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Understanding the Fibromyalgia Syndrome

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Abstract and Introduction

Abstract

The fibromyalgia syndrome (FMS) is the most frequent cause of chronic, widespread pain. This review, which is targeted at the psychiatry and psychopharmacology communities, summarizes the state-of-the-art as it relates to both the pathophysiology and treatment of FMS. Toward this end, the anatomy and physiology of pain pathways are summarized, followed by a review of the altered biology of pain processing, neurotransmitter function, and neuroendocrine systems in FMS. The categories of current drugs employed to treat the disorder are detailed, along with a critical review of the literature supporting such use.

Introduction

The fibromyalgia syndrome (FMS) is the most frequent cause of chronic, widespread pain, with estimates of world-wide prevalence ranging from 0.5 to 5.0%.[1,2] FMS is second only to osteoarthritis (OA) as the most common diagnosis among patients seen in rheumatology offices, and it is diagnosed approximately 4 times more frequently in women than in men. There are presently no diagnostic tests for fibromyalgia. Rather, the accepted diagnostic criteria require that spontaneous pain be present for over 3 months duration along the spine and in all four quadrants of the body, and pain upon digital palpation must be elicited at 11 out of 18 "tender points" (Figure 1).[3] It should be appreciated that a number of treatable and/or life-threatening conditions may present with symptoms that resemble those of FMS, and these obviously need to be excluded before a definitive diagnosis is made.[4]

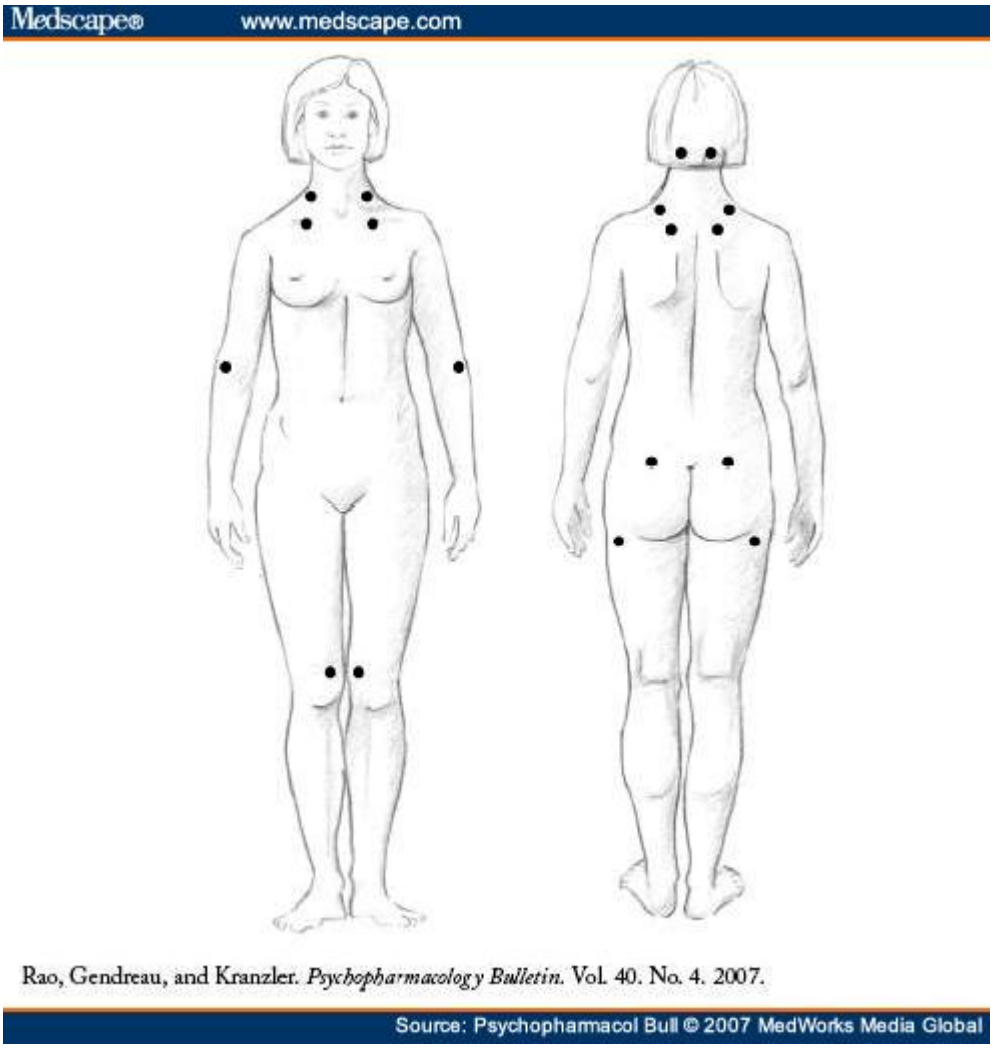

Figure 1.

Fibromyalgia Tender Points

Patients with FMS display quantitative abnormalities in pain perception under experimental conditions, in the form of both allodynia-perceiving pain even from a non-painful stimulus, such as light touch-and hyperalgesia-an augmentation of pain processing in which a painful stimulus is magnified and perceived with higher intensity than it would be by a normal volunteer.[5-10] These data are suggestive of a state of sensitized pain perception in FMS.[8,11] In theory, such a state can conceptually result from widespread changes within the target organs (i.e., skin, muscles, etc.), from alterations in nociceptive processing within the central nervous system, or some combination of both processes. Indeed, some early theories of FMS pathophysiology posited that FMS pain was a result of peripheral abnormalities, particularly alterations in skeletal muscle.[12] However, more recent studies have generally failed to confirm the presence of such alterations,[12-15] though it is recognized that peripheral insults may play a role in instigating or maintaining FMS.[11,16] On the other hand, several lines of inquiry support the role of altered central pain processing (ie, "central sensitization") as underlying the pain of FMS, as will be discussed in detail below.

Though not reflected in the diagnostic criteria, FMS patients typically present with a number of symptoms beyond pain. Fatigue is cited as a significant cause of morbidity for the vast majority of FMS patients.[17] Subjective sleep disturbances, particularly in the form of non restorative sleep, are reported to occur in over three-quarters of FMS patients.[18] A majority of patients complain of difficulties with concentration and memory, a situation that has been termed "fibro fog."[19] Approximately 20-40% of individuals with FMS have an identifiable current mood disorder such as depression or anxiety disorder at the time of diagnosis, with a lifetime incidence as high as 70%.[20-23] Taken on the whole, FMS can result in severe disability, comparable to that seen in other rheumatic diseases such as OA or rheumatoid arthritis, despite the absence of "objective" findings.[24,25]

FMS has been included as one of the so-called "unexplained clinical conditions"[26,27] or "functional somatic syndromes"[28,29] that are characterized more by symptoms, suffering, and disability than by consistent tissue abnormality. As such, there have been suggestions that FMS and other related syndromes may represent a form of somatization disorder.[30] Nonetheless, FMS is treated today primarily within the medical model. It is most often diagnosed in the primary care setting and almost half of the office visits are to internal medicine and family practitioners 1998 National Ambulatory Medical Care Survey.[31] Rheumatologists are the leading specialty group seeing FMS patients, representing 16% of office visits. The remainder of office visits are to a variety of tertiary care providers, including pain centers, physical medicine specialists, and psychiatrists.

FMS remains a controversial diagnosis almost 15 years after the establishment of the diagnostic criteria. Some authors express concern that placing the label of FMS on these individuals promotes helplessness and disability.[32-34] Others focus on the legal and social consequences of identifying FMS as a disorder that can be caused by certain exposures (eg, motor vehicle accidents), thus promoting litigation.[35] Others question the validity of the criteria for diagnosis, especially the requirement for a certain number of tender points.[36,37]

Overview

This paper is intended as follow-up to a previous review by the same authors,[38] detailing some of the changes in the FMS landscape that have occurred in the intervening 2 years. Overall, FMS has attracted a great deal of attention recently, both within the lay and scientific press. The overall validity of FMS as a therapeutic indication has been augmented by the FDA's recognition of the significant unmet medical need that FMS represents.[39,40] This need has also lead to interest in FMS on the part of pharmaceutical companies; indeed, the results of several relatively large, well-controlled industry-sponsored clinical trials have recently been published and will be detailed below.

