TARGETING NEUROTRANSMITTERS: MODULATING PAIN RESPONSE*

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ABSTRACT

The publication of the American College of Rheumatology criteria for fibromyalgia syndrome (FMS) is often considered the starting point of a major paradigm shift. By establishing a standardized case definition for FMS, the criteria enabled researchers to move forward and changed the way clinicians and researchers think of FMS, and more broadly, chronic pain. Whereas chronic pain was once thought to be acute pain that merely lasted too long, it is now recognized that the mechanisms underlying acute and chronic pain are markedly different from each other, and that acute and chronic pain respond to entirely different treatments. This article reviews the paradigm shift that needs to occur to take care of chronic pain more effectively, as we appreciate intra-individual differences in the neural processing of pain and recognize that various pharmacologic and nonpharmacologic modalities are better at treating central pain states such as FMS than treatments such as nonsteroidal anti-inflammatory drugs, opioids, and surgery that work well for acute and "peripheral" pain. The article also presents a recommended approach to the treatment of FMS and its associated comorbidities.

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Effective treatment of any chronic pain syndrome is dependent on identifying the underlying mechanism(s) responsible for the pain, and choosing therapeutic modalities that target the mechanism(s) and the neurotransmitters and other factors involved in augmenting or reducing the pain response.

In the case of fibromyalgia syndrome (FMS), this would include pharmacologic agents that reduce levels of neurotransmitters known to increase pain and sensory processing or raise levels of neurotransmitters known to inhibit pain and sensory processing. It would also include nonpharmacologic interventions to reduce pain and other somatic symptoms.

Before examining specific therapeutic options, however, it would be helpful to review the paradigm shift in FMS as we come to understand the genetic and environmental factors that are operative in leading to augmented central nervous system processing of pain, and to a "central" pain state.

PARADIGM SHIFT

The publication of the American College of Rheumatology criteria for FMS in 1990[1] is considered by many to mark the beginning of a major paradigm shift. The criteria, which were never intended to be used as a diagnostic tool in clinical practice, established a standardized case definition of FMS and enabled researchers to move forward. In fact, nearly all of the scientific data supporting FMS as a disorder of central pain processing have been collected since 1990.

Fibromyalgia syndrome was once thought of as a discrete disease, much like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), but characterized by chronic widespread pain and tenderness, and accompanied by psychological and behavioral factors. However, although it is still considered by some to be a discrete disease or illness, it may be more useful to consider FMS as a "final common pathway" as

well, with pain augmentation occurring via spinal and brain mechanisms, as it does in many other chronic pain states.

The paradigm shift has changed the way researchers and clinicians think of pain. Unlike the historical view that chronic pain was simply acute pain that lasted too long, the contemporary view recognizes that chronic pain can originate from 3 different sources and that any combination of these sources may be present in a given individual (Figure 1). It also recognizes that the mechanisms that underlie chronic pain are markedly different from the mechanisms that underlie acute pain, and that chronic pain originating from each of the 3 sources respond to entirely different treatments.

In reality, it should come as no surprise that in some individuals, chronic pain might not be occurring solely because of damage or inflammation of peripheral tissues. In fact, there is no chronic pain state that shows a strong relationship between what can be identified in the peripheral tissues and how much pain the patient is experiencing. For example, population-based studies have shown that 30% to 40% of patients with osteoarthritis (OA) of the knee who have radiographic and magnetic resonance imaging (MRI) evidence of severe joint damage have absolutely no pain, whereas 10% to 20% with severe knee pain have normal X rays and MRI scans.[2] Conversely, only approximately 30% of patients with diabetic peripheral neuropathy have pain, while the remaining 70% actually have hypoalgesia, or reduced sensation, rather than hyperalgesia.[3]

What is important to bear in mind is that chronic pain is a complex experience and that central factors that are front and foremost in FMS, such as augmented pain and sensory processing, also play significant roles in subsets of individuals with any chronic pain state.

Influence of Genetics

Genetic factors play an important role in pain, pain sensitivity, and pain processing. They explain, in part, why some individuals are more sensitive to pain than others and why some are more likely to develop FMS as well as a variety of different chronic pain states and psychiatric disorders.

Although chronic pain states frequently overlap with each other as well as with psychiatric and mood disorders, population-based twin studies have clearly demonstrated that pain and depression or anxiety are clearly separable and have different underlying biological processes.[4,5] It is likely that the observed overlap between individuals with one type of chronic pain and another occurs because the underlying mechanisms of any chronic pain state are similar. In contrast, the reason for the overlap between pain and psychiatric disorders is likely that some neurotransmitters, such as serotonin and norepinephrine, are involved, albeit in different brain regions, in pain and sensory processing, as well as in modulating mood.

