

Fibromyalgia then, nociplastic pain now

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Disclosure

- No financial disclosures
- **Health Canada:** Core member of Science Advisory Committee on Health Products Containing Cannabis (SAC-HPCC).
- **Australian** Centre for Cannabinoid Clinical and Research Excellence (ACRE): international advisory member
- **Arthritis Foundation US:** international advisor
- **Canadian Rheumatology Association:** lead for pragmatic approach to medical cannabis use for persons with rheumatic diseases

Objectives

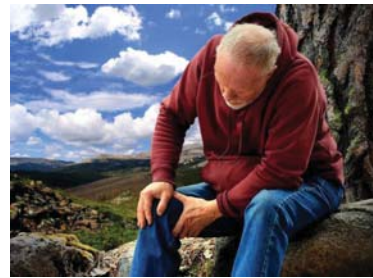
By the end of this lecture participants will be able to:

1. appreciate the concept of nociplastic pain as it pertains to fibromyalgia syndrome
2. describe current treatment options for fibromyalgia
3. know how to apply this knowledge to improve patient care

Understanding fibromyalgia

- A valid condition with pathogenesis centered in the nervous system
- Characterized as **nociplastic pain**, a third pain mechanism ¹
- Sensitization of the nervous system
- Occurs uniquely (4% population), also as secondary with some other primary pain condition (20-40% osteoarthritis, rheumatoid arthritis, etc)

Unique FM, or nociplastic overlap with an underlying pain process



A fired up nervous system

Mechanistically defined as pain arising from altered function of sensory pathways in periphery and central nervous system causing increased sensitivity.

Nociplastic pain conditions

- Combined peripheral and central pain sensitization
- Hyper-responsiveness to painful and non-painful sensory stimuli
- Associated features
 - Fatigue
 - Sleep disturbance
 - Cognitive disturbances
 - Hypersensitivity to environmental stimuli
 - Anxiety and depressed mood



SUPRASPINAL MECHANISMS

- Hyper-responsiveness to pain stimuli
- Hyper-activity and connectivity in and between brain regions involved in pain
- Decreased activity of brain regions involved in pain inhibition (i.e. descending inhibitory pathways)
- Elevated CSF substance P and glutamate levels, decreased GABAergic transmission
- Changes in the size and shape of gray and white matter regions involved in pain processing
- Glial cell activation

PERIPHERAL MANIFESTATIONS

- Minor local muscle pathology (e.g. changes in pH, muscle fiber composition, latent and active trigger points)
- Peripheral sensitization (e.g. expansion of receptive fields, elevated cytokine and chemokine levels)
- Hyperalgesia, dysesthesia and allodynia
- Localized and/or diffuse tenderness

SPINAL MECHANISMS

- Regional clustering and convergence of signals from different pain loci
- Spinal cord reorganization
- Amplified spinal reflex transmission
- Diminished spinal inhibition
- Wind-up and temporal summation
- Glial cell activation



The umbrella of nociplastic pain

Chronic primary pain



Chronic
widespread
pain/
fibromyalgia

Chronic
musculoskeletal
pain

Chronic
headaches
& facial pain

Chronic
visceral pain

??? Complex
regional pain

Nicholas M et al. Pain 2019

Simplified criteria for fibromyalgia



Chronic widespread pain (6/9 sites)

+

Moderate to severe

Fatigue ±

Unrefreshed sleep

1. Arnold L et al. J of Pain 2019

Management of FM/nociplastic pain remains a challenge

No “gold standard”
But we are treating PAIN

The essence of treatments...