Like the predecessor publication , the primary goal of the current article is to provide a summary of the state-of-the art pertaining to FMS, with psychiatrists as the target audience,focusing primarily its pathophysiology and current therapeutic options . Historically, pain has not been the typical purview of psychiatrists , despite the fact that a relationship between pain and affective disorders has been known to exist for sometime.[41] However, this connection has come under increasing scrutiny lately.[42,43] Of particular relevance to the practicing psychiatrist is the finding that over 50% of patients that are ultimately diagnosed with depression present initially only with asomaticsymptoms.[44] Further more, the inadequate treatment of pain makes the task of treating comorbid depression much more challenging.[45] Conversely, it should be noted that cognitive behavioral therapy has been used successfully in some patients with FMS and other related chronic pain conditions , even in the absence of an overt affective disorder.[27,46-48]

The body of the review will be divided into three parts: First, as FMS is a clinical demonstration of the existing links between pain sensation, the stress response, and mood, we briefly describe the neuroanatomy, pharmacology, and connectivity of the relevant pathways. Second, we review the

neurochemical and neuroendocrinological differences that exist in FMS patients and compare these observations to other conditions where appropriate. Finally, we summarize the literature on the effectiveness of drugs in treating FMS and will try, where possible, to tie the empirical findings back to both normal physiology and FMS pathophysiology.

Pain Pathways: Review

It has been recognized for some time that nociception is not a passive, uni-directional process;[49] rather, there is a complex interaction between ascending and descending pathways with the ability to dramatically alter the relationship between stimulus and response (see Figure 2).[50] Nociceptive input from the periphery is relayed via peripheral afferent fibers (PAF) to the dorsal horn of the spinal cord. After significant local processing, signals are sent to higher centers, and these impulses form the basis for pain perception. The two major descending pain-modulating systems employ the neurotransmitters serotonin (5-HT) and norepinephrine (NE), and originate from the rostral ventromedial medulla (RVM) and the dorsolateral pontine catecholamine cell groups (DLP), respectively. At the level of the spinal cord , the projections from the RVM appear to have both pro- and anti-nociceptive effects, while the pontine projections appear to be mainly anti-nociceptive. These two systems are tightly interconnected,[51] and their respective anti-nociceptive effects appear to be additive under some circumstances.[52]

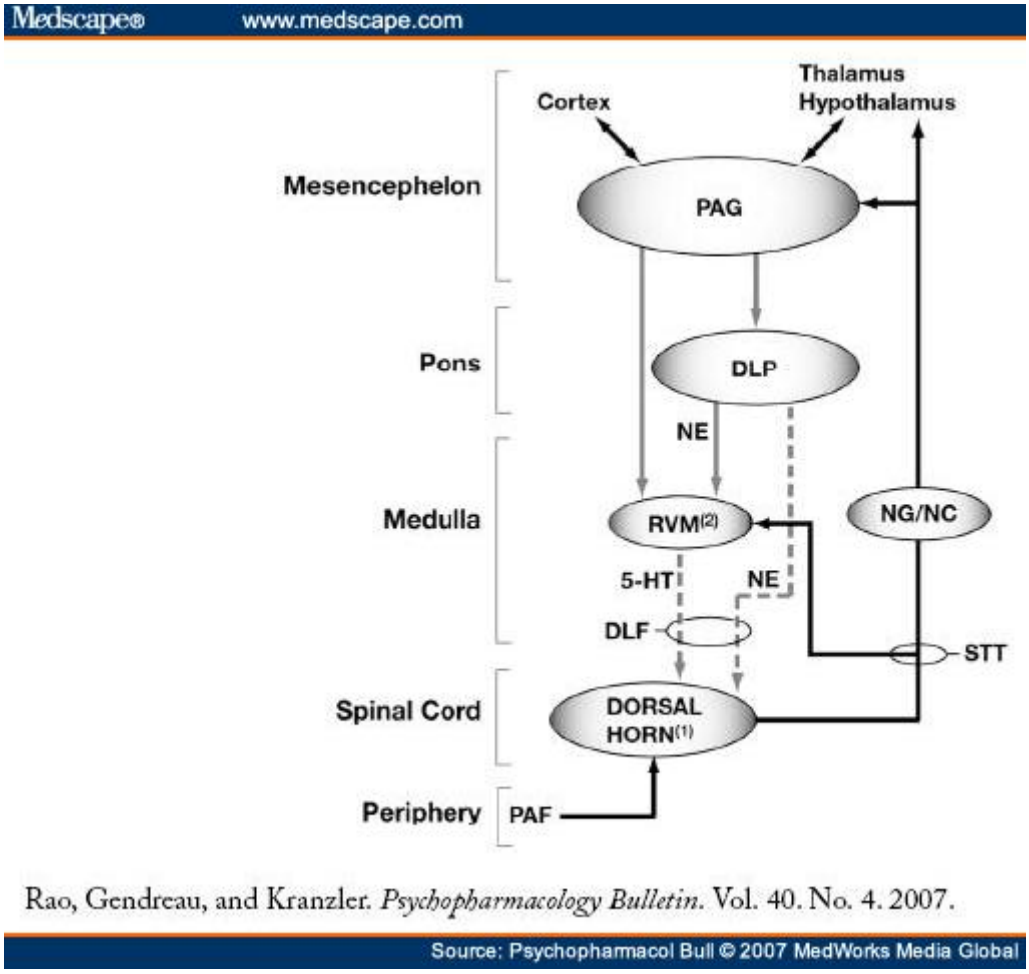

Figure 2.

The Ascending and Descending Pain Pathways

As shown in Figure 3, the main excitatory transmitter from the PAF to the dorsal horn neuron is glutamate (Glu) acting at several postsynaptic receptors, including those of the NMDA variety. In addition, neurokinins including substance P (SP), calcitonin gene related peptide (CGRP) and neurokinin A (NKA) are co-localized with Glu. The descending pathways from the RVM and DLP carrying 5-HT and NE, respectively, modulate the activity of the PAF terminals. For example, NE acting at $_{2}$ receptors can inhibit the PAF terminal and cause a reduction in glutamate and SP release, and a similar effect can be observed with activation of muopioid receptors located on the PAF terminals. Conversely, 5-HT acting at 5-HT_3 receptors can increase the release of these neurotransmitters. Finally, increasing local 5-HT concentrations or a 2 mediated neurotransmission within the RVM itself has been shown to be anti-nociceptive.[53-54]

