
KNOW
CENTRAL SENSITIZATION
/DYSFUNCTIONAL
PAIN

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This program was sponsored by Pfizer Inc.

Learning Objectives

- After completing this module, participants will be able to:
  - Discuss the prevalence of various syndromes involving central sensitization/dysfunctional pain, focusing on fibromyalgia
  - Understand the impact of syndromes involving central sensitization/dysfunctional pain, such as fibromyalgia, on patient functioning and quality of life
  - Explain the pathophysiology of central sensitization/ dysfunctional pain
  - Recognize core clinical features of fibromyalgia
  - Select appropriate pharmacological and non-pharmacological strategies for the management of fibromyalgia

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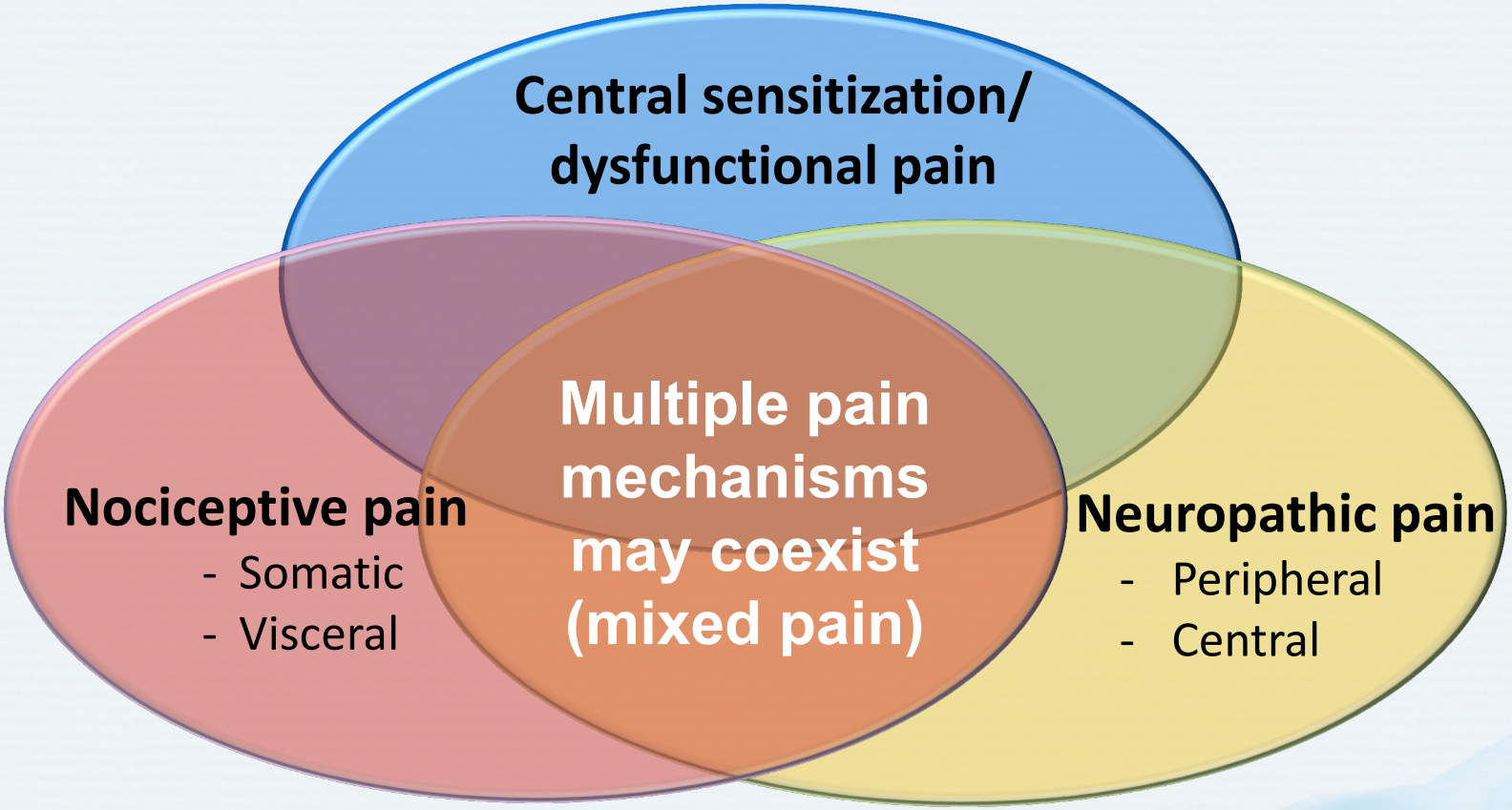
Pathophysiological Classification of Pain



Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90; Jensen TS *et al*. *Pain* 2011; 152(10):2204-5;
Julius D *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
Ross E. *Expert Opin Pharmacother* 2001; 2(1):1529-30; Webster LR. *Am J Manag Care* 2008; 14(5 Suppl 1):S116-22; Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

Why do patients suffering from central sensitization experience dysfunctional pain?

- During central sensitization, the sensation of pain is enhanced as a result of:
  - Changes in nerve fibers and the environment
  - Modifications of the functional properties and the genetic programming of primary and secondary afferent neurons

Fornasari D. *Clin Drug Investig* 2012; 32(Suppl 1):45-52.

What is central sensitization/ dysfunctional pain?

Definition

- Amplification of neural signaling within the CNS that elicits pain hypersensitivity

Examples

- Fibromyalgia
- Tension-type headache
- Irritable bowel syndrome
- Interstitial cystitis
- Temporomandibular joint pain
- May be present in many patients with chronic low back pain, osteoarthritis and rheumatoid arthritis

Pain Quality

- Often diffuse
- Frequently with allodynia and/or hyperalgesia
- Rarely burning, lancinating or electric shock-like

CNS = central nervous system

Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

Clinical Features of Central Sensitization/Dysfunctional Pain

Pain

- Pain all over body
- Muscles stiff/achy
- Headaches
- Pain in jaw
- Pelvic pain
- Bladder/urination pain

Anxiety/depression

- Sad or depressed
- Anxiety
- Stress makes symptoms worse
- Tension in neck and shoulder
- Grind/clench teeth

Fatigue

- Do not sleep well
- Unrefreshed in morning
- Easily tired with physical activity

Other symptoms

- Difficulty concentrating
- Need help with daily activities
- Sensitive to bright lights
- Skin problems
- Diarrhea/constipation

Mayer TG *et al. Pain Pract* 2012; 12(4):276-85.

Discussion Question

HOW OFTEN DO YOU SEE PATIENTS WITH THESE CLINICAL FEATURES?

How common is central sensitization/ dysfunctional pain?

~40%

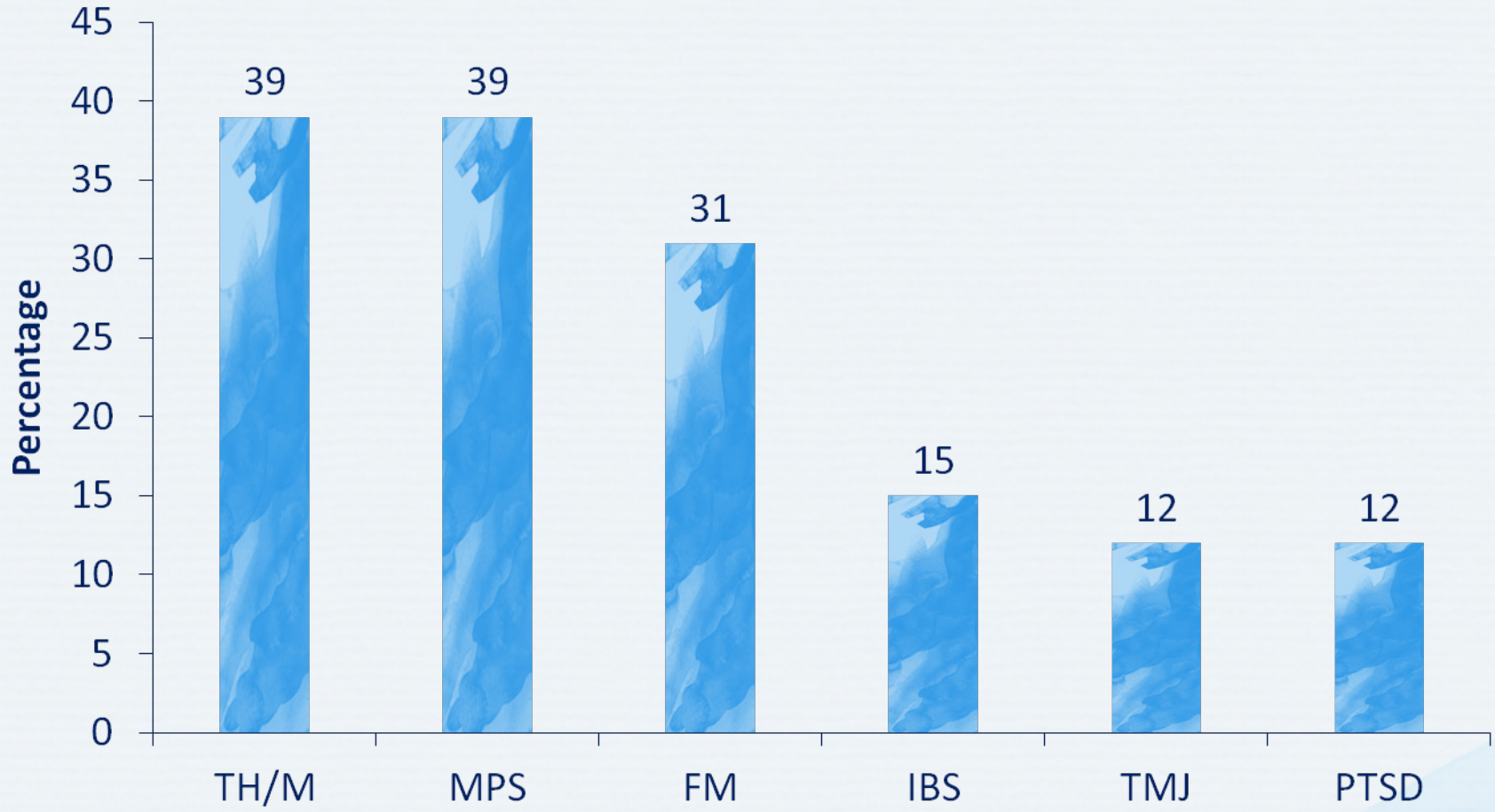
of adults suffer from ***chronic pain***[1]

17–35%

of chronic pain patients suffer from ***generalized hypersensitivity and conditioned pain modulation***[2]

1. Tsang A *et al. J Pain* 2006; 9(10):883-91; 2. Schliessbach J *et al. Eur J Pain* 2013; 17(10):1502-10.

Common Diagnoses Among Patients Suffering from Central Sensitization/Dysfunctional Pain



Note: some patients had more than one diagnosis; less common diagnoses included restless leg syndrome (8%); chronic fatigue syndrome (4%) interstitial cystitis (4%), complex regional pain syndrome (2%) and multiple chemical sensitivity (1%) FM = fibromyalgia; IBS = irritable bowel syndrome; MPS = myofascial pain syndrome; PTSD = post-traumatic stress disorder; TH/M = tension headache/migraine; TMJ = temporomandibular joint disorder

Neblett R *et al. J Pain* 2013; 14(5):438-45.