- Patient tailored treatment according to pain, sleep disturbance, mood, fatigue
- **Modest effect of drugs**
- Multimodal treatments ideal
- Aim for symptom relief, not cure and maintain function
- Categorize patients ...mild, moderate, severe ± mental health disorder

Some specific drug treatments...keep in mind the evidence and the real world

- Antidepressants
- Anticonvulsants
- Opioids
- Cannabinoids
- Naltrexone
- Natural products
- Non pharmacologic interventions
 - Exercise
 - Diet

European League against rheumatism (EULAR) FM guidelines..drugs are not great

• Amitriptyline	13 trial, 900 pts	NNB 3.5
• Cyclobenzaprine	5 trials, 312 pts	NNB 4.8
• SNRI	8 syst rev, 2249 pts	NNB 6
• Pregabalin	7 trials, 3300 pts	NNB 9
• Tramadol	2 rev, 30% ↓pain	RR 1.7

Antidepressants...the evidence

- Amitriptyline
 - Older studies, methodology poor, but moderate effect on pain, sleep and fatigue ¹
- (Cyclobenzaprine)
 - Structurally related to TCA's, improves pain and QOL, not fatigue ¹
- Duloxetine
 - Moderate effect on pain regardless of depression, but 11-27% discontinue in long term studies¹

1. Calandre EP. *Expert Opin Pharmacother* 2015;

Anticonvulsants...the evidence

- Gabapentin
 - Effects are uncertain ¹
- Pregabalin
 - Effective and safe ²
- Topiramate ³
 - No RCT in FM, but neuropathic pain had no convincing evidence 200 or 400 mg/day
 - High rate side effects

1. Cooper TE *Cochrane* 2017; 2. Derry S *Cochrane* 2016; 3. Wiffen PJ *Cochrane* 2013

Opioids....not recommended...but

- Patients attest to +ve effects opioids
- Even when prescribed “FM treatments”..SNRI’s, gabapentinoids, continued opioid use ^{1,2}
- US 11 yr longitudinal, 3000 pts, almost 50 % on opioids ³

1. Kim SC et al. *Arth Care Res* 2013; 2 Halpern R et al. *Pain Pract* 2013; 3. Wolfe F et al. *Eur J pain* 2013

Poorer outcome for FM patients on opioids

- Canadian Tertiary care pain clinic, 457 FM patients, 30% opioids ¹
 - ↓education, ↑unemployment
 - ↑disability, ↑ unstable mental health, ↑substance abuse, ↑suicide attempts
- Canada, 12 month prospective FM patients, 400 opioid users, 1000 non-users ²
 - Non users had better function, sleep, depression and ↓pain interference

Little support for long term opioids in FM

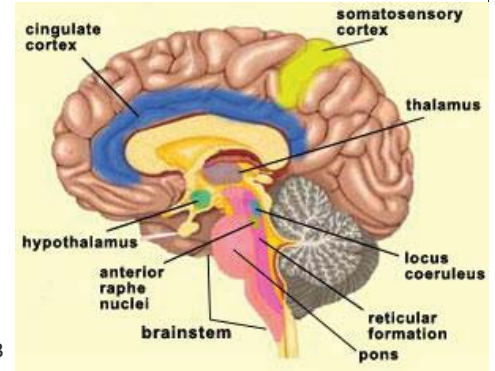
1. Fitzcharles M et al. *Pain res Treat* 2013; 2. Peng X et al. *Clin J Pain* 2015.

Why might opioids not work for nociplastic pain

↑ activation opioid system, ↑ opioid release, ↓ receptor availability

FM may have fewer opioid receptors, more pain

- ↓ endogenous opioids blood mononuclear cells in FM and CFS ¹
- ↑ endogenous opioids in CSF ²
- ↓ μ-opioid receptor in dorsal cingulate, amygdala, nucleus accumbens ³



1. Panerai AE et al. *clin J Pain* 2002; 2. Baraniuk JN et al *BMC MSK dis* 2004; 3. Harris RE et al. *J Neuroscience* 2007;

Cannabinoids...is there promise

- **Analgesic drugs provide only modest effect**
- Patients expect pain to be treated with a medication
- Patients seek to self-medicate with cannabinoid preparations
 - Pain, sleep, mood (anxiety)
- Media promotion of cannabinoids buoyed by +++++ anecdote