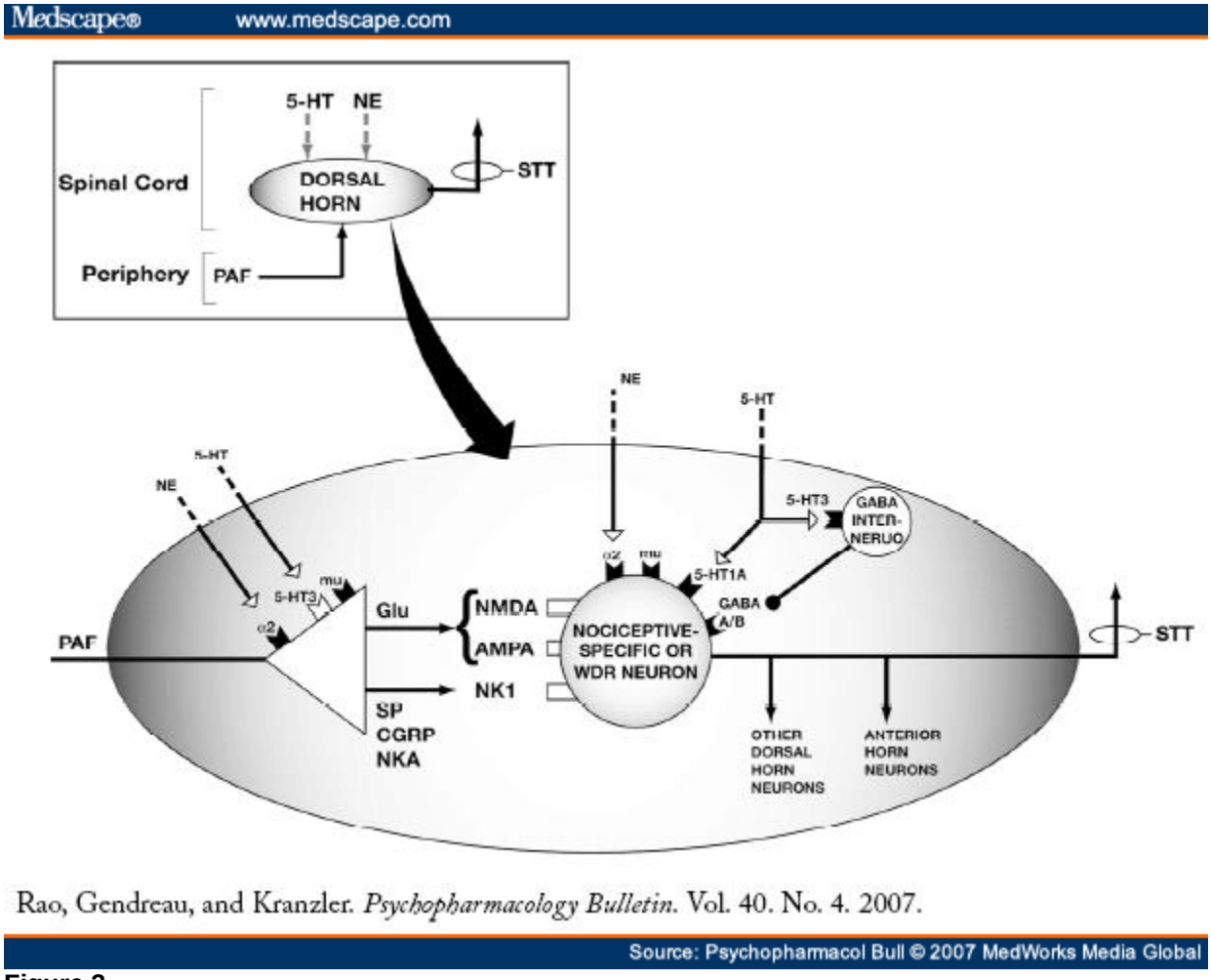

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Figure 3.

The Dorsal Horn

The dorsal horn neuron is also subject to NE, 5-HT, and opiate input, acting respectively at $_{2}$, 5-HT_{1A}, and muopioid receptors. Note that all of these receptors are predominantly inhibitory, and while 5-HT has excitatory effects on the PAF terminals, it can inhibit the dorsal horn both directly (via 5-HT_{1A} activation) or indirectly (through activation of a GABAergic interneuron).

Chronic Pain: Changes in Nociceptive Processing

Over the past decade, it has been recognized that chronic pain is quite different from acute pain, clinically and pharmacologically.[55] As described below, a number of alterations occurring both within the central nervous system and at the periphery may contribute to the chronic pain state. One can envision that disabling one or more anti-nociceptive pathways or augmenting a pro-nociceptive pathway can lead to a state of central sensitization. "Wind-up" is an example of this phenomenon which occurs at the PAF-dorsal horn neuron synapse. The term refers to a specific pattern of augmentation in the response to a dorsal horn neuron that results from tonic, peripheral nociceptive input. Such augmentation is thought to underlie certain components of allodynia and hyperalgesia.[56-58] A number of studies suggest that NMDA and NK1 receptor activation represents critical steps in initiating "windup" and related phenomena in dorsal horn neurons.[56,59-66]

The descending systems may also play a role in central sensitization. For example, recent studies have demonstrated that reduced spinal NE outflow from the DLP results in a chronichyperalgesic state in laboratory animals.[66] Likewise, a significant body of research has implicated the RVM in maintaining the hyperalgesic state. For example, inactivation of the RVM (by lesion, injection of lidocaine, or spinal transection) can reverse the all odynia and hyperalgesia seen in animal models of chronicpain.[67] Further, the application of cholecystokinin (CCK-B) receptor antagonists reverses the mechanical all odynia seen in animal models of chronic neuropathic pain.[68] Finally, in addition to its role within the dorsal horn in initiating wind-up, direct injection of NMDA antagonists into the RVM reverses the hyperalgesia present in several chronic pain paradigms,[70-71] suggesting that NMDA receptors at the level of the RVM may also play a role in maintaining a hyperalgesic state.

Laboratory Findings In FMS Patients

Like many psychiatric diseases, the study of FMS is hampered today by the lack of well-validated animal models that can serve as proxies for study of the human condition, although it should be noted that significant strides are being made toward this end.[72-73] Nonetheless, based on an understanding of normal physiology, and armed with clues from similar diseases in humans, much insight can be gained from monitoring the status of biochemical pathways or physiological processes that may be affected by the disease process. A focus on the former, such as measurement of a neurotransmitter level in cerebrospinal fluid (CSF), facilitates the design of experiments that are relatively simple and easy to control, with the outcome potentially providing a target for drug discovery. However, the result from any single analysis may be difficult to interpret, as it may represent only one piece of a complex and dynamic puzzle at a single point in time. In contrast, tests of physiological function, such as brain imaging or sleep monitoring, provide a more integrative perspective. However, the data obtained may be of less practical use for the discovery or development of pharmaceutical compounds.

While there are hundreds of papers in the literature attempting to identify quantifiable, objective, and meaningful biological differences in FMS patients, many are designed as "pilot" studies lacking sufficient power or controls to be conclusive. Therefore, we will limit our focus in this review to findings that have achieved a critical mass of published data and which may be of interest to the psychiatric community. On the biochemical side, we will summarize the changes in neurotransmitter function and neuroendocrine status in FMS patients. Thereafter, we will review the data garnered in more "functional" assays, including sleep lab and brain imaging analyses.

Neurotransmitter Function in FMS

Many of the assays developed in previous efforts to dissect the role and relationships of various neurotransmitter systems in human psychiatric disease have been employed toward the study of

FMS. While various publications have examined the potential roles of a number of neurotransmitters in FMS,[74-76] most is known about alterations in 5-HT and SP in affected patients. In summary, the available data suggest a potential decrease in serotonergic activity in FMS patients and support an increase in SP as associated with the disease.

Changes in 5-HT

Evidence for involvement of 5-HT in FMS has been reviewed recently by Alnigenis and Barland.[77] Many of the symptoms of FMS can be hypothesized as being related to alterations in central serotonergic neurotransmission. The relevance of descending serotonergic pathways to chronic pain was elucidated in the previous section. However, serotonin may also mediate the fatigue that is a frequent complaint of patients with FMS through a number of different mechanisms, including the role that 5-HT plays in regulating the hypothalamic-pituitaryadrenal axis.[78] Sleep disturbances reported by the majority of FMS patients may also implicate 5-HT due to its central role in the regulation of sleep-wake cycles. (Indeed, 5-HT was the first neurotransmitter hypothesized to be involved in FMS for precisely this reason).[79,80] Finally, the frequent comorbidity of psychiatric conditions such as depression in FMS patients further supports a disturbance in monoamine function.[81,82]

To confirm an abnormality in 5-HT mediated neurotransmission, levels of 5-HT itself, its precursor tryptophan, and its metabolites 5-HTP and 5-HIAA, have all been measured in various compartments from FMS patients. As only 1-2% of the body's 5-HT is found in the brain (with the rest derived from platelets, mast cells, and enterochromaffin cells of the gastrointestinal tract), the most consistent results of alterations of 5-HT function in FMS are derived from sampling CSF. While 5-HT levels were not measured directly, both Houvenagel et al. and Russell et al. reported decreased levels of 5-HIAA in the CSF of FMS patients versus controls.[83,84] In the former case, controls included patients with lower back pain, as well as pain-free subjects, with significant separation in both cases. No correlation between degree of pain and 5-HT levels in FMS patients was documented.While a more recent study by Legangneux et al. was only able to replicate this difference in CSF 5-HIAA levels in female FMS patients versus controls, the small number of male subjects within the study precludes drawing any definitive conclusion.[85]