What is fibromyalgia?

FIBROMYALGIA IS A COMMON CHRONIC WIDESPREAD PAIN DISORDER, CHARACTERIZED BY AN AMPLIFICATION OF PAIN SIGNALS, ANALOGOUS TO THE "VOLUME CONTROL SETTING" BEING TURNED UP TOO HIGH.

Clauw DJ *et al. Mayo Clin Proc* 2011; 86(9):907-11.

Epidemiology of Fibromyalgia

Fibromyalgia is one of the most common central sensitization/dysfunctional conditions.[1]

Prevalence in USA is estimated to be 2–5% of the adult population.[1]

Fibromyalgia is highly underdiagnosed:[2]

- Only 1 in 5 is diagnosed
- Diagnosis takes an average of 5 years[3]

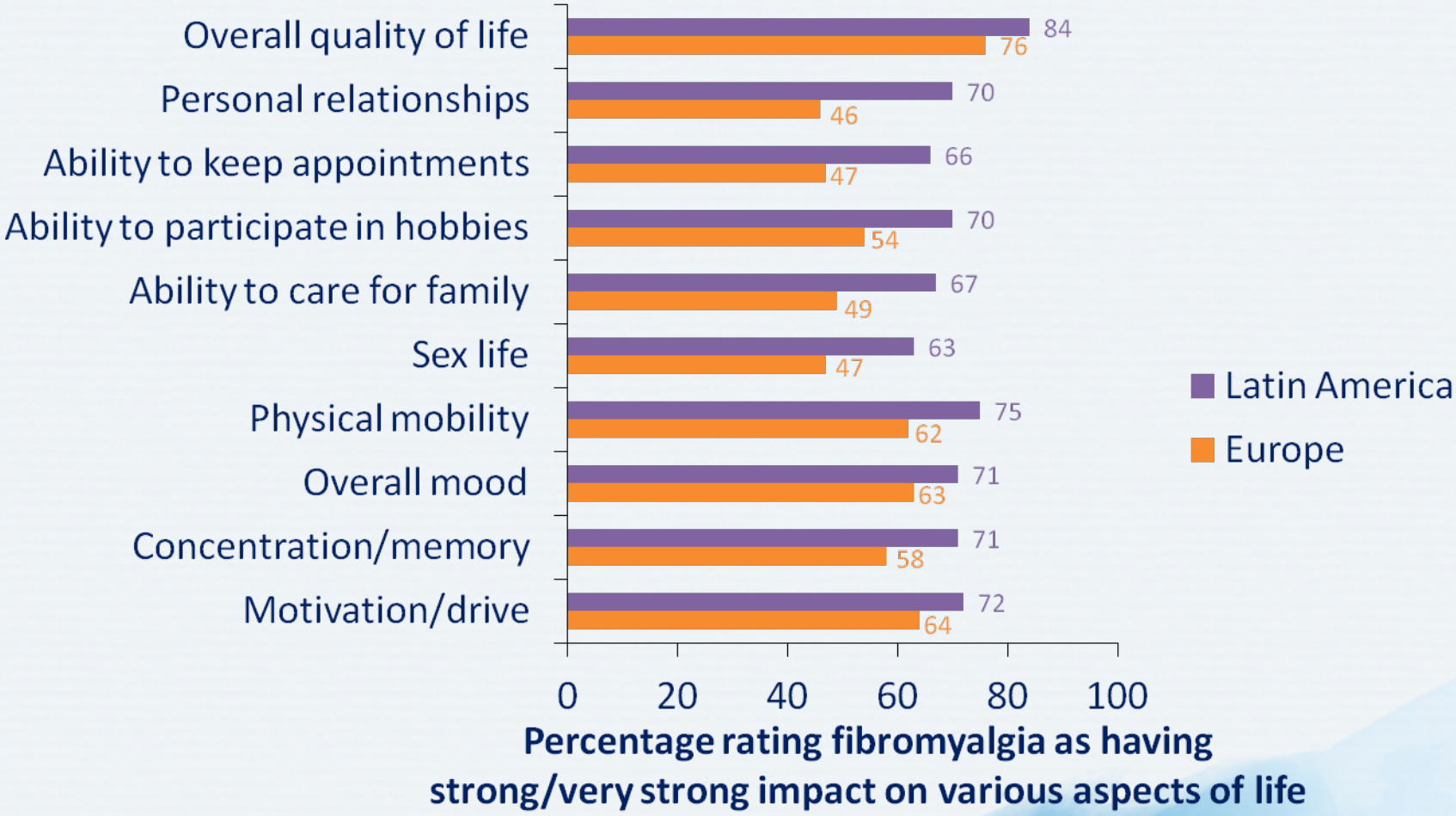
Fibromyalgia occurs in all ages, both sexes and all cultures but occurs more frequently in:[4]

- Women
- Those between the ages of 35 and 60 years

USA = United States of America

1. Wolfe F *et al. Arthritis Rheum* 1995; 38(1):19-28; 2. Weir PT *et al. J Clin Rheumatol* 2006; 12(3):124-8;
3. National Pain Foundation. *Fibromyalgia: Facts and Statistics*. Available at: http://nationalpainfoundation.org/articles/849/facts-and-statistics. Accessed: July 21, 2009; 4. White KP *et al. J Rheumatol* 1999; 26(7):1570-6.

Patient-Reported Impact of Fibromyalgia

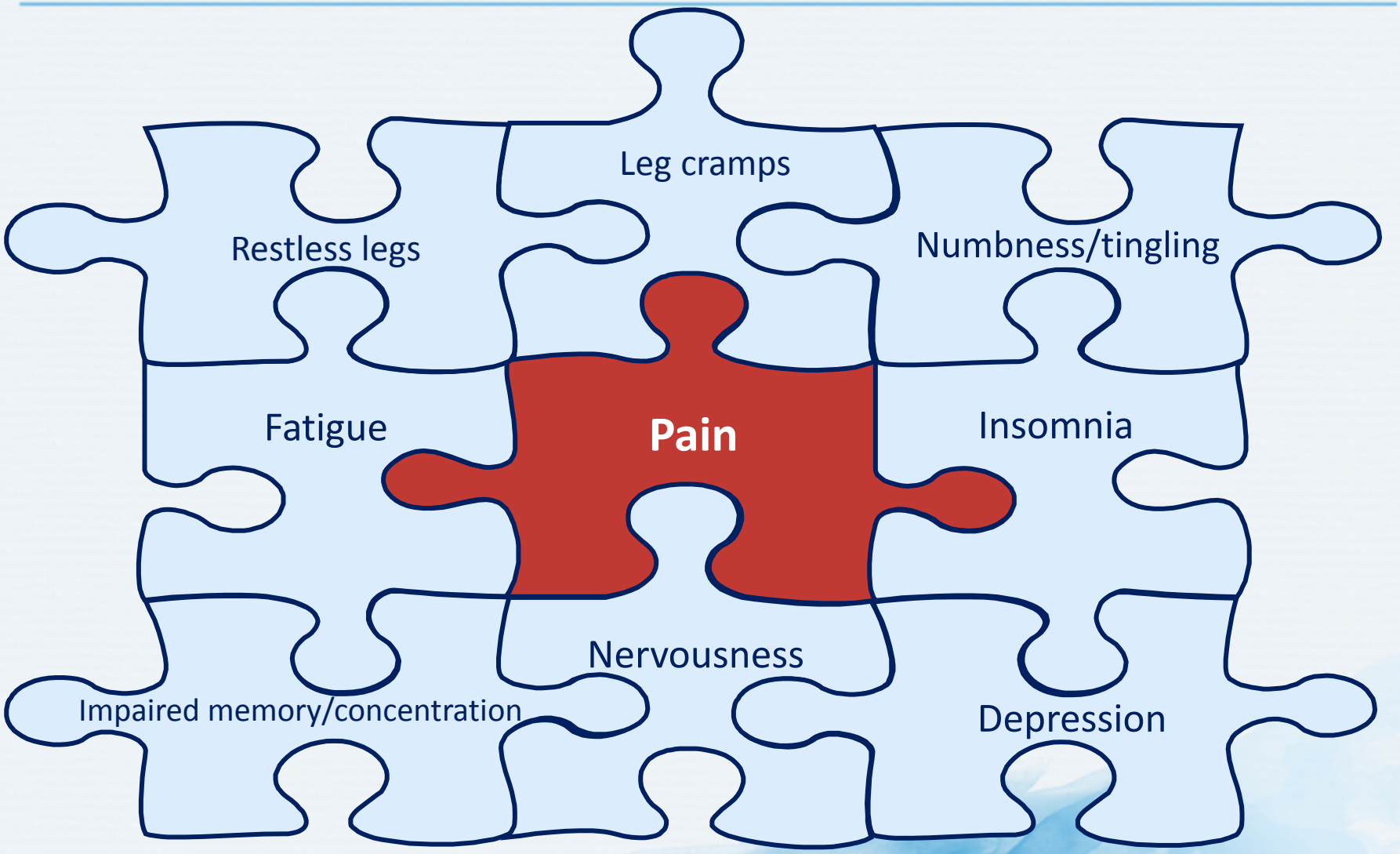


Clark P *et al. BMC Musculoskelet Disord* 2013; 14:188.

Discussion Question

HOW DO YOU IDENTIFY PATIENTS WITH FIBROMYALGIA IN CLINICAL PRACTICE?

