. *Curr Opin Investig Drugs*. 2008 Jan; 9(1): 65-75.

# Sodium Oxybate.....

- Gamma-hydroxybutyrate (GHB)
- treatment of cataplexy ass with narcolepsy
- Controlled substance & restricted distribution system
- A small RCT (n=16)
  - Better sleep (↑ total sleep time, ↑ slow-wave sleep, ↓alpha intrusion, ↓ nighttime awakenings)
  - ↓ daytime fatigue.
  - ↓ pain & tender point index

1. Scharf MB, et al. *J Rheumatol* 2003; 30: 1070–1074.

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# Fatigue

Nothing in literature

- Exercise activity
- ??? Stimulants
  - Modafinil
    - 3 reports in FM
    - Affects cytochrome P450
  - Methylphenidate
    - Beware anxiety, bipolar



# The mood

Depression and/or anxiety

*a drug to treat mood and pain*

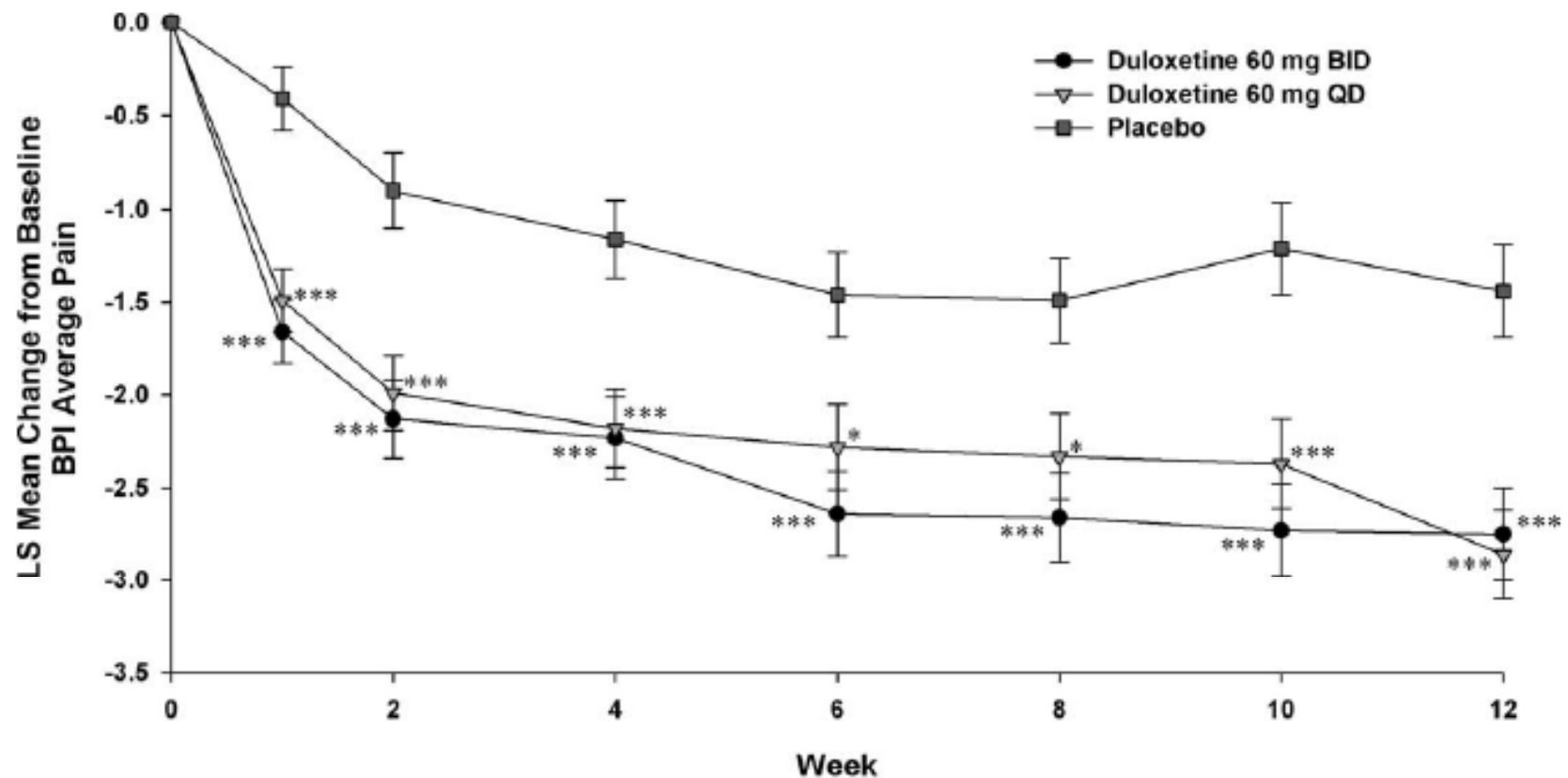
Norepinephrine, serotonin, dopamine

- Venlafaxine – anxiety
- Bupropion – need a boost
- Mirtazapine – need to sleep
- Duloxetine - mood and pain
- Milnacipran – mood, fatigue and pain

