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Katherine J. Carpenter

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November 2–6, 2006
Orlando, Florida

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Deconstructing psychiatric disorders to achieve remission
Stephen M. Stahl and Meghan Grady

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PsychEd Poll

How valuable are the following controlled-release products in psychiatric practice? (e.g., Concerta, Effexor XR, Wellbutrin XL)

A. mostly patent extension gimmicks
B. incremental therapeutic advance over the immediate release
C. significant therapeutic advances
D. some are advances, others are gimmicks

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The Mystery of Fibromyalgia

Part 1—Is fibromyalgia real pain, and what causes it?

**Issue** Fibromyalgia is a mysterious condition that can destroy quality of life for its sufferers. Stigma and uncertainty surround the disease, often compromising its diagnosis and rational treatment.

**Actions** Learn the possible biological basis of fibromyalgia.

**Benefits** Understanding the pain pathways underlying fibromyalgia will lift some of the mystique and stigma surrounding this disease and help the prescriber improve the quality of life of patients with fibromyalgia.

Attitudes among clinical practitioners about fibromyalgia range from “it’s all in the mind” to “it’s all in the joints.” That is, that fibromyalgia is a psychosomatic condition that reflects life crises and that it is an autoimmune rheumatoid condition that affects the joints and muscles. The discovery that antidepressants can reduce pain in fibromyalgia seems to suggest that the “all in the mind” theory is correct; that fibromyalgia is caused by depressed mood. In fact, fibromyalgia is not in the mind, but in the brain, caused by aberrant processing in the pain transmission pathway. The antidepressants that are effective treatments target these pain pathways and have effects independent of their antidepressant properties.

This is the first part of a two-part article that addresses some common questions about fibromyalgia. This first installment reviews experts’ current understanding of this painful and destructive condition and its possible biological basis.

**Is fibromyalgia real pain?**
The short answer is “yes.” The longer answer includes evidence from pathological, psychophysical, and imaging studies.

Fibromyalgia has an estimated prevalence of 2% and is more common in women than men. It is diagnosed by a history of widespread pain in all four body segments, and pain in 11 of 18 tender point sites on digital palpation. Although pain is felt in these tender muscle and joint sites, no identifiable pathology has been found here. About one-third of patients with fibromyalgia also meet criteria for major depressive disorder. Anxiety disorders, low self-esteem, difficult family circumstances, and poverty are not uncommon, and patients have often seen many practitioners over many years before arriving at a diagnosis of fibromyalgia. These factors, along with the absence of any identifiable pathology, led many experts to see fibromyalgia’s physical symptoms as psychosomatic manifestations of unconscious conflicts, and sufferers as difficult, malingerers, and catastrophizers.

Reduced activity in descending 5-HT and NE pathways would reduce the inhibitory controls, allowing non useful and uninformative pain signals to get through the “gate.”

However, there is now much evidence that pain in fibromyalgia is very real and associated with measurable changes in pain processing systems: (1) Patients with fibromyalgia perceive a painful stimulus as more painful than healthy controls do, a phenomenon known as “hyperalgesia”; (2) In healthy, pain-free controls, repeated application of a painful stimulus causes a progressive increase in the perceived pain intensity (wind-up pain or central sensitization); this increase is greater in fibromyalgia patients; (3) Imaging studies have shown that when the same painful stimulus is applied, there is increased activity in pain processing brain centers in patients with fibromyalgia compared with normal controls.

These measurable alterations in pain processing support the concept that the pain of fibromyalgia is real, slowly replacing the concept that the pain is psychosomatic.

**What causes it?**
If fibromyalgia is not a psychosomatic illness, and is not caused by damage to muscles or joints, what does cause it? The best explanation we have currently is aberrant processing in the pain pathway. A state of “central sensitization,” seems to exist in patients with fibromyalgia, where pain signals coming in from the periphery to the spinal cord are inappropriately augmented, probably as a result of deficient descending inhibitory controls.

Neurons in the pain pathway run from the periphery (skin, joints, viscera), into the spinal cord, where they synapse with projection neurons that ascend to relay centers like the thalamus, hypothalamus and brainstem nuclei, and from there to higher centers where the location and intensity of pain is deciphered (the somatosensory cortex) and emotional and motivational aspects generated (amygdala, cingulate, and prefrontal cortex). At many points in this pathway, but particularly in the spinal cord, the basic pain signal is open to modulation, both augmentation and inhibition. One important inhibitory pathway is the opioid pathway, which descends from the brainstem to the spinal cord. It is recruited in times of severe physical and physiological stress, acting as an endogenous pain killer when the body needs to function through severe pain. The other major descending inhibitory pathways are the serotonin (5-HT) and norepinephrine (NE) pathways. These seem to be active mostly in basal conditions, damping down transmission of small, everyday noxious events that arise just from normal functioning of the human body.

This “brake” is hypothesized to be lacking in patients with fibromyalgia: reduced activity in descending 5-HT and NE pathways would reduce the inhibitory controls,
allowing nonuseful and uninformative pain signals to get through the "gate" (Figure 1). The increased incoming barrage inappropriately activates processes that are designed to augment pain signals in times of need. A state of "central sensitization" results, giving greater output (from the spinal cord to higher centers) for a given level of input. This explains the observations of hyperalgesia and greater magnitude of wind-up in fibromyalgia patients. Accordingly, levels of 5-HT and NE metabolites in cerebrospinal fluid and serum have been shown to be reduced in fibromyalgia patients, lending more evidence to the theory of insufficient 5-HT and NE.