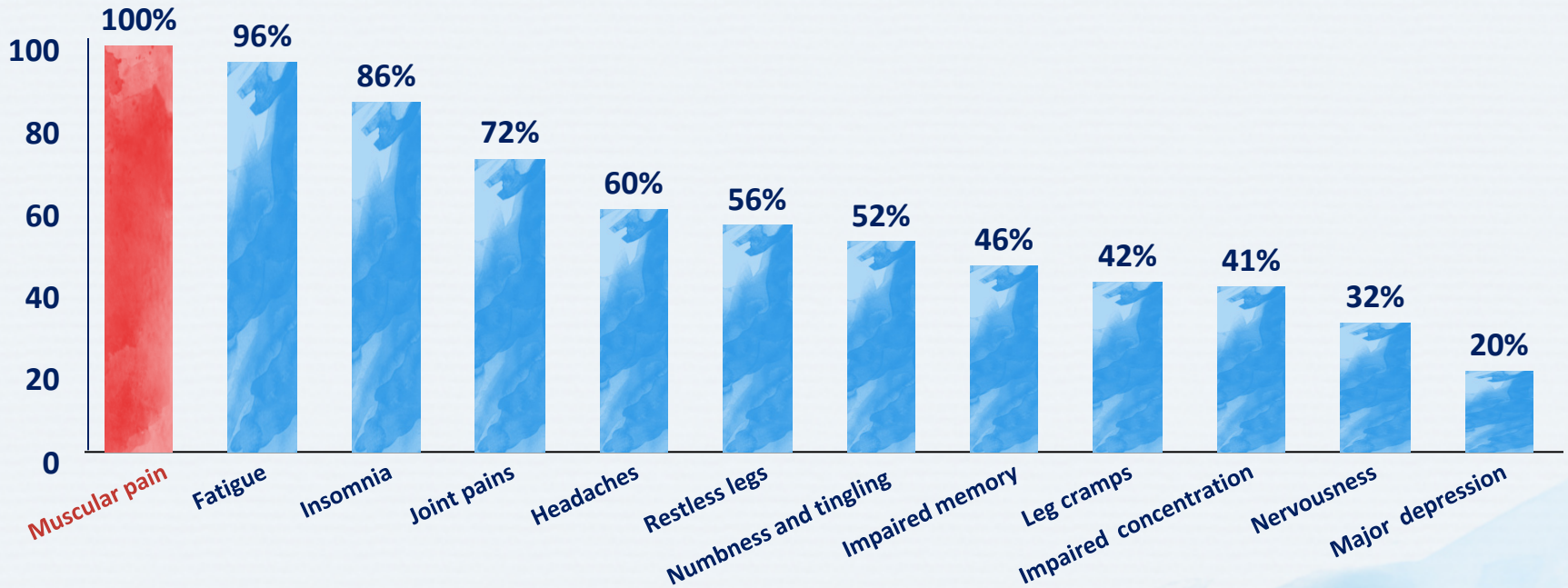
How to Recognize Fibromyalgia: Pain Is the Common Piece of the Puzzle



Wolfe F *et al Arthritis Rheum* 1990; 33(2):160-72.

Symptoms of Fibromyalgia

- Pain, fatigue and sleep disturbance are present in at least **86% of patients***



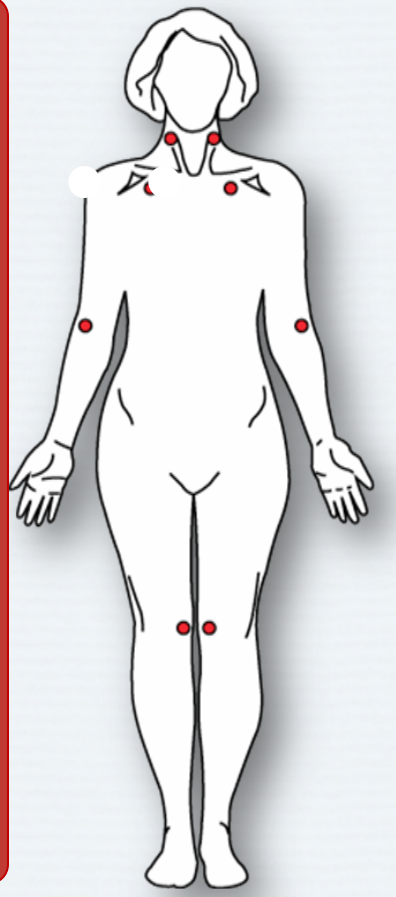
***United States data**

Wolfe F *et al Arthritis Rheum* 1990; 33(2):160-72.

Core Clinical Features of Fibromyalgia

Widespread pain

- Chronic, widespread pain is the defining feature of fibromyalgia
- Patient descriptors of pain include:
  - Aching
  - Exhausting
  - Nagging
  - Hurting



Neurocognitive impairment ("fibro fog")

Sleep disturbance/fatigue

Mood disorders

Morning stiffness

Carruthers BM *et al. J Chron Fat Synd* 2003; 11(1):7-115; Harding SM. *Am J Med Sci* 1998; 315(6):367-37; Henriksson. *J Rehabil Med* 2003; 41(41 Suppl):89-94; Leavitt *et al. Arthritis Rheum* 1986; 29(6):775-81; Roizenblatt S *et al. Arthritis Rheum* 2001; 44(1):222-30; Wolfe F *et al Arthritis Rheum* 1990; 33(2):160-72; Wolfe F *et al. Arthritis Rheum* 1995; 38(1):19-28.

Many Fibromyalgia Patients Have Cognitive Complaints: "Fibro Fog"

- Compared to those without the condition, patients with fibromyalgia complain more often of:[1]
  - Mental confusion
  - Memory decline
  - Speech difficulty
- Performance on cognitive tests shows they have poorer performance than age-matched controls on tasks involving:[2]
  - Working memory
  - Recognition memory
  - Free recall
  - Verbal fluency
  - Verbal knowledge

1. Katz RS *et al. J Clin Rheumatol* 2004; 10(2):53-8; 2.Park DC *et al. Arthritis Rheum* 2001; 44(9):2125-33.

Sleep Disturbances and Fibromyalgia

- Fibromyalgia patients may complain of:
  - Non-restorative sleep
  - Insomnia
  - Early morning awakening
  - Poor sleep quality

Bradley LA. *Am J Med* 2009; 122(12 Suppl):S22-30.

Mood Disorders and Fibromyalgia

20–40% have an identifiable mood disorder

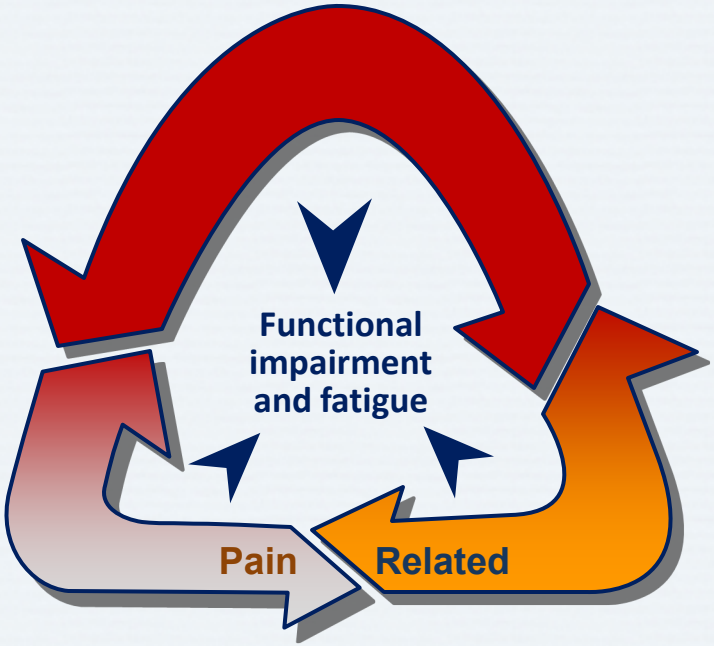
- Depression: 75%
- Anxiety: 60%

In many cases, depression or anxiety may be the result of chronic pain.

Arnold LM *et al. Arthritis Rheum* 2004; 50(3):944-52; Boissevain MD, McCain GA. *Pain* 1991; 45(3):227-38; Boissevain MD, McCain GA. *Pain* 1991; 45(3):239-48; Fishbain DA *et al. Clin J Pain* 1997; 13(2):116-37; Giesecke T *et al. Arthritis Rheum* 2003; 48(10):2916-22; Katon W *et al. Ann Intern Med* 2001; 134(9 Pt 2):917-25.

The Paradigm of Pain: Interrelationship Among Pain, Sleep Disturbance and Psychological Symptoms

Sleep disturbances
can directly result from and/or contribute to fibromyalgia.



Psychological symptoms
are strongly associated with fibromyalgia.

Management strategy for fibromyalgia patients is to **improve overall patient functionality.**

Adapted from: Argoff CE. *Clin J Pain* 2007; 23(1):15-22.

Diagnosing Fibromyalgia

- On average it takes patients **>2 years** to be diagnosed with fibromyalgia
- A estimated **75%** of people with fibromyalgia remain undiagnosed

Overview of Diagnosis

- History of fibromyalgia or related conditions
  - Personal and family history
- Physical examination
  - Most important to identify any other possible conditions
- Differential diagnosis
  - Clinical/laboratory evaluation to identify other possible conditions

Consequences of Non-diagnosis

- Failure to diagnose fibromyalgia is associated with increased costs and increased use of medical resources

Annemans L *et al. Arthritis Rheum* 58(3):895-902; Choy E *et al. BMC Health Serv Res* 2010; 10:102; Clauw DJ *et al. Mayo Clin Proc.* 2011; 86(9):907-11; Mease P. *J Rheumatol* 2005; 32(Suppl 75):6-21; Wolfe F *et al. Arthritis Rheum* 1990; 33(2):160-72.

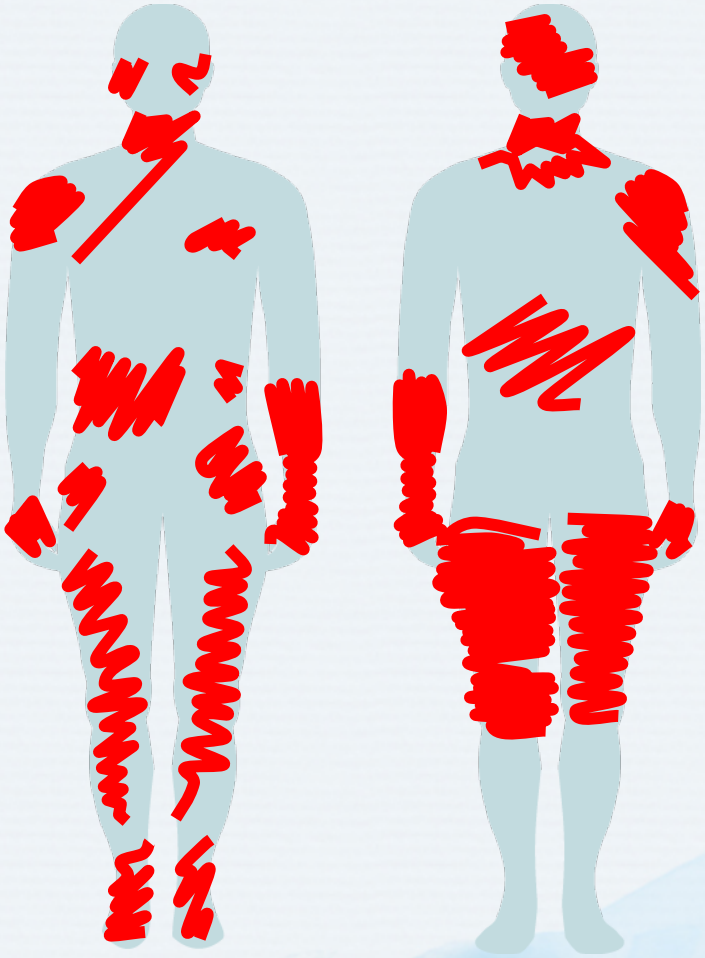
Differential Diagnosis of Fibromyalgia

- Hypothyroidism
- Vitamin D deficiency
- Inflammatory rheumatic disease
- Cancer
- Inflammatory muscle diseases

Rahman A *et al. BMJ* 2014; 348:g1224.