These overlaps have also been shown in FMS, where first-degree relatives of patients with FMS have an 8-fold risk of developing FMS and other chronic pain states, and are much more likely to have increased sensitivity to touch (tenderness) than relatives of controls.[6] First-degree relatives are also nearly twice as likely to have a major mood disorder, suggesting that FMS and mood disorders may share some of the genetic factors involved in pain sensitivity.

Humans and animals have a "volume control" setting that determines how the brain and spinal cord process pain and other sensory information. It appears that volume control is set by genes and modified by neurohormonal factors and neural plasticity.[7] The higher the setting, the greater the pain sensitivity, irre-

Figure 1. Mechanistic Characterization of Pain

Any combination may be present in a given individual.

Peripheral (Nociceptive)	Neuropathic	Central (Non-nociceptive)
• Inflammation or mechanical damage in tissues • NSAID, opioid-responsive • Responds to procedures • Classic examples – Osteoarthritis – Rheumatoid arthritis – Cancer pain	• Damage or entrapment of peripheral nerves • Responds to both peripheral (NSAIDs, opioids, and Na^+ channel blockers) and central (TCAs and neuroactive compounds) pharmacologic therapy • Classic examples – Diabetic neuropathic pain – Postherpetic neuralgia	• Characterized by central disturbance in pain processing (diffuse hyperalgesia) • Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission • Classic examples – Fibromyalgia – IBS – Tension headache – Idiopathic low back pain

IBS = irritable bowel syndrome; NSAID = nonsteroidal anti-inflammatory drug; TCA = tricyclic antidepressant.

spective of peripheral nociceptive input. The clinical result of increased volume control is diffuse hyperalgesia or allodynia.

Data from studies of twins and other investigations suggest that approximately 50% of an individual's pain sensitivity is predicted by his or her genes and approximately 50% by his or her environment.[4,7] Thus far, 3 sets of genes have been shown to predict a substantial amount of variance in human pain sensitivity: genes involving sodium channels; genes involving catechol methyltransferase, or CMT, the enzyme that breaks down catecholamines; and genes involving GTP cyclohydrolase, an enzyme involved in serotonin and norepinephrine metabolism.

From Mechanism to Treatment

The primary objective of treatment for FMS and other chronic central pain states is to modulate the augmented pain response by targeting the neurotransmitters involved in increasing or decreasing the volume control setting.

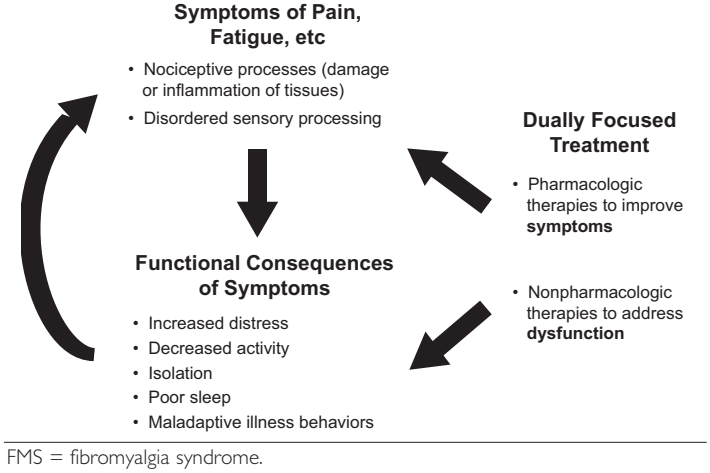
Elevated levels of substance P, glutamate and other excitatory amino acids, and nerve growth factor in the cerebrospinal fluid (CSF) *increase* pain transmission.[8-12] In contrast, elevated CSF levels of norepinephrine, serotonin, dopamine acting via descending analgesic pathways, opioids, γ-aminobutyric acid (GABA), cannabinoids, and adenosine typically *decrease* the volume control setting.[13] In FMS, hyperalgesia or allodynia is characterized by high CSF levels of some or all of the pain-facilitating neurotransmitters and/or low CSF levels of some or all of the pain-inhibiting neurotransmitters. Thus, reducing the levels of facilitating neurotransmitters and increasing the levels of inhibitory neurotransmitters should modulate the augmented pain response, but one of the problems in clinical practice is that there are no antagonists or agonists for most of these neurotransmitters.