Patient perspective of cannabinoids

- Recreational legalization has ↑ medical use ¹
 - 15-30 % rheumatology patients tried cannabis
 - About half continue to use
 - Many do not disclose to MD
- Cohort reports are very +ve
 - Often from dispensaries, growers
 - 984 pts, **medical cannabis dispensaries** NE USA²
 - **>70% effective for all pains**

1. Fitzcharles et al. ACR Open May 2020; 2 Piper, Pain 2017,

19

CBD tried by 60% FM patients surveyed in USA 2020

Survey 2700 participants, USA, fibromyalgia ¹

- 2/3 ever use CBD with 1/3 continued use
 - CBD use associated with past year cannabis use, number conditions
 - 2/3 disclosed use to MD, but only 1/3 asked MD for advice
 - Moderate effect across all symptom domains/ minor side effects
 - Discontinuation due to safety concerns, lack of effect, cost
- Dosing CBD in 878 FM persons ²
 - Tinctures and topicals, but inhalation if used high THC cannabis
 - 16-27 mg CBD/day (1/3 did not know dose)

1. Boehnke K. J of Pain 2021; Boehnke K. J Pain 2021

CBD products

- CBD : OTC, wellness, dietary supplements, hemp oils
- Artisanal products
 - enriched with added cinnamon, cloves, turmeric etc
 - “pure” or boosted CBD up to 20%
 - “full-spectrum” with terpenes, flavonoids (entourage effect)
- **Inaccuracy labelling in US, Europe, Canada** ^{1,2,3}
 - 84 CBD commercial products analyzed ²
 - 30% accurate
 - 21% contained THC
 - Mislabeling: vaping products 88%, oils 55%
- **FDA warnings**



1. Hazekamp A. *Med canna & cannabinoids* 2018. 2. Bonn-miller MO et al. *JAMA*, 2017. 3. Pavlovic R et al. *Molecules* 2018

CBD...the evidence for anxiety, pain, sleep

- Anxiety
 - Some promise small clinical trials ^{1,2,3}
 - 20-1000mg CBD
- Pain
 - Insufficient evidence CBD alone, limited evidence combination THC + CBD ⁴
- Sleep promotion
 - CBD differential sleep effects according to dosage (low dose stimulating, higher doses sedating)

1. Skelley et al 2019; 2. Larsen et al 2020; 3 Sharpe et al. 2019; 4 Svensson 2020;

Naltrexone...nociplastic modulator¹

- Naltrexone semisynthetic opioid
 - 50-100mg opioid antagonist
 - Low dose...0.1-4.5mg ↓ neuroinflammation via glial cells (antagonism of TLR4)
- Fibromyalgia..RCT, 28 completers, 12 weeks....active vs. placebo ²
 - ↓Daily pain severity: 29 vs 18%
 - Better mood & life satisfaction
 - SE: vivid dreams, headaches

1. Hatfield E. JADA 2020; 2 Younger J. Arthritis Rheum 2013;

Combinations of drugs

Various combinations ¹

- 16 studies with 1474 subjects
- Tramadol + acetaminophen, amitriptyline + fluoxetine, amitriptyline + melatonin, malic acid + magnesium, pregabalin +duloxetine
- No or inadequate evidence for primary or secondary outcome
- Risk of bias mostly high, small size, selective reporting
- Adverse events common, but not serious