Pregabalin – anxiety, sleep and pain

# Duloxetine Efficacy: Pain

## 3-Month Study



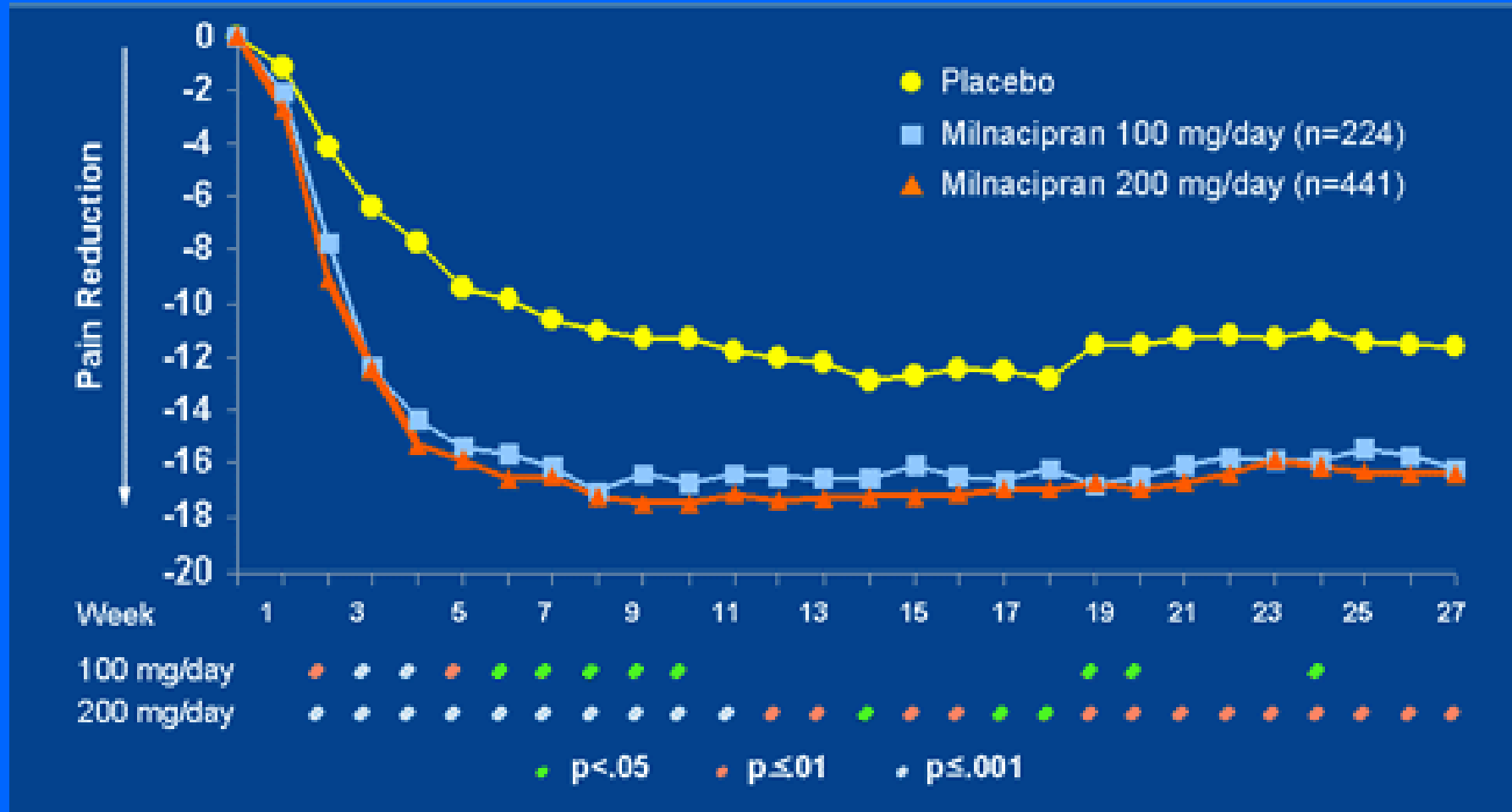
Russell IJ, et al. *Pain*. 2008;136(3):432-444.

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# Milnacipran Efficacy : Pain

## 6 month study



# Dual Reuptake Inhibitors: side effects

- Nausea ~ 35%
- Headaches ~ 20%
- Dry mouth
  - 5% (milnacipran)
  - 20% (duloxetine)
- Constipation ~ 14%
- Dizziness ~ 10% to 13%

1. Clauw DJ et al. Data presented at American Society of Regional Anesthesia and Pain Medicine, 2007.  
2. Clauw DJ et al. *Arthritis Rheum.* 2007;S306; 3. Arnold LM, et al. *J Womens Health (Larchmt)*;16(8):1145-56.

# Non-pharmacologic Therapies

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## Strong Evidence

- Aerobic exercise
  - Cognitive behavioural therapy
  - Patient education
  - Multidisciplinary therapy
- 

## Moderate Evidence

- Strength training
  - Acupuncture
  - Hypnotherapy
  - Biofeedback
  - Balneotherapy
- 

## Weak Evidence

- Chiropractic, manual, and massage therapy
  - Electrotherapy
  - Ultrasound
- 

## No Evidence

- Tender (trigger) point injections
  - Flexibility exercise
-

# Physical activity

- reset goals
- exercise within tolerance
- do what is enjoyable
- continue exercise program
- **does exercise really work ?**
- Some patients have more pain with exercise.....