Patients with Fibromyalgia Present with a Global Pain Disorder

- This is a pain drawing
  - Patient colors all areas of the body in which he or she feels pain[1]
- The diagram shows that the pain of fibromyalgia is widespread[2]

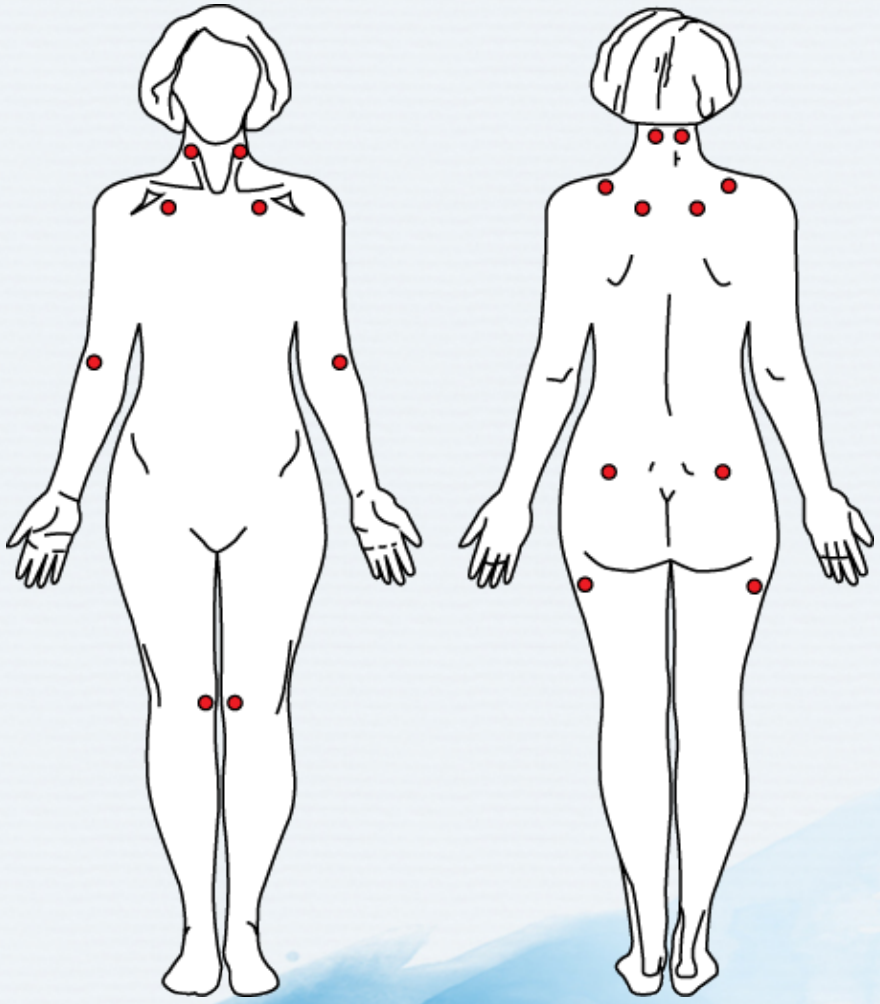


Adapted from pain drawing provided courtesy of L Bateman.

1. Silverman SL, Martin SA. In: Wallace DJ, Clauws DJ (eds.). *Fibromyalgia & Other Central Pain Syndromes*. Lippincott, Williams & Wilkins; Philadelphia, PA: 2005; 2. Wolfe F *et al. Arthritis Rheum* 1990; 33(2):160-72.

ACR Classification Criteria for Fibromyalgia (1990)

- ACR criteria:
  - History of chronic widespread pain ≥3 months
  - Patients must exhibit ≥11 of 18 tender points
- ACR criteria are both sensitive (88.4%) and specific (81.1%)



ACR = American College of Rheumatology

Wolfe F *et al. Arthritis Rheum* 1990; 33(2):160-72.

Performing a Manual Tender Point Survey

- Digital palpation with an approximate force of 4 kg
  - **Estimated pressure needed to turn the examiner's thumbnail white upon depressing**
  - For a "positive" tender point, subject must state palpation was painful
- Accuracy for fibromyalgia:
  - Sensitivity: **88.4%**
  - Specificity: **81.1%**
- **Controversies** regarding tender point evaluation:
  - Subjective
  - May not be necessary for diagnostic studies
  - What about fewer than 11 of 18 tender points?

National Fibromyalgia Association. *The Manual Tender Point Survey*. Available at http://www.fmaware.org/News2eb58.html?p. Accessed August 13, 2013; Wilke WS. *Cleve Clin J Med* 2009; 76(6):345-52; Wolfe F *et al. Arthritis Rheum* 1990; 33(2):160-72.

ACR Proposed Diagnostic Criteria for Fibromyalgia (2010)

- Fibromyalgia can be diagnosed if:
  - Patient experiences widespread pain and associated symptoms
  - Symptoms have been present at same level for ≥3 months
  - No other condition otherwise explains the pain

Associated symptoms include:

- Unrefreshed sleep
- Cognitive symptoms
- Fatigue
- Other somatic symptoms

ACR = American College of Rheumatology

Wolfe F *et al. Arthritis Care Res (Hoboken)* 2010; 62(5):600-10.

FiRST: Fibromyalgia Rapid Screening Tool

- Self-administered 6-item questionnaire
- Score of ≥5 is indicative of fibromyalgia
- Sensitivity: 90.5%
- Specificity: 85.7%

Items

1. I have pain all over my body.
2. My pain is accompanied by continuous and very unpleasant general fatigue.
3. My pain feels like burns, electric shocks or cramps.
4. My pain is accompanied by other unusual sensations throughout my body, such as pins and needles, tingling or numbness.
5. My pain is accompanied by other health problems such as digestive problems, urinary problems, headaches or restless legs.
6. My pain has a significant impact on my life, particularly on my sleep and my ability to concentrate, making me feel slower generally.

Perrot S *et al. Pain* 2010; 150(2):250-6.

Discussion Question

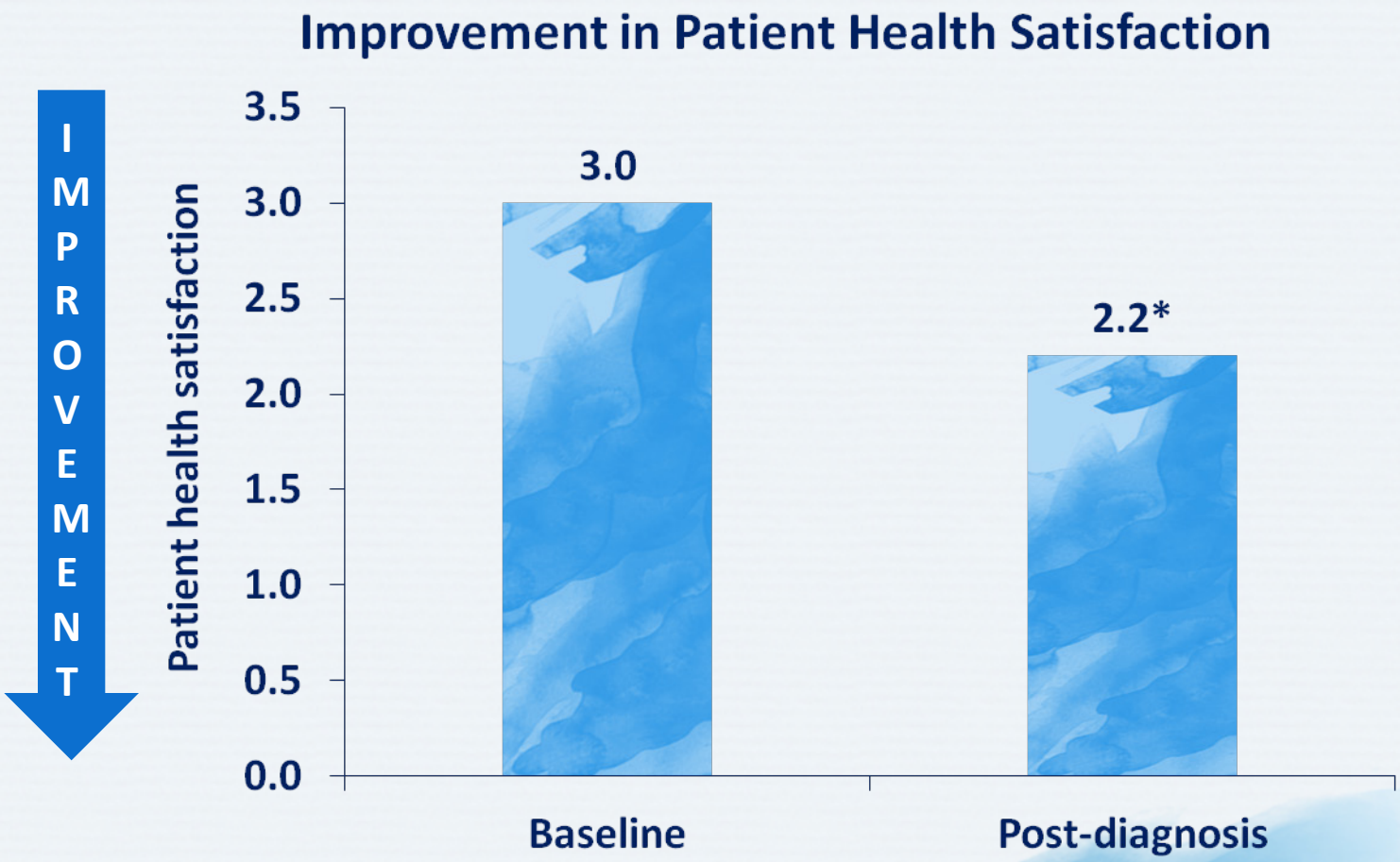
What do you tell your patients you think are suffering from fibromyalgia?

Tips on Providing the Diagnosis of Fibromyalgia

- Be **specific** about the diagnosis
- Be **positive** about the diagnosis
- Promote and encourage patient self-efficacy around the disease but...
  - Set realistic expectations
  - Emphasize there is no cure but improved control of symptoms is usually possible

Arnold LM *et al. Mayo Clin Proc* 2012; 87(5):488-96.