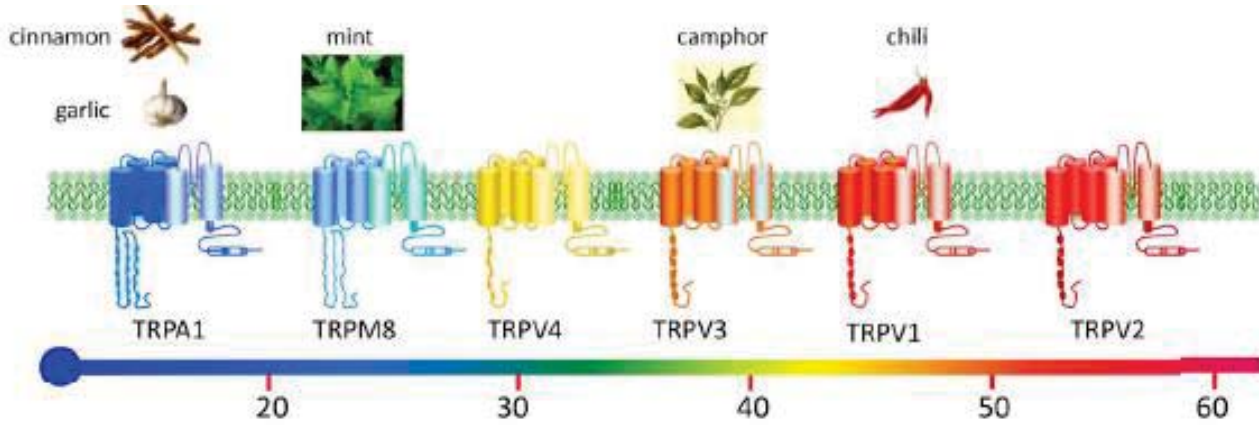
Conclusion

- Few high quality studies, cannot support or refute effect

But some evidence for amitriptyline + fluoxetine, amitriptyline + melatonin, pregabalin+duloxetine

1. Thorpe J Cochrane 2018;

Plants acting on pain receptors



Topicals: have a background of science



capsaicin 0.025%; balsam, birch oil, juniper berry oil, yarrow extract, all 0.0053%

menthol, eucalyptol (TRPM8)
camphor (TRPV1, TRPV3)



...and some herbs?

All show effect on pain in inflammation in animal studies

- Curcumin up to 4800mg

- Mild effect in OA
- Diarrhoea



- Ginger 500-1000mg

- Middle and Far East
- No difference from placebo



- Echinacea

- clicks onto cannabinoid receptor



Dietary manipulation

- Fibromyalgia ¹

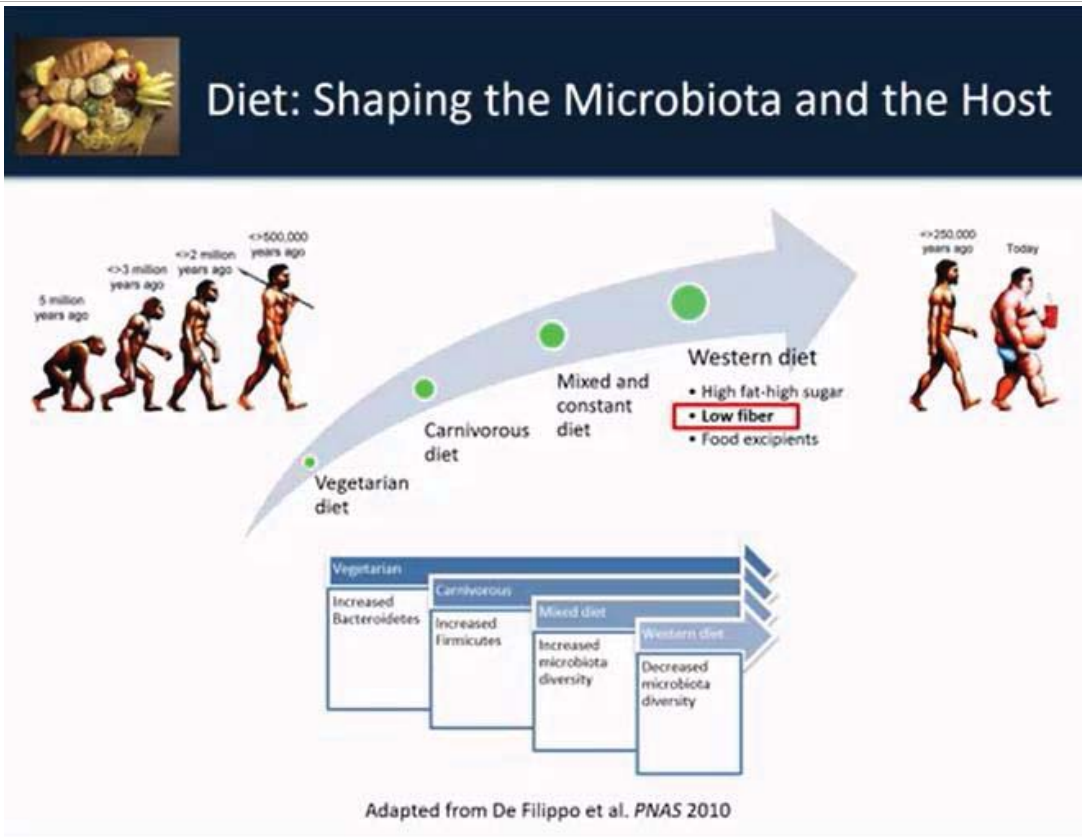
- High risk of bias, poor quality studies
- Some effect hypocaloric, raw vegetarian, low FODMAPS