The only neurotransmitter system studied to date in FMS that is abnormal in a direction that would cause hyperalgesia is the opioid system, which appears to be already maximally activated in FMS. This may explain why exogenous opioids are largely ineffective in central pain states compared with peripheral pain states.[14] In addition, serotonin can either increase or decrease the volume control setting, depending on which serotonin receptor it binds to, although it appears to play a stronger role in pain inhibition than in pain facilitation.[15]

Fibromyalgia syndrome and other central pain states are associated with neurobiological factors, including abnormal sensory processing, dysfunction of the autonomic nervous system and hypothalamic-pituitary-adrenal axis, and possibly peripheral nociceptive input, as well as psychosocial factors, such as general "distress," maladaptive illness behaviors, and secondary gain issues.[16] All of these need to be addressed when choosing treatment, as do the functional consequences of pain and associated symptoms (Figure 2).[17]

Treatment of FMS and other central pain syndromes employs 4 different modalities: education, pharmacologic therapy, aerobic exercise, and cognitive-behavioral therapy (CBT). Pharmacologic agents for FMS must target the central factors that play a critical role in this syndrome, which is primarily a neural disease. Drugs and injections aimed at the periphery are not particularly efficacious. Moreover, because FMS is a polygenic disorder, there will be subgroups of patients with FMS needing different treatments. And because there is a deficiency of noradrenergic/serotonergic activity and/or elevated levels of excitatory neurotransmitters in patients with FMS, drugs that raise levels of

Figure 2. Dually Focused Treatment of FMS Symptoms and Dysfunction



FMS = fibromyalgia syndrome.
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norepinephrine and serotonin or lower levels of excitatory neurotransmitters will be efficacious in some.

Exercise, sleep hygiene, and other behavioral interventions are effective in FMS for biological reasons, as lack of sleep or exercise increases pain and other somatic symptoms, even in those without FMS. Similarly, cognitive therapies, which have a biological substrate, are effective in FMS because they help patients recognize that how they think about their pain may directly influence pain levels.

Pharmacologic Therapies

Many pharmacologic agents have been used to treat FMS, with strong evidence to support the efficacy of some and lesser degrees of evidence to support the efficacy of others (Figure 3).[18] Among the drug classes with strong evidence of efficacy, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) raise norepinephrine and serotonin levels, while α-2-δ ligand anticonvulsants (pregabalin and gabapentin) likely work, at least in part, by inhibiting release of substance P and glutamate. Many patients with chronic pain, particularly those with FMS, are treated with all 3 of these drug classes—typically a low-dose TCA at bedtime, an SNRI during the day, and pregabalin or gabapentin once a day (at bedtime, to take advantage of their sedative properties) or twice a day (morning and bedtime).

Antidepressants are often categorized as serotonergic, noradrenergic, or mixed, with recommended doses of serotonergic agents exerting antidepressant effects and recommended doses of mixed and noradrenergic agents exerting analgesic/antidepressant effects.[19] At higher doses, however, serotonergic agents such as the selective serotonin reuptake inhibitors (SSRIs) sertraline, paroxetine, and fluoxetine become more adrenergic and can produce analgesic effects in both humans and animals. Duloxetine and venlafaxine are mixed agents with slightly more serotonergic activity, and milnacipran, nortriptyline, and imipramine are mixed agents with slightly more noradrenergic activity. Desipramine, maprotiline, and reboxetine are predominantly noradrenergic. Although nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are effective and very commonly used to treat nociceptive pain, there is no evidence to support their efficacy in treating central pain and FMS.[18] Yet both classes of drugs are often prescribed for FMS, and both classes are associated with adverse effects—namely, NSAID-induced gastrointestinal problems and opioid-induced hyperalgesia.

Nonpharmacologic Therapies

Of the numerous nonpharmacologic therapies for FMS, only 3 have strong evidence to support their effectiveness: education, aerobic exercise, and CBT.[18] There is modest evidence for strength training, hypnotherapy, biofeedback, and balneotherapy, and weak evidence for acupuncture, chiropractic therapy, manual and massage therapy, electrotherapy, and ultrasound. Nevertheless, many patients with FMS are willing to pay out-of-pocket for these therapies. There is no evidence supporting the efficacy of tender-point (trigger-point) therapy.

Aerobic exercise is almost always beneficial in patients with FMS. The major limiting factors are tolerance, stamina, and compliance with the exercise regimen. To maximize the benefits of aerobic exercise, both the physician and the patient should consider it a "drug" for FMS. The exercise program should be started several months after pharmacologic therapy has been initiated, and it should begin with low-impact exercises. Strength training can be added later on.