Diagnosis of Fibromyalgia Can Improve Patient Satisfaction



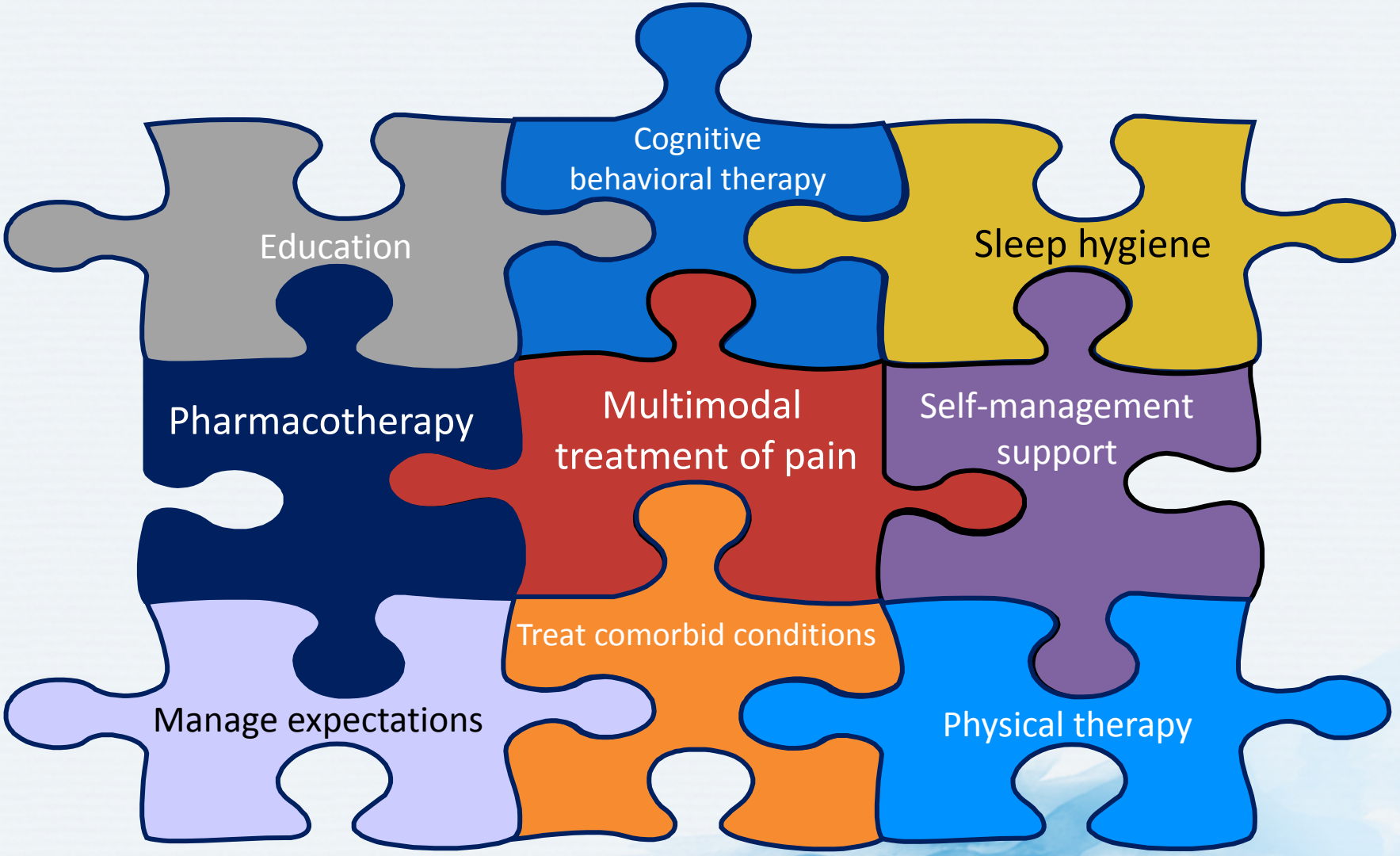
***Statistically significant vs. baseline (confidence interval -1.2 to -0.4)**

White KP *et al. Arthritis Rheum* 2002; 47(3):260-5.

Discussion Question

WHAT NON-PHARMACOLOGICAL APPROACHES COULD YOU USE TO HELP ADDRESS FIBROMYALGIA FROM A BIOPSYCHOSOCIAL PERSPECTIVE?

Multimodal Treatment of Fibromyalgia Based on Biopsychosocial Approach



Arnold LM *et al. Mayo Clin Proc* 2012; 87(5):488-96.

Non-pharmacological Treatment of Fibromyalgia

Sleep hygiene

Physical activity

Cognitive behavioral therapy

Self-management support

Seek support from other health care professionals – nurses, social workers, occupational therapists, physiotherapists, psychologists, psychiatrists, etc.

Arnold LM *et al. Mayo Clin Proc* 2012; 87(5):488-96.

Non-pharmacologic Interventions to Improve Sleep in Fibromyalgia

1. Avoid stimulants
2. Go to bed and rise at regular times
3. Avoid napping through day
4. Exercise regularly, particularly in the afternoon
5. Use the bed only for sleep and sex
6. Relax before bed
7. Printed information on sleep for patients

University of Maryland Medical Center. *Sleep Hygiene*. Available at: http://umm.edu/programs/sleep/patients/sleep-hygiene. Accessed: August 21, 2013.

Physical Activity and Fibromyalgia

Benefits

- Stimulates release of endorphins and enkephalins within 30 minutes
- These bind to opioid receptors, reducing pain by an action on both ascending and descending neural pathways

Recommendations for Fibromyalgia

Type of Exercise

- Try to include different types in one session (*e.g.*, aerobic, strengthening, stretching)
- Patient preference and availability should guide selection

Intensity

- Start low, go slow
- Gradually increase to reach moderate intensity level

Busch AJ *et al. Curr Pain Headache Rep* 2011; 15(5):358-67; McGovern MK. *The Effects of Exercise on the Brain.* Available at: http://serendip.brynmawr.edu/bb/neuro/neuro05/web2/mmcgovern.html. Accessed: July 25, 2013.

Cognitive Behavioral Therapy in Fibromyalgia

Technique

Learn to identify emotions that influence cognitive and affective components of pain (anxiety, helplessness, depression)

Employ active cognitive, problem-solving and distraction/relaxation techniques to modify emotions

Develop active strategies targeting well-being and control

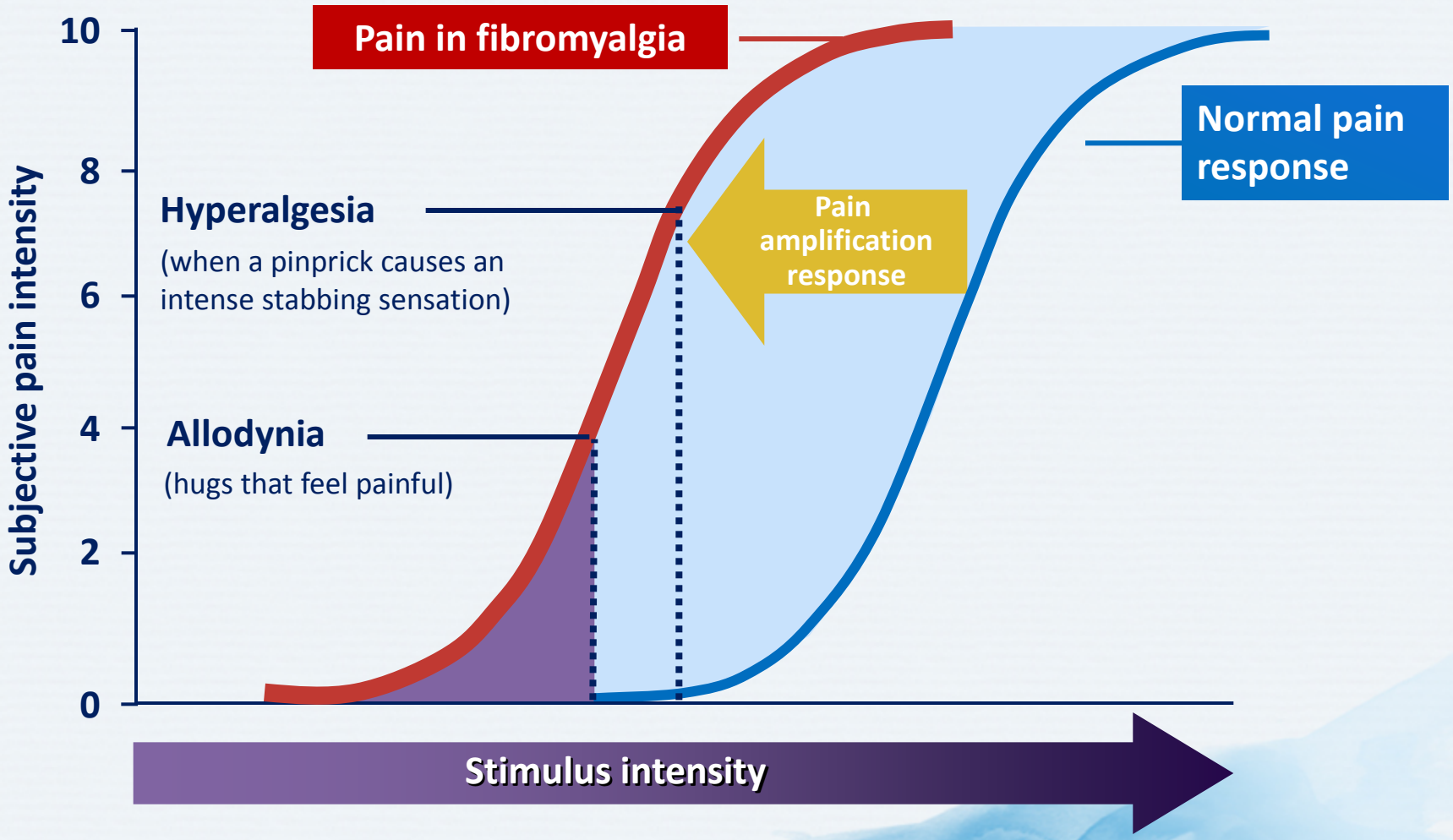
Thieme K, Turk DC. *Reumatismo* 2012; 64(4):275-85.

Discussion Question

IS FIBROMYALGIA "ALL IN THEIR HEAD"?

