

- Second Messenger -

The Mystery of Fibromyalgia

Part 2: What drugs are effective in treating fibromyalgia and how do they work?

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Issue Pharmacological treatment of fibromyalgia pain is an important aspect of multidisciplinary management of this condition.

Actions Learn the mechanisms of action of pharmacotherapies for fibromyalgia

Benefits Understanding the basis for treatment of fibromyalgia will lift some of the mystique and stigma surrounding this disease and should help the prescriber improve the quality of life of patients with fibromyalgia.

This is the second of a two-part article that addresses some common questions about fibromyalgia. This second installment reviews the current pharmacological treatments for fibromyalgia, describing their mechanism of action and likely efficacy, and how they fit within the holistic treatment approach for patients with fibromyalgia.

Part 1 discussed some of the issues surrounding diagnosis of fibromyalgia, and presented evidence that pain in fibromyalgia is real pain, not "all in the mind." The pain likely arises from inappropriate augmentation of pain transmission at a central site, likely the spinal

cord. This may be due to reduced activity of descending serotonin and norepinephrine pathways.¹

What drugs are effective in treating fibromyalgia?

No pharmacotherapy is yet approved for treating fibromyalgia, but several approaches have reasonable clinical evidence. The first-line choice should be an antidepressant that elevates both 5-HT and NE levels. Duloxetine and milnacipran have good evidence at doses matching or exceeding those prescribed for depression.² There is also good evidence for low-dose tricyclic antidepressants³ and, by

association, mirtazapine (which elevates both 5-HT and NE) should also be effective. Choice should be directed by toleration of side effects and ability to reach a dose that is effective.

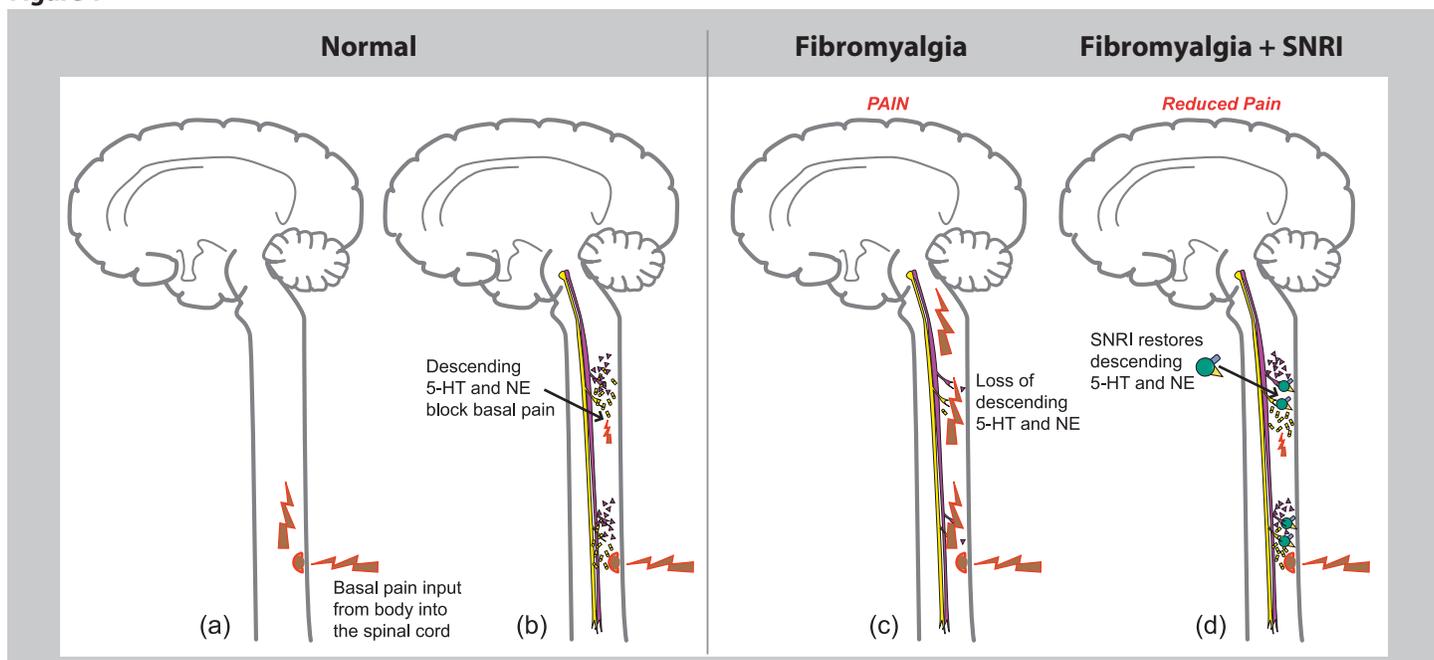
Anticonvulsants are also promising. The most studied drug is pregabalin, which has been shown in randomized controlled trials to reduce pain intensity, as well as improve sleep quality and fatigue.⁴ By analogy, the anticonvulsant gabapentin may also be useful, although it tends to be less well tolerated than pregabalin. Other anticonvulsants may help, but none have been studied in depth.