- The evolving message of the microbiome

- Diet can change microbiome
 - ↑ fibre & resistant starch
 - ↓ fat & sugar
- “good” and “bad” bugs



1. Silva AR et al. 2019. Ann Int Med.



A Neolithic diet...High fibre & resistant starch

- Lentils, white beans, legumes, uncooked oats
- Persimmons, potato skins
- **Brown** rice, bread, +++ whole grains
- Bananas
- Cold rice & potatoes



Exercise: the evidence, the reality...

- Exercise: EULAR guides.... **STRONG FOR 100%AGREEMENT**
 - Aerobic exercise ¹
 - Resistance training ²
 - Land exercise=aquatic exercise³
 - Meditative movement ⁴ (weak for, 71% agreement)



- ...but patients DO NOT adhere to exercise recommendations⁵
 - OA studyaccelerometry , 1,111 adults, 62 yrs, 55% female
 - **90% inactive or low activity, pts self report more activity**

1. Busch. Cochrane 2008 2. Busch. Cochrane 2013. 3. Bidondi. Cochrane 2014, 4. Langhorst Rheum Int, 2013. 5. Dunlop. Arthritis Rheum. 2011; 63:3372-3382

..but exercise causes more pain

- More pain with exercise in 30% FM patients
- Dysfunction of endogenous pain inhibition in FM ¹
 - 21 control, 20 shoulder myalgia, 20 FM
 - Pressure pain threshold (PPT) after static muscle contraction
 - FM pts failed to increase PPT

1. Lannersten, Koch. Pain 2010

...and real life experience of drugs

- Most patients using at least 2 drugs
- NSAIDs and simple analgesics....often as prn
- Duloxetine: seldom continued in absence of depression
- Pregabalin: some use in very low dose...25-50mg/day
- TCA: occasional excellent effect, especially nortriptyline
- Naltrexone: a big disappointment
- Opioids: tramadol and tapentadol (if insured), 50-100mg/day
- Cannabinoids: seldom see continued use over time

Conclusion

1. No “gold standard” or “one size fits all”
2. Drugs often not continued over time
3. Drugs give only a modest effect
4. Low doses with combinations seen mostly in clinical practice
5. Pay attention to non-pharmacologic strategies
 - Exercise, weight control, pacing, routine, mood

Suggested reading

- Calandre EP et al. An update on pharmacotherapy for the treatment of fibromyalgia. Expert Opin Pharmacother 2015
- Sarzi-Puttini P et al. Fibromyalgia: an update of clinical characteristics, aetiopathogenesis and treatment. Nat Rev Rheumatol. 2020
- Fitzcharles M et al. Nociceptive pain: towards an understanding of prevalent pain conditions Lancet 2021

With thanks