Several studies have examined peripheral 5-HT levels and most studies find lower levels of 5-HT in the serum of FMS patients as compared to normal controls. In one report, the serum and platelet 5-HT levels were demonstrated to correlate.[76] A significant inverse correlation between serum 5-HT level and the number of tender points in FMS patients was noted by Hrycaj, who compared FMS patients with RA patients and normal controls.[86] Similarly, Ernberg et al. found lower serum 5-HT levels in FMS patients than in RA patients.[87] They speculated that the lower serum 5-HT levels were the result of increased platelet activation in FMS patients, leading to release of 5-HT into the plasma fraction of the blood, whereupon some of the 5-HT is sequestered by binding to nociceptors. Indeed, they found that a high plasma-to-serum 5-HT ratio was associated with orofacial pain and anxiety in FMS patients. How ever, this result and explanation is in conflict with the recent findings of Legangneux et al., who reported higher levels of 5-HT in FMS samples versus controls, despite using platelet rich plasma (PRP) as the source for assay.[85]

The studies described above primarily examined the steady-state aspects of 5-HT metabolism in FMS patients. A recent study focused on the dynamic aspects of 5-HT metabolism in FMS via the tryptophan depletion (TD) paradigm.[88,89] A total of 17 FMS patients and 17 controls were examined in this double-blind, randomized crossover study (ie, TD vs . sham-TD). Eleven patients were antidepressant free for a period of more than one year; the remaining six patients were washed off of antidepressants for 7 days (note that this wash off duration may be considered inadequate for a variety of commonly used agents, including amitriptyline and fluoxetine). At three different time points after the actual or sham TD procedure, blood

concentrations of 5-HIAA, tryptophan, and kynurenine were assessed in both patients and controls. In addition, patients were asked to rate their pain via a 10cm visual analog scale. At baseline, no significant differences were found in 5-HIAA levels between patients and controls. In controls, these levels decreased significantly (44% of baseline) as a result of TD. However, in patients, two distinct responses were noted. El even patients showed decreased 5-HIAA (60.7% of baseline), like the controls. However, in six patients, 5-HIAA levels increased by 203.6%, suggesting that at least a subgroup of patients have altered 5-HT processing. This altered 5-HT processing was not reflected in pain scores and was not a function of age, antidepressant use, or any other parameter that was measured.

The lack of consistency in measurement of compounds related to 5-HT in body fluids is not surprising, since such variability has been observed when attempting to document reduced 5-HT in depression as well, even within the CSF.[90] In fact, the selective 5-HT reuptake inhibitors (SSRIs), which increase 5-HT centrally, lead to decreased CSF 5-HIAA, presumably because increased 5-HT within synaptic cleft resulted in feedback inhibition.[91] Based on analyses of postmortem samples of suicide victims, it has been suggested that CSF 5-HIAA is most reflective of 5-HT activity in the prefrontal.[92]

In contrast to CSF 5-HIAA levels, the measurement of reduced 5-HT uptake by platelets has proven to be a consistent marker for melancholic depressionas, to a lesser extent, has the measurement of 5-HT transporter binding.[81,93] However, the experience to date in FMS patients has not been quite as satisfying. We have not found any published studies examining platelet 5-HT uptake in FMS patients, while multiple attempts to identify changes within the 5-HT transporter by measurement of platelet [$_3$H] imipramine or [$_3$H] paroxetine binding have yielded conflicting results, ranging from higher,[75] to lower,[94] to the same,[85,95] as controls. A genetic study in FMS patients has demonstrated a possible association of the syndrome with a polymorphism in the 5-HT transporter gene regulatory region.[96] Specifically, FMS patients in this study had a significantly higher distribution of the S/S genotype (homozygotic "shortallele," consisting of a 44-basepair insertion in the transcriptional region of the 5-HT transporter gene), which is associated with decreased 5-HT transporter messenger RNA transcription and decreased 5-HT uptake capacity in vitro. These patients also had higher mean levels of depression and psychological distress than the controls.

In summary, at best, the body of published data is suggestive of a dysregulation of 5-HT metabolism in a subset of patients with FMS. However, the assays performed of 5-HT levels and/or its precursors and metabolites, as well as platelet [$_3$H] imipramine or paroxetine binding (representing 5-HT reuptake sites), are often variable in their reported results despite the fact the different laboratories were using similar techniques. While it may very well be possible in some cases to reconcile some of the discrepancies, the analogy to depression (which prompted much of this work to begin with) does not provide much comfort of this being the most productive avenue of research. Specifically, while the monoamine hypothesis of depression was suggested over thirty years ago—and despite an extraordinary amount of effort and resources devoted toward collecting data to establish a direct link between neuro transmitter dysregulation and depression—the goal remains elusive. In hindsight, given the complexity of the clinical presentation of depression and the possible affects on neuro transmitter circuitry, it is not surprising that even if a discrete neuro transmitter defect were to exist, it may very well be masked when measured systemically. Arguably, since depression may appear as only one of multiple symptoms within the FMS complex, the task of sorting out cause and effect within a single neuro transmitter system may prove even more formidable than in the depression experience.

Changes in SP

SP is an 11 amino acid neuropeptide thought to be involved in nociception.[97,98] It is often co-localized with glutamate in both small, thinly myelinated A_ and nonmyelinated C-fiber afferents terminating in the dorsal horn of the spinal cord. Direct application of SP to dorsal horn sensory neurons causes slow and prolonged excitation similar to the response elicited by noxious stimuli. It has been suggested that SP acts as a neuromodulator via the NK1 receptor, sensitizing the neurons to the effects of other excitatory neurotransmitters.[99] Because of its presumed role in pain transmission, multiple studies have attempted to document changes of SP in chronic pain states.

In contrast to the 5-HT results, the differences described for SP in FMS have been reproduced by multiple groups. While SP levels in serum and urine of FMS have been reported as normal,[73] levels of SP in the CNS have been found to be consistently high in four different studies.[76,100-102] In all of the above, the SP elevation in CSF was two- to three-fold than that of normals, with little overlap between the values of the two groups.

However, the significance of these results and their relationship to FMS pathophysiology remains unclear. Russell suggests that a trend exists toward correlation of CSF SP levels and pain severity in FMS patients over time.[74] The source of the increased SP levels is unknown. While it would be anticipated that CSF SP would derive primarily from diffusion of neuropeptides released by afferent nerve fibers into the dorsal horn,[103] no increase in lumbar-level CSF SP could be induced by noxious pressure on the lower body tender points, which would be expected to stimulate the primary afferents.[76] This result is inconsistent with extensive animal work that demonstrates release of SP into the dorsal horn in response to noxious stimuli,[104-106] and therefore bears repetition. Significant concentration of both SP and NK1 receptors are found in other areas of the brain, including the striatum, hippocampus, raphe nucleus, and the lateral nucleus of the hypothalamus.[107] However, it is difficult to attribute, directly or indirectly, the increased CSF levels of SP to increased supraspinal levels.[108-110]

It is of interest that while high CSF levels of SP have been reported in trigeminal neuralgia[110] and chronic daily headache,[112] other chronic pain states, including low back pain and painful diabetic neuropathy, are accompanied by low levels of CSF SP and/or monoamines including 5-HT.[113-115] Clearly, proposing a one-fit model, such as "wind-up," to all chronic pain disorders is too simplistic to explain the full complement of data collected to date. Nevertheless, as the single most concrete neurochemical difference identified to this point in FMS patients, the high CSF concentrations of SP must be taken into account in any future investigation of mechanisms underlying FMS. Moreover, the potential inverse relationship between 5-HT and SP should be explored further. In this regard, Schwarz et al. reported a clearer result in serum, where, despite normal levels of SP and 5-HT, a strong negative correlation could be documented between SP and the 5-HT precursor and metabolite, tryptophan and 5-HIAA, respectively.[116] Furthermore, in these experiments, high serum 5-HIAA and tryptophan levels showed a significant relation to low pain scores while high 5-HIAA levels were related to good sleep quality and high SP levels to sleep disturbance.

Neuroendocrine Changes

A variety of neuroendocrine alterations have been proposed to underlie the pathophysiology of FMS.[38] The rationale behind such proposals is that certain endocrinological conditions—particularly hypocortisolemia, hypothyroidism, and growth hormone (GH) deficiency—have symptoms that strongly resemble those of FMS.While these conditions are generally characterized by hypothalamic hypoactivation, FMS may also be framed as a stress-related disorder. Conceptually, such a state should be associated with hypercortisolemia due to increased hypothalamic-pituitary adrenal axis activation. Several excellent reviews specifically addressing neuroendocrinological perturbations in FMS have recently been published,[117-119] as summarized below.