There is also a place for non-steroidal anti-inflammatory drugs (NSAIDs) and even slow-release opioids, and every patient should be considered individually. Accompanying symptoms should be treated as necessary; for example, short-term courses of hypnotics can help improve sleep and perhaps fatigue.

Mechanism of action: Antidepressants

Duloxetine and milnacipran are serotonin-norepinephrine reuptake inhibitors (SNRIs) and so elevate both 5-HT and NE levels. Most tricyclic antidepressants also elevate 5-HT and NE, as does mirtazapine (by inhibition of α_2 -adrenergic receptors). By elevating levels of 5-HT and NE, which are inhibitory in most instances in the spinal cord, these agents are

Figure 1



(a) Normally, basal pain signals arrive in the spinal cord from the body. (b) Descending serotonin (5-HT) and norepinephrine (NE) pathways inhibit the pain signal, preventing these everyday inputs being detected. (c) In fibromyalgia, the descending 5-HT and NE inhibitions are lost, allowing everyday pain impulses to ascend the spinal cord and be perceived as widespread pain. (d) Treating fibromyalgia with antidepressants that elevate 5-HT and NE (like the SNRIs and tricyclic antidepressants), restores the normal descending 5-HT and NE signals. These inhibit transmission in the pain pathway, reducing the perception of pain.

thought to inhibit transmission between the first neurons in the pain pathway and the spinal cord neurons that project up to higher centers. These agents therefore seem to restore the normal dampening of everyday pain information that is lost when 5-HT and NE levels are low or circuits are malfunctioning (Figure 1).

Although the ability of antidepressants to relieve pain in fibromyalgia seems to be independent of their antidepressant activity,² there is no doubt that relieving any comorbid depression and/or anxiety will help improve function and pain levels in fibromyalgia patients.

Mechanism of action: Gabapentin and pregabalin

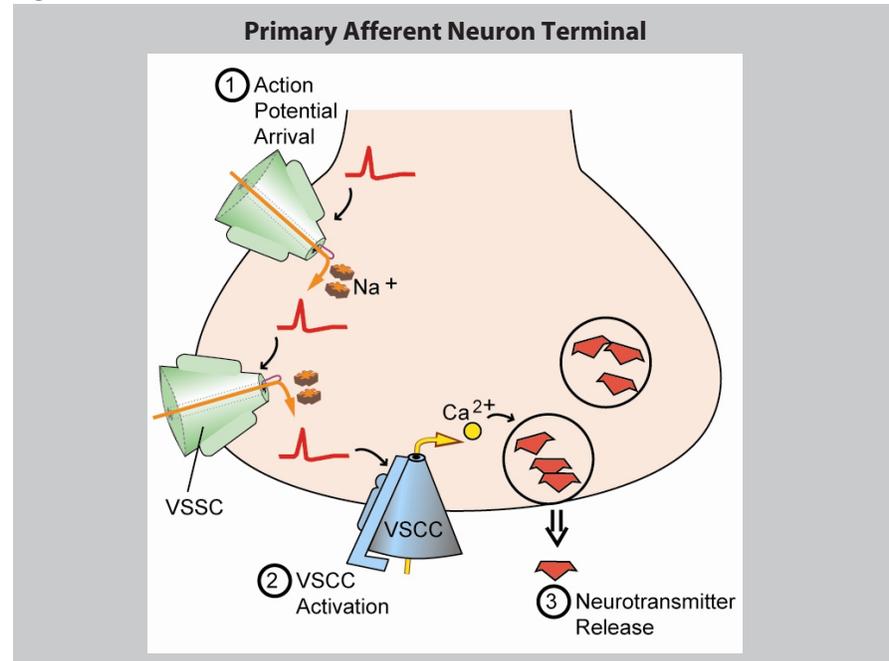
Gabapentin and pregabalin also target neurotransmission in the pain pathway but through a different mechanism. These drugs block a type of calcium channel that is required for synaptic transmission and therefore block neurotransmission of pain signals from nociceptive neurons in the periphery to higher brain centers.