Figure 3. Pharmacologic Therapies for FMS

Strong Evidence	• Dual reuptake inhibitors such as – Tricyclic compounds (amitriptyline and cyclobenzaprine) – SNRIs and NSRIs (milnacipran, duloxetine, and venlafaxine ?)
Modest Evidence	• Tramadol • SSRIs • γ-hydroxybutyrate • Dopamine agonists
Weak Evidence	• Growth hormone, 5-hydroxytryptamine, tropisetron, and SAMe
No Evidence	• Opioids, corticosteroids, NSAIDs, benzodiazepine and nonbenzodiazepine hypnotics, and guaifenesin

NSAID = nonsteroidal anti-inflammatory drug; NSRI = norepinephrine-serotinin reuptake inhibitor; SAMe = S-adenosyl-L-methionine; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
Modified from Goldenberg et al. *JAMA*. 2004;292:2388-2239.[18]

A Cochrane review of the effects of exercise training on patients with FMS found that aerobic exercise has beneficial effects on physical capacity and FMS symptoms.[20] The review also found that strength training may have salutary effects on some FMS symptoms.

Cognitive-behavioral therapy is effective for virtually all chronic medical illnesses. It is, in essence, education in that it teaches patients how to reduce symptom intensity and stress, develop coping strategies, and identify and eliminate maladaptive behaviors. It is important to note, however, that CBT programs vary and are very dependent on the program, the content, and the therapist. For example, a pain CBT program is very different from an insomnia CBT program, and both are very different from a depression CBT program.

The effectiveness of CBT was demonstrated in a study of patients with FMS who were randomly assigned to standard medical care or standard care plus 6 sessions of CBT aimed at improving physical functioning.[21] Standard care included pharmacologic therapy and suggestions for aerobic fitness. At 1 year, 25% of patients receiving standard care plus CBT achieved clinically meaningful levels of long-term improvement in physical functioning versus 12% of those receiving standard care alone.

Recommended Approach to Treatment

A recommended approach to treatment of FMS is summarized in the Table.[17] As with all chronic illnesses, patient education is the logical first step of any treatment regimen. Education should include an explanation of FMS, suggestions for how to cope with it, and printed materials with a list of resources to contact for additional information.

It is important to identify and treat peripheral pain generators (eg, OA of the knee) because they can lead to regional and central sensitization if left untreated. In this instance, it is reasonable to use an NSAID because it is directed at relieving the pain of OA, not at treating FMS.

Many physicians initiate therapy of FMS with a TCA, but many others start with an SNRI or an α-2-δ ligand instead. Choosing between the latter 2 drug classes, either as first- or second-line therapy, depends on the patient's most prominent symptoms. A mixed or dual reuptake inhibitor such as duloxetine, milnacipran, or perhaps even venlafaxine will be more effective in patients with comorbid depression, memory problems, and/or fatigue. Increasing the dose of an SSRI such as fluoxetine, paroxetine, or sertraline above the doses often used for depression (eg, to 40–50 mg of fluoxetine) increases the drug's noradrenergic activity and analgesic effects, and is also an option, particularly in patients who are doing well on SSRIs with respect to depression, but who need more analgesia. In contrast, pregabalin or gabapentin might be more appropriate initial therapy for patients whose most prominent symptom is a sleep disturbance. Once-a-day dosing at bedtime is recommended for patients who cannot tolerate a split dose because of daytime "fogginess."

Before starting therapy with a dual reuptake inhibitor, it is important to tell patients that these drugs may be associated with severe nausea for the first 7 to 10 days. Patients who are thus informed are more likely to continue treatment and give the drug an adequate therapeutic trial. Starting with a low dose, increasing it slowly, and advising the patient to take the

Table. Recommended Approach to Treatment of FMS

- Education
- Identify and treat "peripheral" pain generators
- For patients who need or want medications, start with low doses of a mixed tricyclic antidepressant (eg, amitriptyline or cyclobenzaprine); start low, go slow
- If patient has depression, memory problems, fatigue as most prominent symptoms:
  - Add a mixed reuptake inhibitor (eg, duloxetine, milnacipran, or venlafaxine) or a selective serotonin reuptake inhibitor (may need high doses)
- If patient has sleep disturbance as most prominent symptom:
  - Use pregabalin or gabapentin first; give higher percentage of dose at night
- If no response, consider use of a dopamine agonist or sodium oxybate
- For additional analgesic effect, add tramadol, tizanidine, opioids
- For sleep, use zolpidem, zaleplon, trazodone if patient does not tolerate a tricyclic antidepressant
- Aggressively introduce nonpharmacologic therapies

FMS = fibromyalgia syndrome.
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drug with food are all helpful in reducing the nausea.