It is widely accepted that the hypothalamic- pituitary adrenal (HPA) axis serves as the link between a stressor, such as pain, and the individual's endocrine, autonomic, and behavioral response.[120] Classically, the HPA axis is regarded as a system programmed to react to changes in the environment by producing chemical messengers that mediate physiological changes to maintain homeostasis.[119,121] However, recent evidence complicates this simple model by suggesting genetic influences, environmental factors early in life, and exposure to chronic stress can permanently affect the HPA axis and predispose to the development of disease.[122] While much of this work has been done in the context of understanding the contribution of these changes to the pathophysiology of affective disorders,[121,122-124] similar mechanisms may be operative in FMS.[125]

The key mediator in the HPA cascade is corticotro phin-releasing factor (CRF), a neuropeptide produced in the paraventricular hypothalamus in response to physical or psychological stress. CRF in turn stimulates the release of corticotropin (ACTH) from anterior pituitary cells, prompting the secretion of glucocorticoids from the adrenal gland to elicit adaptive reactions to the perceived threat, such as increasing blood glucose levels.[119,125] CRF can also exert secondary inhibitory effects on growth hormone and thyroid-stimulating hormone (TSH) by increasing the secretion of somatostatin from hypothalamic and cortical neurons[126] and inhibiting hypothalamic LHRH release.[127] Simultaneous to activation of the HPA axis, an organism will react to stress with a "fight or flight" response mediated by the autonomic nervous system and resulting in physiologic changes such as tachycardia and hypertension.

HPA axis function can be experimentally assessed through two broad strategies: assessment of basal function in the absence of specific stressors and assessment of dynamic responsiveness. Overall basal HPA axis function has been investigated in FMS patients through several approaches. Of note, two studies directly measuring serum cortisol levels, sampled every 10-20 minutes over 24-40 hours, revealed no differences in the phase or amplitudes of cortisol release rhythms between FMS patients and controls.[128-129] Further, measurements of 24-hour urinary-free cortisol (reflecting integrated 24-hour serum cortisol levels) suggest low to normal cortisol levels in patients vs. controls.[130-134]

The dynamic responsiveness of the HPA axis in FMS has been assessed using several different types of stressors including exercise, hypoglycemia, IL-6, and exogenous ACTH.[118] The exercise studies have been difficult to interpret with different studies implying low, normal, or high HPA axis activity in FMS patients. On the other hand, the studies utilizing hypoglycemia and IL-6 as stressors suggest an impaired ability to increase ACTH (though normal cortisol response) in FMS patients.[130,135] Furthermore, a blunted cortisol response and exaggerated ACTH response to CRF challenge has been noted.[133,136,137]

Two other neuroendocrine systems—the hypothalamic-GH axis and the autonomic nervous system—also deserve mention. A number of studies have examined both GH and insulin-like growth factor 1 (IGF-1) dynamics in FMS patients. IGF-1 is a factor produced in the liver, primarily in response to GH secretion; thus, its concentration serves as a proxy for GH release. In general, data support the notion that at least a subset of FMS patients have subnormal GH secretion.[118] However, results from a recent study suggest that much of the quantitative differences in GH and IGF-1 levels between FMS patients and controls seen in previous studies may be the result of obesity in the FMS population.[138] Finally, the autonomic nervous system of FMS patients is characterized by increased sympathetic and decreased parasympathetic tone, as evidenced by exaggerated changes in blood pressure and heart rate with postural change.[139] There is disagreement, however, as to the interpretation of these findings.

In summary, one interpretation of these data is that FMS is characterized by HPA axis hypoactivation as a result of decreased CRF release. If this hypothesis is true, one can further speculate that the paucity of CRF may contribute to the hyperalgesia in FMS, via CRF's known antinociceptive effects.[140] The dysautonomia in FMS is attributed in this model to lack of

stimulatory input by CRF neurons to central control nuclei (A1, A2, A6) within the dorsolateral pons (DLP; see Figure 2) of the sympathetic nervous system[141] resulting in relative hypovolemia and exaggerated NE response. Further control of CRF neurons is via stimulatory 5-HT containing neurons projecting from the midbrain raphe,[78] stimulatory NE containing neurons from the locus ceruleus,[142] and inhibitory SP containing central neurons.[143] Therefore, it is tempting to link the hypocortisolism model of FMS to reduced central 5-HT and/or NE, or increased central SP, consistent with Russell's earlier work cited above. Likewise, the observed hypoactivity of the growth hormone (GH) axis in FMS can be attributed to low levels of growth hormone-releasing hormone, that, due to diminished direct stimulation by NE containing neurons, must counterbalance and overcome the tendency of lower levels of CRF to increase somatomedin release.[135] Whether the characteristic hormonal profile of FMS is involved in the pathophysiology of the disease or is a reflection of the patient's symptoms remains to be determined.

Alterations in Sleep

In addition to pain and fatigue, subjective sleep complaints—particularly nonrestorative sleep—is a common problem in FMS reported to occur in over three-quarters of patients.[18,144-146] Furthermore, formal sleep electroencephalography has demonstrated a number of abnormalities in the sleep architecture of FMS patients including: prolonged sleep latency; low sleep efficiency; a reduction in slow-wave sleep (SWS); an increase in alpha (stage 1) sleep; and an increased number of awakenings.[146-150] A fairly common finding in FMS patients is the presence of so-called "alpha-delta" sleep abnormalities—the presence of alpha waves during SWS—which appear to correlate with increased vigilance.[146,151-153] Other associated sleep problems seen commonly in FMS patients include periodic limb movements and sleep apnea.[147,154-155]

Sleep abnormalities are, of course, not specific to FMS; they are also seen in other chronic pain conditions[148,156] and in depression.[157] In fact, it has been shown that sleep deprivation in normal individuals can result in a myalgic syndrome that resembles FMS.[158-161] This finding has led to the hypothesis that sleep abnormalities may play a causal role in FMS pathophysiology.[158,161-162]

The initiation and regulation of the sleep state is quite complicated , with a number of mid-brain and pontine serotonergic , NE, and cholinergic nuclei playing a role.[161] Thus, it comes as no surprise that agents that affect neurons within these nuclei or neuro transmitter systems may also have profound effects upon sleep. Such agents include antidepressants, benzodiazepines, and ã-OH butyrate; agents which augment SWS may be particularly beneficial.[157,163] As discussed elsewhere, all three classes of agents have been tested with varying degrees of success in FMS. However, studies correlating drug therapeutic effects with alterations in sleep architecture have been limited and, so far, inconclusive.[164]

Neuroimaging Studies

Several studies have utilized functional imaging to investigate abnormalities in CNS function in FMS patients.[5,10,87,165,166] Two of these[5,87] used single-photon emission tomography (SPECT) imaging, and one used positron emission tomography (PET).[166] Both of these techniques are similar, employing radioactive tracers to measure regional cerebral blood flow (rCBF) in brain areas of interest. The main difference, at the current state of technology, is that PET uses radioactive tracers with a shorter half-life than SPECT, thus resulting in improved temporal resolution.[167] In contrast, Gracely et al. utilized functional magnetic resonance imaging (fMRI), a technique that directly tracks local changes in blood flow (through changes in water molecule density).[7,168] Of the three techniques, fMRI has the highest spatial and temporal resolution.[168]

A study by Mountz et al. found bilateral hypoperfusion of the thalamus and head of the caudate nucleus in ten women with FMS as compared to seven age and education-matched controls.[5] Concerns with this study (beyond the small size) were the medication status and the

psychological state of the patients. Based on self reports, patients discontinued their medications 4 days prior to the initiation of the study. However, the serum half-lives of some of the medications—including fluoxetine and amitriptyline are measured in days;[5,169] thus, significant serum levels of such medications were likely present in some patients at the time of their scans. More significant, however, was the fact that the patient population appeared significantly more depressed and/or anxious (per the Center for Epidemiological Studies Depression Scale (CES-D) and the Trait Anxiety Inventory (TAI), respectively) than the controls.