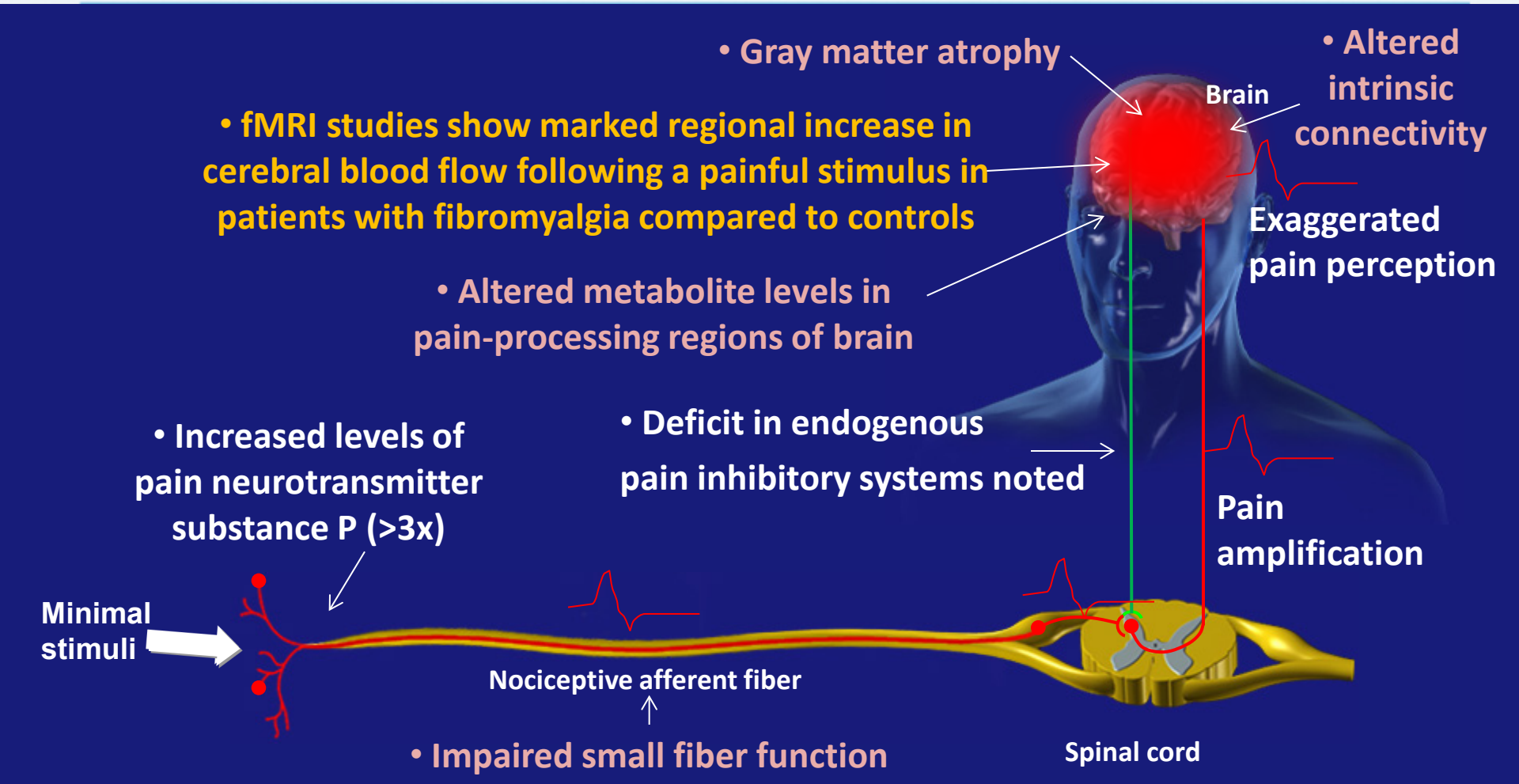
WHAT ARE THE PATHOPHYSIOLOGICAL MECHANISMS BEHIND THE PAIN THESE PATIENTS EXPERIENCE?

Fibromyalgia: An Amplified Pain Response



Adapted from: Gottschalk A, Smith DS. *Am Fam Physician* 2001; 63(10):1979-86.

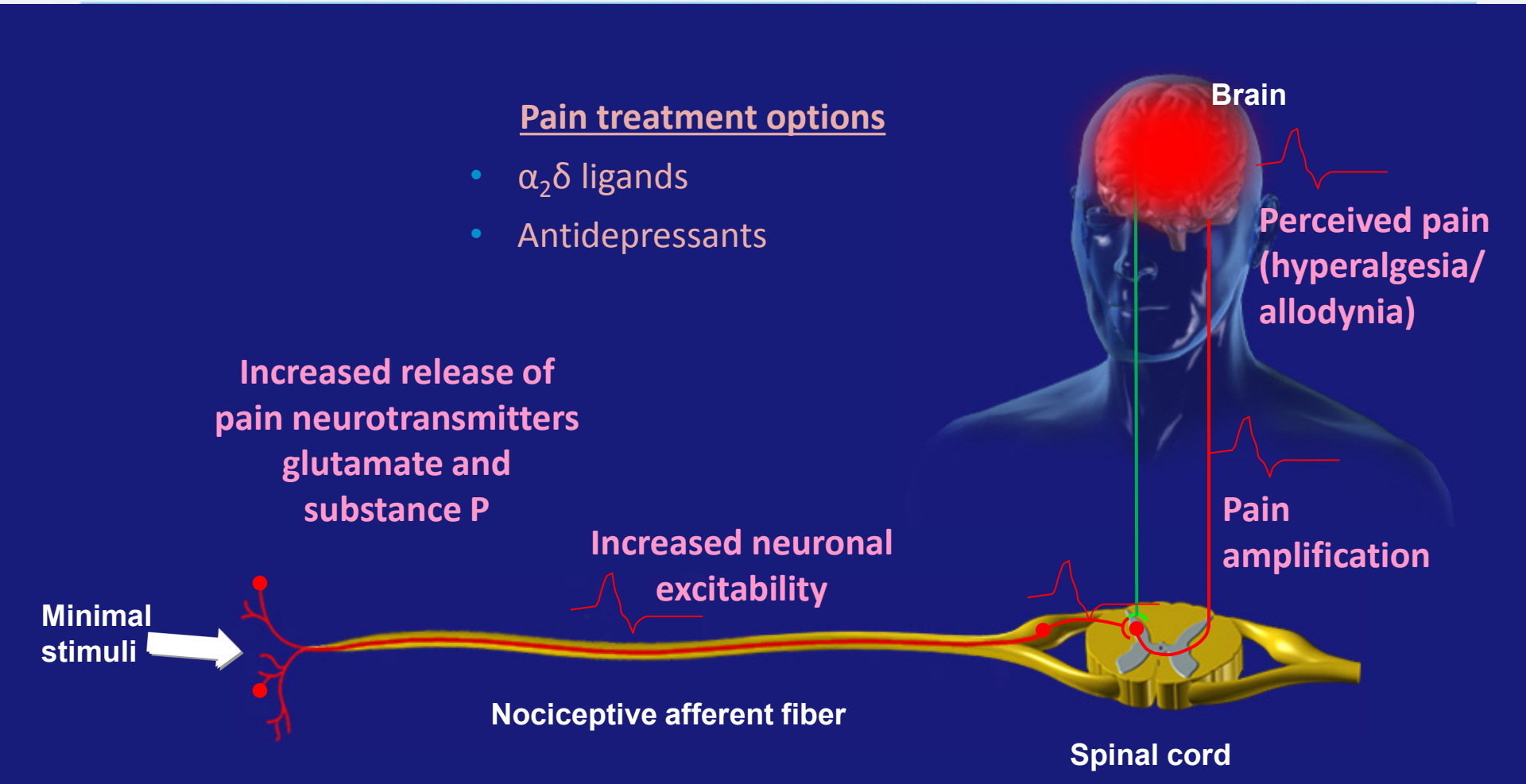
Pathophysiological Changes in Fibromyalgia



fMRI = functional magnetic resonance imaging

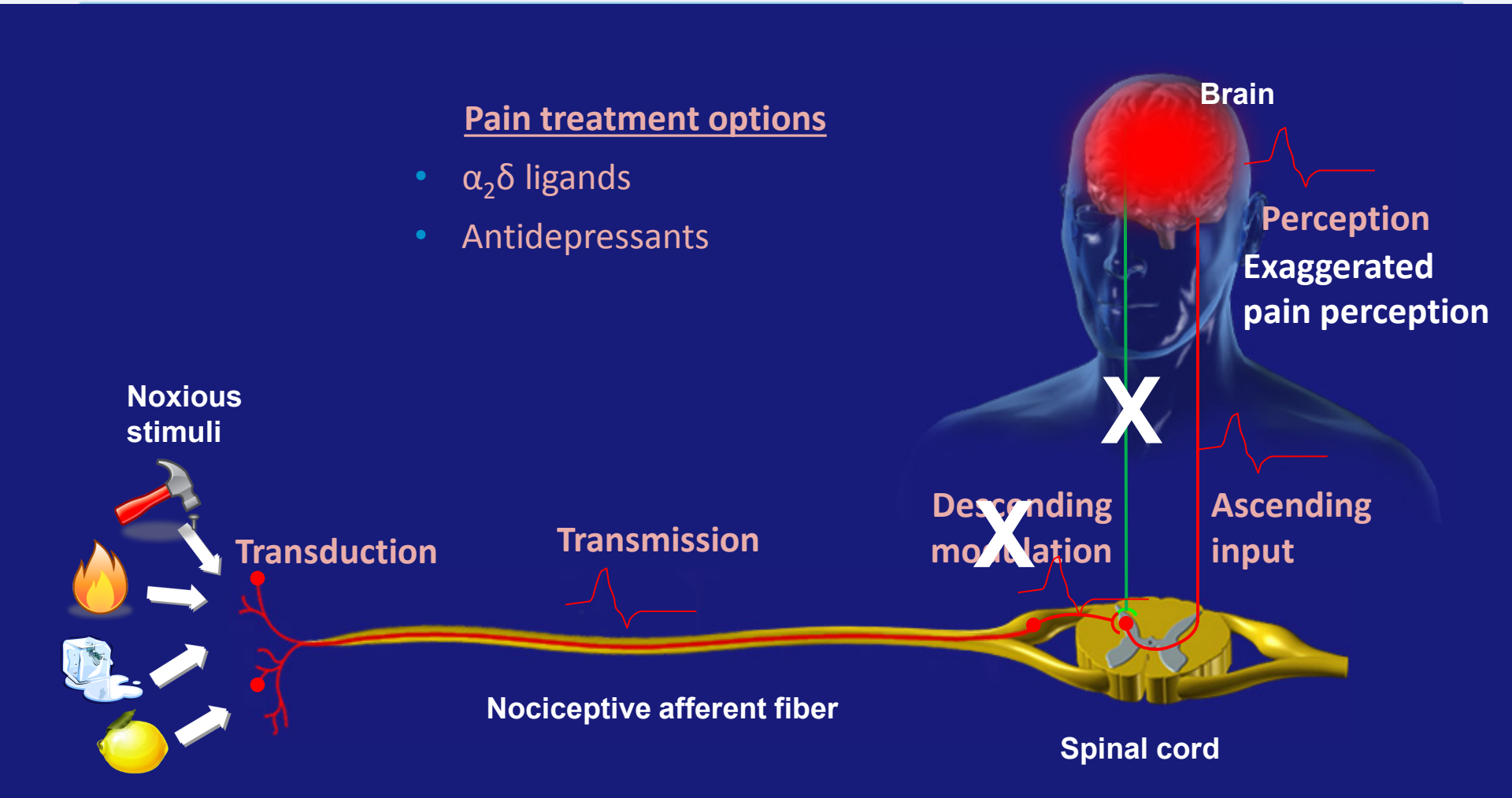
Feraco P *et al. AJNR Am J Neuroradiol* 2011; 32(9):1585-90; Gracely RH *et al. Arthritis Rheum* 2002; 46(5):1333-43; Julien N *et al. Pain* 2005; 114(1-2):295-302; Napadow V *et al. Arthritis Rheum* 2010; 62(8):2545-55; Robinson ME *et al. J Pain* 2011; 12(4):436-43; Russell IJ *et al. Arthritis Rheum* 1994; 37(11):1593-1601; Üçeyler N *et al. Brain* 2013; 136(Pt 6):1857-6; Vaerøy H et al. *Pain* 1988; 32(1):21-6.