Tramadol, tizanidine, or opioids can be added if more analgesia is needed, and zolpidem, zaleplon, or trazodone can be used to improve sleep in patients who do not tolerate TCAs. However, because these latter 3 agents do not share the analgesic properties of TCAs or of the α-2-δ ligands, they typically improve sleep, but do not alleviate other symptoms.

The use of nonpharmacologic modalities is a key component in the treatment of FMS, and any other chronic pain state. The underuse or delayed use of these nonpharmacologic therapies may be one of the biggest problems in chronic pain management. These therapies have been shown to be at least as effective as drugs at reducing pain and symptoms, and are often more effective than drugs at improving function. Both exercise and CBT might be best begun after pharmacotherapy has had a chance to reduce pain and fatigue.

Conclusions

The paradigm shift over the past 2 decades has changed the way physicians and researchers think of pain. The contemporary view recognizes that the mechanisms underlying chronic pain are markedly different from the mechanisms that underlie acute pain, and that chronic pain originating from peripheral, neuropathic, and central sources responds to largely different treatments.

Genetic factors explain, in part, why FMS and other chronic pain states frequently overlap with each other and with psychiatric disorders. Moreover, the volume control setting that determines how the brain and spinal cord process pain and other sensory information also appears to be strongly influenced by genetics.

The goal of FMS treatment is to modulate the augmented pain response by targeting the neurotransmitters involved in increasing or decreasing the volume control setting. Therapy should therefore be aimed at reducing the levels of neurotransmitters that facilitate pain transmission and raising the levels of neurotransmitters that inhibit pain transmission.

As a central pain state, FMS responds poorly, if at all, to treatments aimed at the periphery. Drugs that raise norepinephrine and serotonin levels or reduce levels of excitatory neurotransmitters will be effective in some patients.

Education, aerobic exercise, and CBT are essential components of FMS treatment and should not be underused.

Case Study

Presentation and History

The patient is a 45-year-old white male who says he feels like he's been "run over by a truck," and complains of diffuse pain that began approximately 3 years ago following a motor vehicle collision. He also complains of insomnia and fatigue.

He is a school teacher and is married. He has a history of arthritis in the neck and back, and has undergone multiple lumbar spine surgeries that failed to alleviate his pain. His mother and grandmother have a lifelong history of severe "arthritis," and his 14-year-old daughter has irritable bowel syndrome.

Physical Examination and Diagnostic Evaluation

A review of systems is positive for dry eyes, headaches, memory difficulties, diarrhea, and mild depressive symptoms without anhedonia. He would like to participate in sports and other activities but cannot because of pain and fatigue.

Physical examination is unremarkable except for diffuse soft tissue tenderness. Standard laboratory test results are also unremarkable. Radiographs and an MRI of the cervical and lumbar spine show postsurgical changes, mild degenerative changes, and a bulging disc at L4-5 without foraminal impingement.

His medications include naproxen twice daily and oxycodone with acetaminophen, approximately 3 to 4 tablets a day. He does not find these medications very effective.

The patient's major complaint—that he feels like he's been run over by a truck—strongly suggests FMS. Any patient who describes his or her pain this way, or says "I hurt all over" or "I feel like I have flu all the time," has FMS until proven otherwise.

Testing for antinuclear antibody and rheumatoid factor is of little value unless there are specific symptoms that suggest RA or SLE. Similarly, ordering tests to determine the erythrocyte sedimentation rate and levels of C-reactive protein and thyroid-stimulating hormone is also of little value in patients whose symptoms have lasted years or decades. However, these tests might be useful in patients whose symptoms or examination findings (eg, joint swelling) suggest an inflammatory problem.

TREATMENT

Although this patient has mild depressive symptoms and memory difficulties, his most prominent comorbidity is insomnia. He was therefore started on pregabalin, 50 mg in the morning and 100 mg at bedtime, and told to increase the dose slowly, up to a maximum of 450 mg/day (with two-thirds of the dose to be taken at bedtime) as tolerated. He reported a slight reduction in pain at the initial dose, and a modest improvement in sleep, but no adverse side effects. His pregabalin dose was increased to 100 mg in the morning and 200 mg at bedtime, which was the highest dose he could take without experiencing side effects. Overall, he felt that the drug reduced his pain by approximately 50% and helped his sleep as well. The addition of milnacipran 50 mg each morning (later increased to 100 mg each morning) led to a further reduction in pain and improvement in his energy level. He was also referred for CBT and a program of aerobic exercise.

CURRENT STATUS

He is currently on this regimen and is doing well.

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