Some of these concerns are addressed in a more recent SPECT study[87] aimed at confirming and extending the results of Mountz. This effort evaluated a total of 17 patients and 22 controls (all women). At the time of the study, ten of the FMS patients were taking antidepressants, benzodiazepines, and/or narcotics. The remaining 7 patients were not taking any medications within these classes at the time of the study. Once again, however, the FMS patients were significantly more depressed and/or anxious than were their control counterparts. The results confirmed that rCBF in FMS patients is abnormal; however, statistically significant changes were only found in the right thalamus (the reductions in rCBF seen in the left thalamus did not reach statistical significance). Further, these authors were unable to confirm the bilateral changes in the heads of the caudate nuclei, as found previously by Mountz et al. Finally, additional abnormalities in the inferior pontine tegmentum were noted. The results for patients not taking medications were similar, although less significant; though it is not clear whether this reduction in significance is a result of differences in neuropharmacology or due to smaller sample sizes.

Taken together, these studies suggest that FMS patients may to have reduced rCBF in one or both thalami. Studies in other forms of chronic pain have also found decreases in thalamic rCBF, and these changes may reverse when the pain is alleviated.[170-173] One concern with both studies is their lack of control for comorbid depression and anxiety. Patients with such conditions, but without FMS, also show abnormalities in regional cerebral blood flow (rCBF), although the overall patterns appear different than those found in the two studies described above.[174,175] Finally, the possibility of rCBF abnormalities in the inferior pontine tegmentum is tantalizing, as a number of nuclei with descending inhibitory effects on nociception are located in and around this region, as described above (Figure 2).

Of particular interest from a pathophysiological perspective is the work of Gracely et al. who used the fMRI imaging modality to investigate differences in cortical activation between 16 FMS patients and 16 controls while they underwent pressure-pain testing (thumb-nail pressure). 7 Each FMS subject had an fMRI performed while subjected to "moderately painful" pressure as defined by the Gracely Scale.[176] The control subjects were scanned under two conditions: (a) the "stimulus pressure control" condition and (b) the "subjective pain control" condition. The former referred to testing the controls with the same level of mechanical pressure as the FMS patients, while the latter involved scanning the controls when they, like the FMS patients, reported moderate pain. It was found that the levels of cortical activation seen in FMS patients and the controls under the "subjective pain control" condition were similar. However, fMRI scans of control subjects under the "stimulus pressure control" condition showed no significant activation. These results are strongly supportive of alterations in the threshold and gain of the nociceptive system in FMS patients and are consistent with a model of central sensitization. Note that while data regarding the effects of psychological state on fMRI results were not presented, this is less of a concern in fMRI than in PET or SPECT scans, as a change from baseline within the same patient is being measured.

Clinical Pharmacology of FMS

At the time the preceding review was written, the vast majority of published results from randomized, controlled studies in FMS examined the use of tricyclic antidepressants; other therapeutic approaches generally had relatively limited data to support their usage.[38] Further, a

large percentage of the existing clinical data was derived from relatively small studies, often with high dropout and placebo response rates.[177,178] These trials tended to be of short duration with very limited information regarding the long-term efficacy of any of the agents. As described below, recent trials have addressed a number of these criticisms.

Other issues still remain, however.While the 1990 ACR criteria for the classification of FMS have helped standardize the identification of patients appropriate for entry into clinical trials,[3,179] the group remains extremely diverse and heterogeneous. The issue of co-morbid depression and its impact on patients' responses to therapeutic interventions is also critical in the design of FMS trials, as will be expanded upon below. Standard practice has been to exclude patients with "severe" psychiatric illness from clinical trials, by incorporating cut-off criteria when using standard psychometric instruments such as the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), or the Beck Depression Inventory (BDI) as prescreening tools.[180-184] However, a great deal more information is required before the complex inter-relationships between depression, pain, and other symptoms of FMS can be ascertained.

The FMS Pharmacopeia

A wide variety of approaches—both pharmacological and nonpharmacological— have been applied, with varying degrees of success, towards the treatment of the symptoms of FMS. At the present time, the management of fibromyalgia patients involves a complex interplay between the pharmacological management of pain and associated symptoms and the use of non-pharmacological modalities. As the elimination of all FMS symptoms is not currently possible (ie, a cure), the philosophy of management is symptom palliation and function a l restoration. The presentation of fibromyalgia symptomatology is highly variable and each patient must have an individualized evaluation before deciding upon an initial treatment plan.[185] Regular follow-up and modification of the initial management strategy is usually required, depending upon the patient's response.

Pharmacological Treatment Strategies

Several recent publications have reviewed the current state of FMS therapy; the data from randomized, double-blind, placebo- or activecontrolled trials are summarized in Table 1 .[178,186-192] In this section, we have chosen to briefly review a number of the many agents that have been employed to treat FMS. A drug was included in the summary if it met one or more of the following criteria:

1. A large quantity of clinical data in FMS patients exists, eg TCAs, SSRIs, DRIs, pregabalin, and $5HT_3$ receptor antagonists.

2. The clinical investigation of the drug has been based on solid preclinical scientific data, eg, NK1 antagonists, NMDA antagonists, and GH.

3. The drugs have other psychiatric indications, eg, "mood stabilizers" or anti-epileptic drugs (AEDs), atypical anti-depressants, anxiolytics, hypnotics, and α2 adrenergic agonists, acting as antispasticity agents, such as clonidine and tizanidine.

Some of these drugs can be supported as primary therapy.Others may have an adjuvant role addressing symptoms other than pain and important in the overall management of these patients.

Antidepressants

The majority of FMS clinical trials have involved antidepressants of one class or another, as is evident from Table 1 . Trials studying the oldest class of agents, tricyclic antidepressants are abundant, though most recent studies have focused on selective serotonin reuptake inhibitors and "atypical antidepressants"—a class that includes dual reuptake inhibitors and monoamine oxidase inhibitors. Despite the multiplicity of antidepressant classes, practically all of the agents currently in clinical use either directly or indirectly increase neurotransmission mediated by the monoamine neurotransmitters, particularly serotonin (5-HT) and/or norepinephrine (NE; also called noradrenaline).[193] These activities are thought to underlie the antidepressant activity of these compounds, though the exact mechanism by which this occurs is unknown. These pharmacological activities also appear to be an important mechanism by which antidepressant compounds effect centrally-mediated analgesia.[193]

Excepting TCAs, current classification schemes have tended to segregate agents based on their in vitro effects upon 5-HT and NE re-uptake activity. As shown in Table 2 , specific agents within a given class vary significantly in terms of their relative actions on the reuptake of these two monoamines or upon binding to their respective transporters.[194-199] Note, however, that the effects of these agents in vivo may differ significantly from those observed in vitro. For example, despite its low affinity for the NE transporter, venlafaxine has been shown to have in vivo effects consistent with NE reuptake blockade, particularly at higher doses.[200-202] Conversely, despite the marked difference in relative affinities for the NE and 5-HT transporters that paroxetine displays in vitro, recent data suggests that this agent may possess dual reuptake inhibitory activity in vivo at clinically relevant doses.[203]

Tricyclic Antidepressants (TCAs). TCAs—particularly amitriptyline and doxepin—are widely employed in the treatment of FMS and other chronic pain conditions. (Cyclobenzaprine is also widely used in the treatment of FMS and is structurally very similar to amitriptyline. However, cyclobenzaprine is typically classified as a muscle relaxant rather than an antidepressant and will be discussed below).[186-188] Multiple studies support the use of TCAs for the treatment of FMS. Members of this class have frequently been used as the positive controls to which newer agents have been compared .[204- 208] The results from TCA trials in FMS have been compiled and analyzed in two meta-analyses by Arnold et al.[176] and O'Malley et al.[188] In essence, the authors both conclude that TCAs provide "moderate" improvement in FMS, with the greatest impact on measurements of sleep, overall well-being, and pain severity. More specifically, Arnold et al. report significant clinical response to TCAs was observed in 25-37% of patients, whereas O'Malley et al. report patients receiving TCAs "four times as likely" to report overall improvement (compared to placebo) and experience moderate reductions in individual symptoms.