Release of neurotransmitters from nociceptive neurons (and at almost all CNS synapses) depends on N-type and P/Q-type voltage-sensitive calcium channels (VSCCs). These channels are located at presynaptic terminals where they are docked to neurotransmitter vesicles (Figure 2). Normally, when an action potential arrives at the presynaptic terminal it depolarizes the membrane and opens the VSCCs. This allows calcium influx through the channel into the neuron, triggering release of neurotransmitters into the synapse and activation of the postsynaptic projection neuron. Gabapentin and pregabalin are thought to work by binding to a specific subunit of VSCCs, the alpha-2-delta ($\alpha_2\delta$) subunit, thereby blocking the channels and transmission in pain pathways to the brain. For more detail of the mechanism of action of gabapentin and pregabalin, see Carpenter, 2005.⁵

Mechanism of action: NSAIDs

NSAIDs like ibuprofen, aspirin, and sodium naproxen act to inhibit cyclooxygenase (COX) enzymes, thereby reducing the generation of inflammatory and pain-causing mediators like the prostaglandins. Ibuprofen, aspirin, and naproxen are relatively non-selective between the COX subtypes COX-1 and COX-2 and are associated with a risk of gastric ulcers with long-term use. Agents like celecoxib (Celebrex®) and rofecoxib (Vioxx®) are more selective for COX-2, and seem to have the same analgesic properties but with lower risk of gastrointestinal side effects. However,

Figure 2



The release of neurotransmitters at a synapse requires activation of voltage-sensitive calcium channels (VSCCs). (1) Action potentials arriving at the presynaptic neuron depolarize the membrane and activate VSCCs. (2) The channels open to allow calcium influx into the neuron. (3) Calcium influx triggers fusion of vesicles with the membrane and release of neurotransmitter into the synapse. Gabapentin and pregabalin block VSCCs by binding to the alpha-2-delta ($\alpha_2\delta$) subunit. This reduces calcium influx through the channel, thereby inhibiting neurotransmitter release and reducing neurotransmission in pain pathways.

there may be increased risk of cardiovascular side effects, and several COX-2 agents have recently been withdrawn from the market. It is not clear whether use of COX-2-selective agents is justified in fibromyalgia.

Mechanism of action: Opioids

Opioids act by mimicking the body's endogenous painkillers, the endorphins and enkephalins. Descending opioid pathways run from pain processing centers in the brain and brainstem down the spinal cord, and are highly effective at blocking transmission of pain signals when activated. Normally only severe events or injuries trigger the endogenous opioid pathways to inhibit pain signals, but the pathways can be hijacked by administering opioid medications. Opioid drugs bind to and activate the mu (μ) opioid receptor, which is expressed on the presynaptic terminals of pain-sensing fibers (nociceptive C-fibers). This inhibits neurotransmitter release from these neurons, inhibiting neurotransmission in the pain pathway. Common side effects result from activation of mu receptors in other tissues, causing constipation, respiratory depression, euphoria, and sedation/drowsiness. Using a slow-release opioid avoids the peaks and troughs of oral dosing, reducing the severity of side effects and providing more sustained control of pain.

Non-pharmacological treatments

A multidisciplinary approach is crucial in fibromyalgia, and patients benefit from many non-pharmacological approaches. Coping strategies and cognitive-behavioral therapy can help the patient function despite ongoing pain. Education about behavior change can help patients plan and perform daily activities to avoid becoming over-tired. Physical therapy and negative feedback can also help the patient understand and manage the pain. Slow, graded introduction of stretching and gentle exercise can also help reduce pain and fatigue and improve sleep. It is important to consider each patient and their needs individually, and to refer them to colleagues as appropriate.

The bottom line—Fibromyalgia is a real and painful condition that is probably caused by inappropriate augmentation of pain transmission at a central site, likely the spinal cord. This may be due to reduced activity of descending serotonin and norepinephrine pathways. Dual action antidepressants and tricyclic antidepressants are first-line treatments to reduce pain, and gabapentin and pregabalin may also be useful. A holistic approach is crucial in fibromyalgia treatment—education, behavior change, cognitive behavioral therapy, and physical therapy are all important in managing fibromyalgia. ❖

Resources

- 1. Carpenter KJ. PsychEd Up 2005;1(3): 2-3.
- 2. Arnold LM et al. Arthritis Rheum 2004;50:2974-2984.
- 3. Offenbecher M, Ackenheil M. CNS Spectrums 2005;15:285-297.

- 4. Crofford LJ et al. Arthritis Rheum 2005;52:1264-1273.
- 5. Carpenter KJ. PsychEd Up 2005;1(3): 2-3.