Central Sensitization Produces Abnormal Pain Signaling



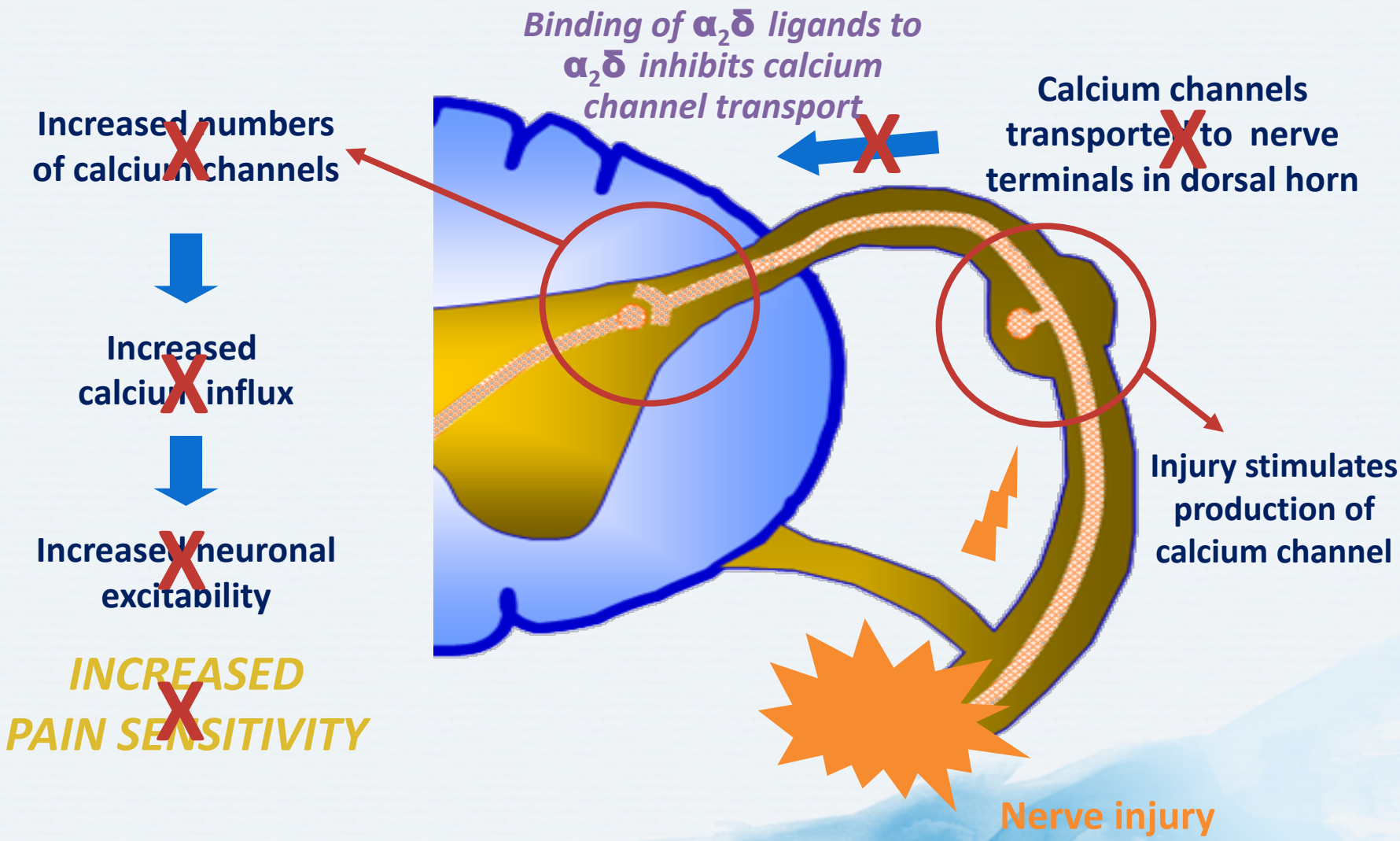
Adapted from: Campbell JN, Meyer RA. *Neuron* 2006; 52(1):77-92; Gottschalk A, Smith DS. *Am Fam Physician* 2001; 63(10)1979-86; Henriksson KG. *J Rehabil Med* 2003; 41(Suppl):89-94; Larson AA *et al. Pain* 2000; 87(2):201-11; Marchand S. *Rheum Dis Clin North Am* 2008; 34(2):285-309; Rao SG. *Rheum Dis Clin North Am* 2002; 28(2):235-59; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14; Staud R, Rodriguez ME. *Nat Clin Pract Rheumatol* 2006; 2(2):90-8; Vaerøy H *et al. Pain* 1988; 32(1):21-6; Woolf CJ *et al. Ann Intern Med* 2004; 140(6):441-51.

Loss of Inhibitory Control: Disinhibition



Attal N, Bouhassira D. *Acta Neurol Scand* 1999; 173:12-24; Doubell TP *et al.* In: Wall PD, Melzack R (eds). *Textbook of Pain*. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999; Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

How $\alpha_2\delta$ Ligands Decrease Pain Sensitivity



Note: gabapentin and pregabalin are $\alpha_2\delta$ ligands

Bauer CS *et al. J Neurosci* 2009; 29(13):4076-88.

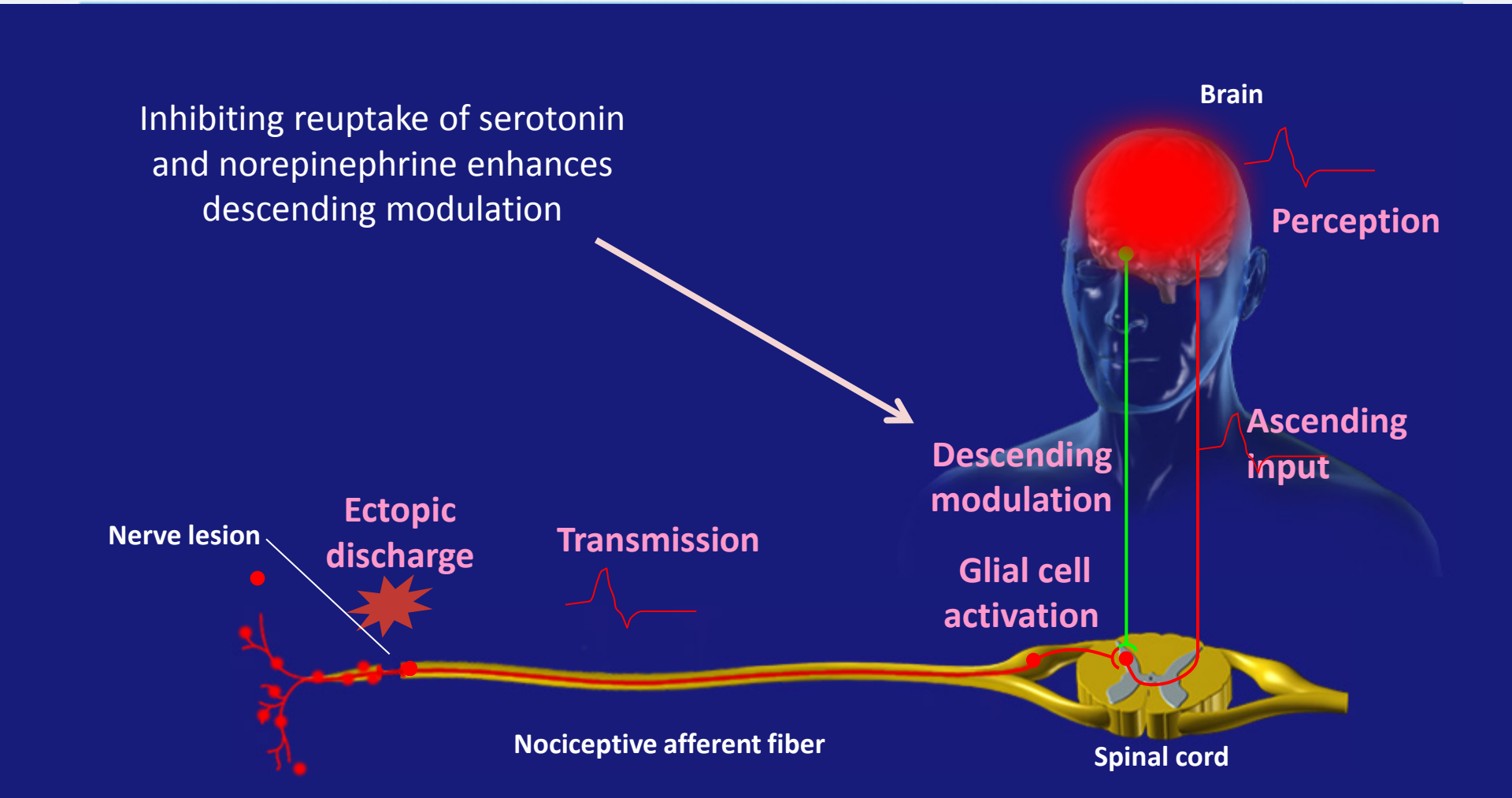
Adverse Effects of $\alpha_2\delta$ Ligands

System	Adverse effects
Digestive system	Dry mouth
CNS	Dizziness, somnolence
Other	Asthenia, headache, peripheral edema, weight gain

$\alpha_2\delta$ ligands include gabapentin and pregabalin
CNS = central nervous system

Attal N, Finnerup NB. *Pain Clinical Updates* 2010; 18(9):1-8.

How Antidepressants Modulate Pain



Verdu B *et al. Drugs* 2008; 68(18):2611-2632.