Pharmacologically, most TCAs block the reuptake of both 5-HT and/or NE, with varying degrees of relative activities (Table 2). However, amitriptyline, nortriptyline, and dexopin all preferentially block the reuptake of NE with greater potency than that of 5-HT, with selectivity ratios (relative ability to block NE versus 5-HT uptake) ranging from 1.1 for amitriptyline to 168 for nortriptyline. Amitrip tyline (with a half-life of 12-36 hours) is metabolized primarily to nortriptyline (with a half-life of 22-88 hours),[169] further adding to the NE bias of amitriptyline especially at the lower dosages which have been historically used to treat chronic pain. The general efficacy of TCAs in treating the pain of FMS, therefore, can be interpreted to support the primacy of NE agonism for analgesic activity. Beyondinc reasing NE and 5-HT levels, TCAs have other important pharmacologic properties, including dopamine reuptake inhibition, NMDA antagonism, and ion-channel blocking activity.[209-216] Therefore, there is overlap between the mechanisms of action of the tricyclics and other agents, such as anti-epileptic agents (ie, ion-channel blockade). TCAs additional anti-cholinergic, anti-histaminergic, and a-adrenergic receptor blockade activities impart a wide assortment of undesirable side effects, which often compromise the tolerability and clinical acceptance of this class.[217]

Somewhat ironically, the data supporting the use of TCAs in treating depressed mood in the context of FMS or other pain states is limited, perhaps as a result of most trials evaluatng sub-

antidepressant doses of TCAs.[38,187] In most forms of major depressive disorder, however, the efficacy and remission rates of TCAs are equal or superior to those of other classes of agents, an effect hypothesized to result from their effects on both the serotonergic and noradrenergic systems.[218]

Although the anti-depressant activity of these agents may contribute to the efficiency seen in certain patients, their role as centrally-acting analgesics appears to be more critical. This premise is supported by results from trials of various SSRIs, which, in general, do not appear to be as effective analgesics as TCAs even at anti-depressant doses (see below).

Selective Serotonin Reuptake Inhibitors (SSRIs). SSRIs have revolutionized the field of psychiatry, providing safe and effective treatment of common psychiatric conditions including major depressive disorder, anxiety, and social phobia. Much of their success is attributable to the fact that SSRIs display improved tolerability compared to TCAs, a result of their much higher degree of pharmacological specificity. As implied by their name, SSRIs primarily inhibit the reuptake of 5-HT, and they typically lack the extra-monoaminergic activities which characterize TCAs. The SSRIs fluoxetine, citalopram, sertraline, and paroxetine have each been evaluated in randomized, placebo-controlled trials in FMS.[219,220] The results of these trials have been somewhat inconsistent, leaving some debate regarding the relative efficacy of the SSRIs, especially in comparison to TCAs. Two studies have demonstrated positive efficacy for fluoxetine when compared to either placebo or amitriptyline in treating sleep, pain, fatigue, and depression.[205,219] However, a third study failed to demonstrate any significant improvement in pain, although mild improvements were noted in sleep and depression.[221] Two placebo-controlled trials of citalopram have been performed; the first was convincingly negative, with citalopram failing to demonstrate any improvements in pain, fatigue, sleep, or mood.[222] The second study demonstrated that citalopram significantly improved mood, though other outcome measures did not improve significantly.[223] One study comparing sertraline to amitriptyline demonstrated that the two compounds were equivalent in producing significant improvements in pain, sleep, and fatigue.[224] Finally, a study comparing paroxetine to amitripty line concluded that, while both improved the symptoms of pain, sleep, and depression, amitriptyline had a larger, more robust effect.[220] Further, amitriptyline was beneficial for fatigue whereas paroxetine did not improve this symptom. Taken together, SSRIs appear to be effective in treating certain FMS symptoms, particularly mood. However, their effect sizes on pain, sleep, and fatigue appear to be less robust in comparison to amitriptyline and the dual reupake inhibitors.

These data—particularly those pertaining to citalopram, the most 5-HT-specific of the SSRIs (see Table 2)—suggest that serotonergic activity alone is not sufficient to effect analgesia in the chronic pain setting. In fact, the SSRIs as a class are, generally, less efficacious than the in chronic pain states, based on the evidence assembled to date,[15,40,90,111,225] although there are some exceptions.[226,227]

Dual-Reuptake Inhibitors (DRIs) Antidepressants. The term "novel" antidepressant covers a great deal of pharmacological variety, including 5-HT/NE dual reuptake inhibitors (DRIs), NE-specific reuptake inhibitors (NRRIs), 5-HT receptor antagonists, and monamine-oxidase (MAO) inhibitors, among others.[217] DRIs are pharmacologically similar to some TCAs in their ability to inhibit the reuptake of both 5-HT and NE, a feature that may improve their analgesic efficacy as reviewed in Rao.[193] Importantly, DRIs differ from TCAs in being gene rally devoid of significant activity at other receptor systems, and this selectivity results in diminished side effects and enhanced tolerability.[193] Venlafaxine is the only DRI currently available within the US and is currently indicated for depression and anxiety. Two open label studies suggest venlafaxine is useful in treating multiple symptoms of FMS.[228,229] However, these results were not replicated by a recent randomized placebo controlled trial, in which patients treated with venlafaxine did not show any significant improvements in pain, fatigue, sleep, or mood compared to those on placebo.[230] These results may be explained by dosing, as the study by Dwight et al.[231] pushed each patient to their maximally tole rated dose or 375 mg/day (mean 167 mg/day) , while a study

by Zijlstra et al.[232] had a single drug arm with a dose of 75 mg/day.Data suggests that venlafaxine is primarily a 5-HT reuptake inhibitor at lower doses (ie,,150 mg), with NE effects apparent on ly at higher doses.[200,201] On the other hand, it should be noted that the open-label trial by Sayar et al.[233] also used a single dose of 75 mg and found it effective against various FMS symptoms.

Milnacipran is a DRI presently available in Japan and parts of Europe for the treatment of depression. This agent is unique among clinically available DRIs in its preferential blockade of NE reuptake over 5-HT (Table 2); additionally, this compound is a low affinity NMDA antagonist. 198 Milnacipran is presently in clinical development for FMS in the US, and the results of a Phase II monotherapy trial were recently announced.[234] Placebo was compared to milnacipran, dosed both once and twice daily (when used as an antidepressant, milnacipran is dosed twice daily). All patients were escalated over a 4-week interval to either the maximum tolerated dose of milnacipran or to a total of 200 mg/day. The total trial duration was 12 weeks, (the primary endpoint was pain) tracked on a near-real-time basis using an electronic diary system. Other symptoms that were followed (some using the diary and others at clinic visits) included patient global impression of change (PGIC), sleep, fatigue, and mood.Ninety patients ultimately completed the trial, 32 in the milnacipran QD arm, 37 in the BID arm, and 21 placebo controls. In summary, 37% of patients taking 100 mg of milnacipran twice daily achieved a 50% reduction in pain compared to only 14% of patients on placebo. Furthermore, milnacipran dosed either once or twice daily, had beneficial effects upon PGIC, fatigue, and mood. Side effects including nausea and headache were mild and generally transient. The subgroup of patients with s diagnosable major depressive episode at the start of the trial bears specific mention. Overall, this group's response to milnacipran was similar to that of non-depressed patients; however, their placebo response rate was 33% compared to 5% in non-depressed patients.

A second dual uptake inhibitor, duloxetine—a DRI that, like venlafaxine, preferentially blocks the reuptake of 5-HT over that of NE— is also in clinical development, and the results of a phase II trial of duloxetine in FMS patients were recently announced.[192] This 12-week monotherapy study compared duloxetine dosed at 60 mg twice daily (120 mg/day) to placebo. Patients were escalated to the final dose over a 2-week escalation period, which followed a 1-week placebo run-in period. The primary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ) total- and pain-subset scores.[192,235] Other measures included the PGIC, pain (via the Brief Pain Inventory), SF-36, and Quality of Life in Depression scale. A total of 207 patients completed the trial, 104 and 103 patients in the active and placebo arms, respectively. Overall, duloxetine treatment resulted in a significant improvement in total FIQ scores; however, changes in the FIQ pain score did not reach statistical significance. On the other hand, pain as measured by the Brief Pain Inventory was improved. No beneficial effects of duloxetine were noted on fatigue or sleep; indeed, insomnia was a significant side-effect of drug therapy. However, an improvement in mood was noted, as measured by the SF-36 and the Quality of Life in Depression scale.