Psychological aspects are still important in fibromyalgia, and depression and anxiety occur in many patients. These may arise as direct consequences of the ongoing pain, or may even result from the same 5-HT and NE deficiency that could underlie the pain. Physical consequences of unrelenting pain can include muscle wasting and deconditioning; physiological consequences include changes in the hypothalamic–pituitary–adrenal (HPA) axis and reduced immune function; vegetative consequences include poor, unrestorative sleep and insomnia; and the emotional anguish of pain (as well as the long journey to an accurate diagnosis) is likely to have psychological ramifications, leading to depression and anxiety.

Reciprocal interactions likely occur between these circuits, which all use 5-HT and NE as important transmitters. It must not be forgotten that 95% of fibromyalgia sufferers are women, suggesting the existence of a sex difference that predisposes to fibromyalgia.

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. Complicated overlap exists between these pain pathways and other important monoaminergic pathways, possibly underlying problems fibromyalgia patients have with sleep, mood, and anxiety.

References
**Mirtazapine**

Dosing tips and prescribing pearls

**Brands**
- Remeron
  - Generic? Yes

**Class**
- Alpha 2 antagonist; noradrenaline and specific serotonergic agent (NaSSA); dual serotonin and norepinephrine agent; antidepressant

**Dosing Tips**
- Sedation may not worsen as dose increases
- Breaking a 15 mg tablet in half and administering a 7.5 mg dose may actually increase sedation
- Some patients require more than 45 mg daily, including up to 90 mg in difficult patients who tolerate these doses
- If intolerable insomnia, activation, anxiety, agitation, or akathisia occur either upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

**Prescribing Pearls**
- Adding alpha 2 antagonism to agents that block serotonin and/or norepinephrine reuptake may be synergistic for severe depression
- Adding mirtazapine to venlafaxine or SSRIs may reverse drug-induced anxiety and insomnia
- Adding mirtazapine's 5-HT₃ antagonism to venlafaxine or SSRIs may reverse drug-induced nausea, diarrhea, stomach cramps, and gastrointestinal side effects
- Phentermine, bupropion, venlafaxine, SSRIs, or stimulants may mitigate mirtazapine-induced weight gain
- It is less likely that weight gain will occur if it has not occurred by the sixth week of treatment
- Has been demonstrated to have earlier onset of action than SSRIs
- May be preferable in patients requiring concomitant medications because it does not affect the CYP450 system
- Preliminary evidence suggests efficacy as an augmenting agent to haloperidol in treating negative symptoms of schizophrenia
- Anecdotal reports of efficacy in recurrent brief depression
- Mirtazapine-induced weight gain is more likely in women than in men and before menopause rather than after
- May cause sexual dysfunction only infrequently
- Patients can have carryover sedation and intoxicated-like feeling if particularly sensitive to sedative side effects when initiating dosing
- Patients may rarely complain of visual "trails" or after-images on mirtazapine

**Stress-Diathesis Model**

The influence of genetic and environmental interactions upon neurocircuitry and disease is modeled here. The bridge represents the genetic makeup of an individual, with each vertical suspension strut symbolizing a single gene, while the traffic represents environmental influences. If the bridge is intact, then it functions normally and allows various environmental inputs to pass without difficulty.
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Symptoms and Circuits
Deconstructing psychiatric disorders to achieve remission

A new conceptualization of the biological basis of psychiatric disorders has been forming—namely, the idea of “symptoms and circuits.” Rather than diagnose and treat a psychiatric syndrome, clinicians can deconstruct these disorders into symptoms and then match those individual symptoms to hypothetically malfunctioning neuronal circuits.

Our current understanding of the association between certain psychiatric symptoms and brain regions is demonstrated in Tables 1 through 5. In addition, key neurotransmitter projections for brain regions associated with emotionality are shown in Figure 1, while key neurotransmitter projections for brain regions associated with somatic symptoms are shown in Figure 2, those associated with cognition are shown in Figure 3, and those associated with sleep are shown in Figure 4.

Table 1: “Emotional” Brain Centers

<table>
<thead>
<tr>
<th>Brain Area</th>
<th>Associated Symptom(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial prefrontal cortex</td>
<td>Depressed mood, guilt, feeling worthless, suicidality</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Depressed mood, guilt, feeling worthless, suicidality</td>
</tr>
<tr>
<td>Orbital prefrontal cortex</td>
<td>Depressed mood, guilt, feeling worthless, suicidality</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Guilt, feeling worthless, suicidality</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>Loss of pleasure, feeling worthless, guilt, suicidality</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Loss of pleasure</td>
</tr>
</tbody>
</table>

Figure 1. Projections to “Emotional” Brain Centers

Figure 2. Projections to “Somatic” Brain/CNS Centers

Figure 3: Projections to “Cognitive” Brain Centers

Figure 4: Projections to “Sleep” Brain Centers
The Bottom Line—The concept of symptoms and circuits may have implications beyond helping to explain the biological basis of symptoms in psychiatric disorders. It may also allow clinicians to base treatment on the specific symptom profile of each patient, rather than select the same treatment for every patient with a particular disorder, since symptoms are associated with divergent parts of the brain and different neurotransmitters project to each of those brain regions. Ultimately, this may optimize the chances of achieving remission of all symptoms and improve patient outcomes.

References
5. Sala et al. Eur Neuropsychopharmacol 2004;14(5); 393-405