# Growth hormone in FM

- Stimulated GH test

↓ Levels IGF-1 suggest GH deficiency

The test:GHRH + somatostatin inhibitor

43% poor response to GHRH

23% GH deficiency (+ somatostatin inhib)

Poor response associated with obesity

A problem in the hypothalamus...HPA axis

# HPA axis dysfunction..a reason for exercise induced pain

Exercise normally causes GH surges

FM patients that were non-surgers..

- ↑ pain, ↑ tenderness, ↑BMI, ↑ inflamm cytokines
- Explanation for exercise intolerance

# Aerobic Exercise

- Meta-analysis of 4 studies:
  - Short-term improvements
    - in cardiovascular fitness
    - decreased tenderness
  - No significant decrease in pain

Busch A, et al. *Cochrane Database Syst Rev.* 2003;3:CD003786.

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# Multicomponent\* Treatment of Fibromyalgia

## Meta-Analysis of 9 RCTs (n=1,119)

- Short term reduction in:
  - Pain
  - Fatigue
  - Depressive symptoms
  - Limitations to HRQOL
- Short term improvement in:
  - Self-efficacy pain
  - Physical fitness
- Long term (7 mths) effect on physical fitness

\*1 educational or psychological therapy + 1 exercise therapy

Häuser W, et al. *Arthritis Rheum.* 2009;61(2):216-24.

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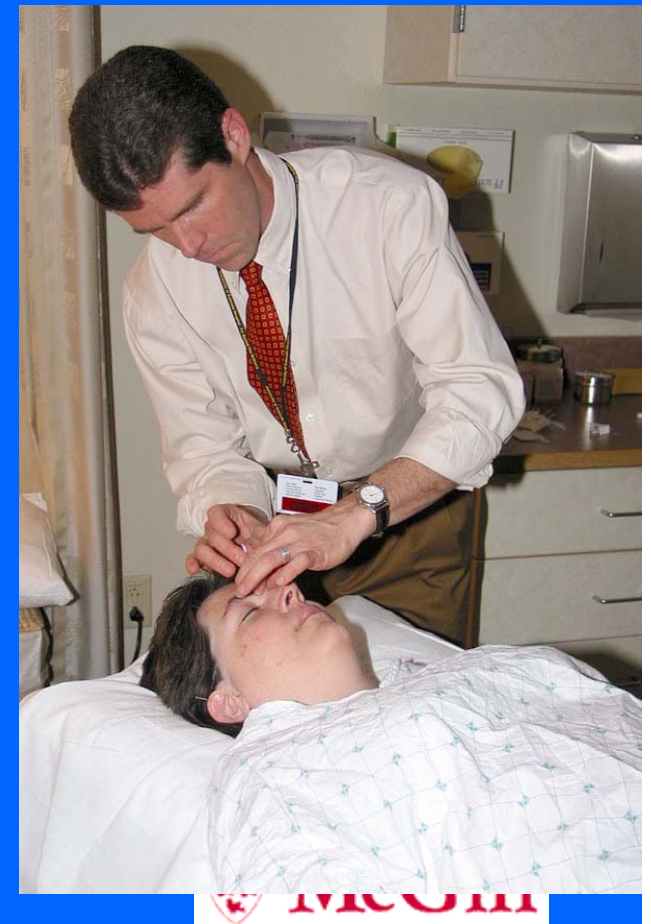


# Cognitive-Behavioral Therapy (CBT)

- CBT alone
  - no better than education or exercise, or both
- Review - 13 programs CBT
  - better pain-related behaviour, self-efficacy, coping strategies & physical function
  - ↓ pain in juvenile FM for individualized CBT
- needs further research.

# Physical treatments do not encourage dependence

- Physiotherapy - instruction in program, not endless sessions
- chiropractor
- massage therapy
- acupuncture
- relaxation - alone not good enough
- Psychotherapy- move away from sick role



# Alternative treatments

- Most not proven, but should not simply reject in ignorance
- Evening primrose oil, turmeric, valerian, St John's wort, omega-3.....
- placebo
- defined time
- trust in MD



# What does not work?

- MD
  - Wrong diagnosis
  - Not attending to mood, sleep
  - Over treating....pills, investigations
- Patient
  - No goals, wants magic pill, unrealistic expectations
  - The passive, negative patient
  - Secondary gain
    - Financial
    - Social support
    - Psychological support

# Conclusions

- Fibromyalgia treatment should be individualized based on symptoms
- Use non-pharma and pharma therapies
- Pharmacologic treatments have different modes of action
  - Most consistent evidence for SNRIs,  $\alpha$ -2 $\delta$  ligands, and tricyclics
- Patient must be active participant

# The way ahead

The beginnings of a success story  
(integration of science & clinic)

- Improved understanding science
- more treatment options
- Tailor treatments
- Still need a reliable clinical measure