Adverse Effects of Antidepressants

System	TCAs	SNRIs
Digestive system	Constipation, dry mouth, urinary retention	Constipation, diarrhea, dry mouth, nausea, reduced appetite
CNS	Cognitive disorders, dizziness, drowsiness, sedation	Dizziness, somnolence
Cardiovascular	Orthostatic hypotension, palpitations	Hypertension
Other	Blurred vision, falls, gait disturbance, sweating	Elevated liver enzymes, elevated plasma glucose, sweating

CNS = central nervous system; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor

Attal N, Finnerup NB. Pain Clinical Updates 2010; 18(9):1-8.

IASP: Pharmacological Treatment for Fibromyalgia

Level 1

A

- Amitriptyline
- Duloxetine
- Milnacipran
- Pregabalin

B

- Gabapentin

Level 2

A

- Cyclobenzapine
- Fluoxetine

B

- Paroxetine
- Tramadol

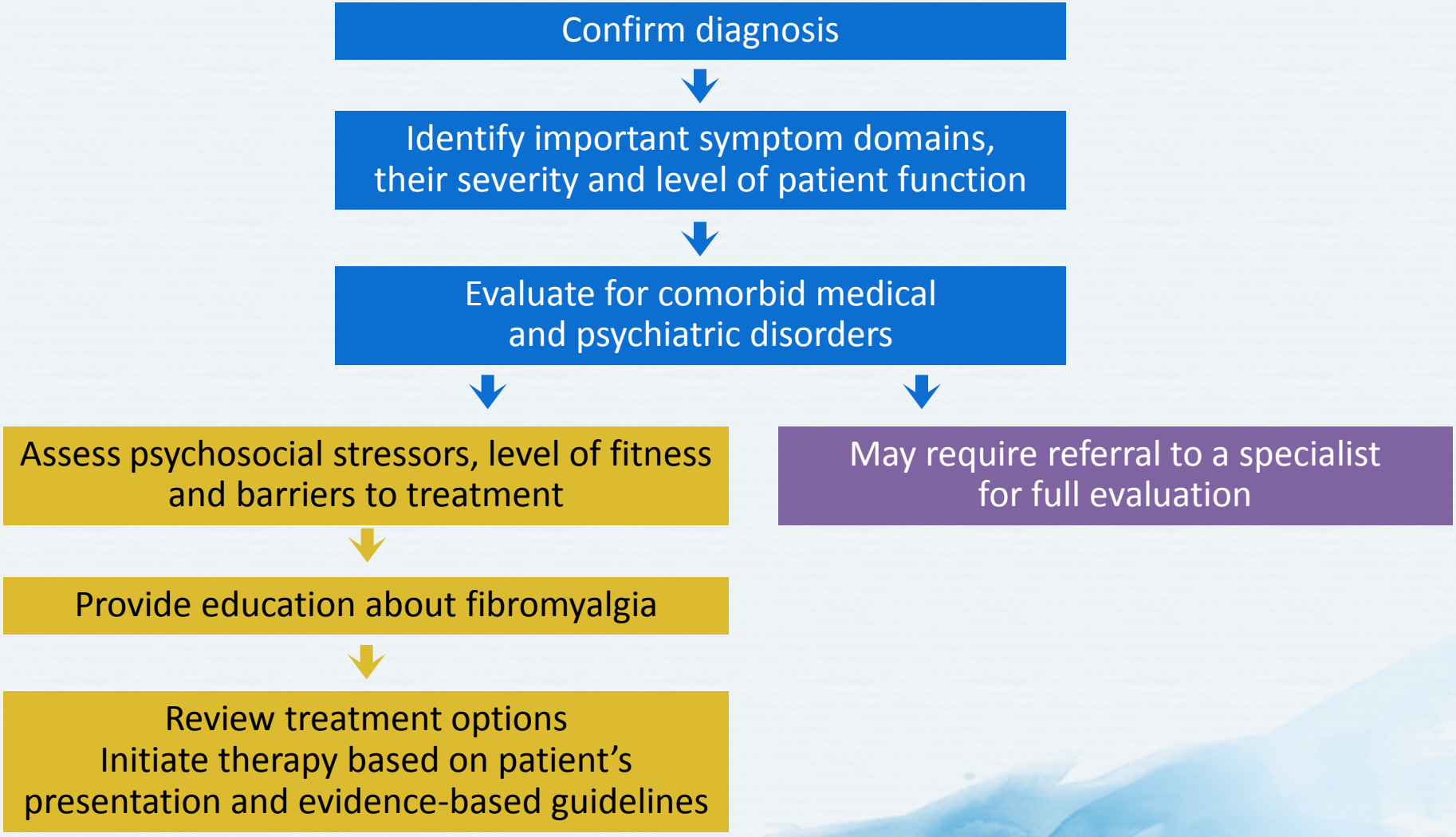
IASP = International Association for the Study of Pain

Sommer C. *Pain Clin Updates* 2010; 18(4):1-4.

Discussion Question

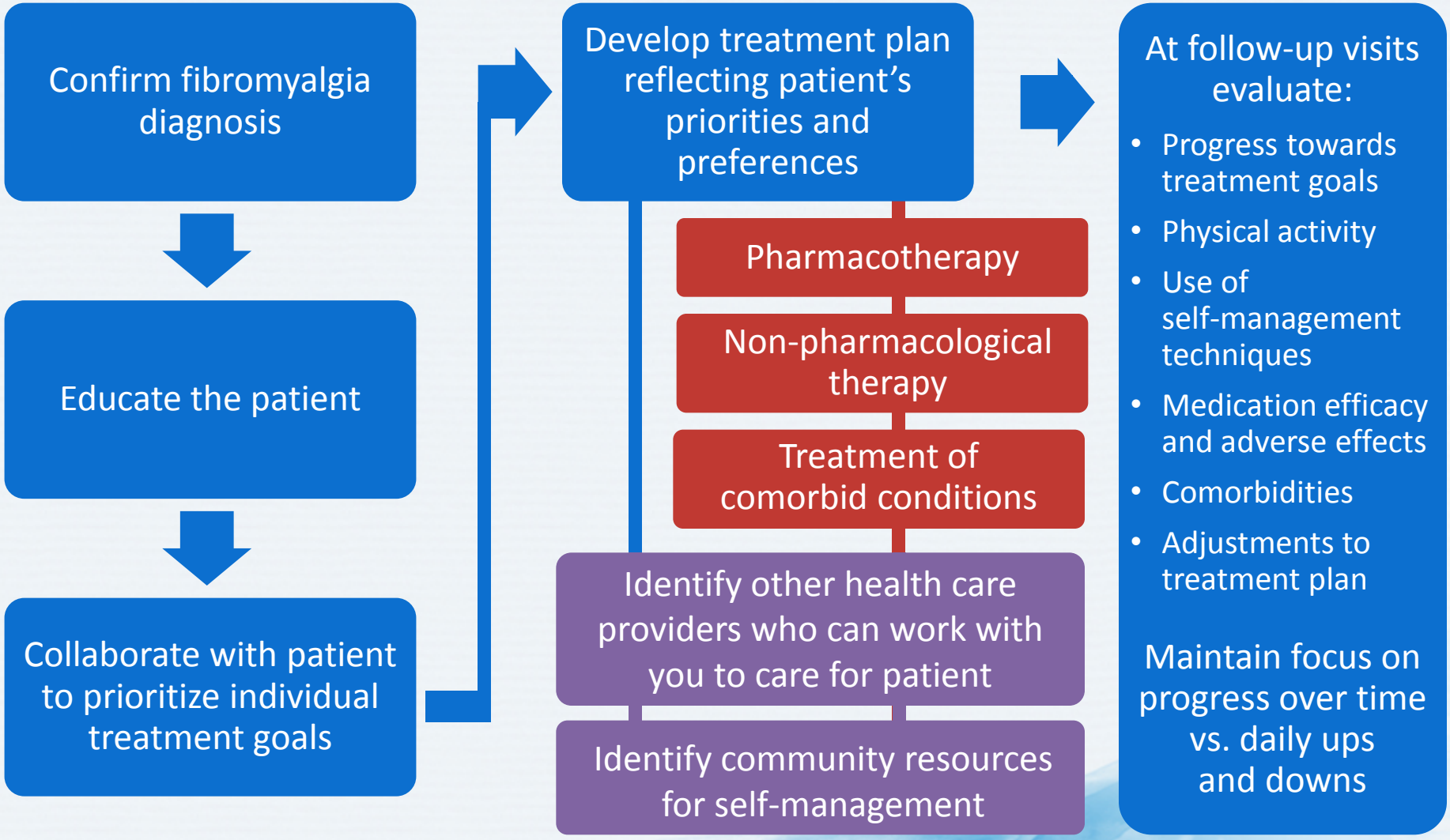
HOW WOULD YOU INTEGRATE THE CONCEPTS DISCUSSED TODAY INTO A CONCRETE TREATMENT PLAN FOR A PATIENT WITH FIBROMYALGIA?

Core Treatment of Fibromyalgia



Adapted from: Arnold LM. *Arthritis Res Ther* 2006; 8(4):212; Goldenberg DL *et al. JAMA* 2004; 292(19):2388-95.

Overview of Fibromyalgia Management



Adapted from: Arnold LM *et al. Mayo Clin Proc* 2012; 87(5):488-96.

Fibromyalgia: Medication Is Just One Part of the Treatment Approach

NOT shown to be effective or recommended:

- Opioids
- Benzodiazepines
- NSAIDs
- Magnesium
- Vitamin B1
- Hormonal agents (thyroxine, DHEA, melatonin, calcitonin)

Pharmacological treatment

3 medications approved by the FDA:

- Pregabalin
- Duloxetine
- Milnacipran

Non-pharmacological treatment

- Aerobic exercise
- Cognitive behavioral therapy
- Strength training
- Acupuncture
- Hypnotherapy
- Biofeedback
- Balneotherapy
- Massage therapy
- Behavioral therapies, such as relaxation
- Transcranial magnetic stimulation?

DHEA = dehydroepiandrosterone; FDA = Food and Drug Administration; NSAID = non-steroidal anti-inflammatory drug

Häuser W et *al. Arthritis Res Ther* 2014; 16(1):201; Fitzcharles MA *et al. Evid Based Complement Alternat Med* 2013; 2013:528952; Sumpton JE, Moulin DE. *Handb Clin Neurol* 2014; 119:513-27.

Key Messages

- Up to 15% of adults may experience central sensitization/ dysfunctional pain, with 2–5% of adults suffering from fibromyalgia
- Central sensitization/dysfunctional pain is hypothesized to be a result of persistent neuronal dysregulation or dysfunction
- Many patients with central sensitization/dysfunctional pain syndromes such as fibromyalgia also suffer from poor sleep, fatigue, anxiety and mood disorders
- Multimodal therapy including both non-pharmacological and pharmacological components should be used to target symptoms of fibromyalgia