Other Novel Antidepressants

Reboxetine, classified as a No repinephrine Reuptake Inhibitor (NERI) due to its selective inhibition of NE reuptake, is on the market as an anti-depressant in parts of Europe; however, it is currently unavailable within the US. A recent open-label trial of reboxetine in 25 FMS patients suggests this compound may be useful for treating pain and fatigue,[236] though more extensive follow-up studies are needed on this point. Another NRI—atomoxetine—has recently been introduced to the US market for the treatment of attention-deficit hyperactivity disorder ADHD). No data of the efficacy of this compound in pain are presently available. However, a randomized, double-blind, placebocontrolled trial in patients with chronic low back pain reported maprotoline—a tetra cyclic nora d renaline reuptake inhibitor (NARI)—to exhibit significantly greater efficacy than paroxetine at standard doses.[237] A different study, however, found maprotoline to be somewhat less effective than amitriptyline in the treatment of post-herpetic neuralgia. 207 Therefore, the results of limited empirical studies as well as scientific considerations lead one to

assume that NARIs may exhibit better analgesic efficacy than the SSRIs, yet somewhat less efficacy than the TCAs and SNRIs which influence both monoamines.[238] Obviously, additional studies are required to confirm the role these agents will play in the treatment of chronic pain.

There are no published studies on the analgesic capabilities of nefazodone, a 5-HT_2A receptor antagonist as well as a weak dual reuptake inhibitor. Animal studies have suggested that its 5-HT_2 antagonism may be anti-nociceptive, due to increases in 5-HT_{1A} mediated neuro-transmission. The clinical relevance of this has yet to be determined, especially since a related molecule, trazadone, has failed to exhibit significant analgesic effects when used for various pain conditions, including FMS.[239]

Mirtazapine is a potent central a2 autoreceptor antagonist as well as a 5-HT_2 and 5-HT_3 receptor antagonist with some anecdotal success as an analgesic.[240] While no controlled studies have been reported, mirtazapine's α2 autoreceptor mediated increases in NE (as well as 5-HT_{1A}) neurotransmission and its ability to inhibit 5-HT_3 (discussed below) may impart some anti-nociceptive activity.

Reversible Monoamine Oxidase Inhibitors (RIMAs). MAOIs increase monoamine levels by blocking their breakdown after release from the neuron, a mechanism distinct from TCAs, SSRIs, and DRIs. Non- enzyme- specific, irreversible, MAOI, such as phenelzine and tranylcypromine, have been on the market in the US for many years as antidepressants, though concerns about potentially fatal interactions with certain foods and medications have limited their widespread usage.[38] Moclebemide and pirlindole represent "second generation" agents that show improved specific and reversible binding compared to older compounds. Both of these agents have been approved in Europe as antidepressants, though they are not presently available within the US. Preliminary studies with moclobemide in FMS have failed to demonstrate significant analgesic activity when compared to amitriptyline.[206] However, a more recent study has demonstrated the efficacy of this compound in CFS, though effects were primarily limited to fatigue.[241] The results of a randomized, double-blind, placebo controlled trial of pirlindole in FMS were more promising, with beneficial effects upon sleep, pain, fatigue, and mood.[242] It is of interest to note that MAOIs show greater efficacy than TCAs in treating atypical depression, a particular depression subtype which is relatively common in patients with chronic pain conditions.[243]

Non-Steroidal Anti-Inflammatory Drugs. Non-steroidal anti-inflammatory drugs (NSAIDs; including COX-2-selective agents) and acetaminophen are used by a large number of FMS patients.[244] However, numerous studies have failed to confirm their effectiveness as analgesics in FMS, though there is limited evidence of patients experiencing enhanced analgesia when treated with combinations of NSAIDs and other agents.[188] This phenomenon may be a result of the painful, inflammatory conditions—including OA, rheumatoid arthritis, and lupus—being frequently comorbid with FMS.

Anti-Epileptic Drugs (AEDs)

The similarities between certain pathophysiological and biochemical mechanisms observed in epilepsy and neuropathic pain led to initial investigations of AEDs in chronic pain states.[245] Agents such as carbamazepine, lomotrigine, phenytoin, benzodiazepines, and gabapentin have been evaluated in neuropathic pain, and have been shown to have analgesic effects to varying degrees.[246] As a result, a number of drugs initially labeled as anti-epileptic agents are used regularly as analgesics.

The majority of AEDs increase the seizure threshold by reducing neuronal excitability through sodium and/or calcium channel blockades; this mechanism of action appears to underlie their analgesic activity as well.[246] Agents such as benzodiazepines, tiagabine, valproic acid, and topiramate also enhance GABAergic neuro transmission.[247] Therefore, although each specific

agents' mechanism of action may differ, AEDs as a class generally reduce excitability, decrease ectopic discharge and reduce neurotransmitter release—effects which have been found to impart varying degrees of anti-nociceptive as well as antiepileptic activity.

The results of a phase II monotherapy trial investigating the use of pregabalin, an AED presently in clinical development, in the treatment of FMS were recently published.[248] Pharmacologically, pregabalin is thought to act by blocking certain calcium channels.[249] Three different doses of pregabalin—150, 300, and 450mg/day—were compared to placebo in this 8 week study. A total of 410 patients completed the trial—131, 103, 111, and 99 in the placebo, 150 mg, 300 mg, and 450 mg/day arms, respectively. The primary endpoint was pain, as measured by paper diary. Other endpoints included sleep, fatigue, and PGIC. In summary, 450 mg/day of pregabalin was found to result in a 50% pain reduction in 28.9% of patients, a significant difference vs. placebo (13.2%). In addition, sleep, fatigue, and PGIC measures all improved in patients in the 450 mg/day arm of the trial. Unfortunately, this high dose was also associated with a significant incidence of CNS side effects; dizziness, in particular was a problem in almost half of the patients taking this dose.

Carbamazepine and gabapentin have been approved as first-line therapies for trigeminal neuralgia and painful diabetic neuropathy, respectively, and the effectiveness of gabapentin in diabetic post-herpeticneuralgia has also been demonstrated.[250,251] Gabapentin is structurally and pharmacology similar to pregabalin; however, the gabapentin's efficacy has not formally been demonstrated in FMS. Other anti-convulsants, such as topiramate and lamotrigine, have received recent attention for their potential efficacy in neuropathic pain conditions.[238,246,252-254] However, no clinical evaluation of the effectiveness of these AEDs in FMS has been published, and the discouraging side effect profile of many of these agents has typically deterred their evaluation as front-line therapies.

Anxiolytic and Hypnotic Agents

Benzodiazepines are GABA agonists with analgesic actions in the spinal cord and brainstem of animal models,[255] as well as anti-epileptic properties as described above and muscle-relaxant properties as discussed below.While several uncontrolled studies have supported the benefit of clonazepam in neuropathic pain (specifically, trigeminal neuralgia), its use is compromised by side effects such as marked drowsiness or frank sedation.[256,257] In general, studies with other benzodiazepines in neuropathic pain have tended to be small and uncontrolled with inconsistant results.[258] The available data are also limited in FMS, but generally, these agents have been ineffective as analgesics.[259,260]

A handful of studies have been published on the use of certain nonbenzodiazepine hypnotics in FMS, such as zopiclone and zolpidem. These reports have suggested that, while improving patients' subjective sleep complaints, these agents do not improve the pain of FMS.[261-263]

Researchers have attempted to elucidate the relationship between circadian rhythms, melatonin secretion and FMS, but have produced inconsistent results.[128,129,264-266] Melatonin, available in the US as an unregulated dietary supplement, has been evaluated in one small open label pilot study involving 21 patients with FMS who were each given 3 mg of melatonin nightly for 30 days.While this study suggested possible benefits in sleep and tender point counts, melatonin did not appear to impact patients' overall levels of pain or fatigue.[264]

Gamma-hydroxybutyrate (GHB, also known as sodium oxybate) is a precursor of GABA with powerful sedative properties indicated for narcolepsy in the US. Of note, this compound has been reported to qualitatively improve sleep by increasing the quantity of slow wave sleep (SWS) and decreasing a-intrusion without significantly changing the quantity of REM sleep.[267] GHB was recently shown to be useful in improving fatigue, pain, and sleep architecture in patients with FMS

in a pilot (18 patient) randomized, double-blind, placebo-controlled, crossover trial.[268] It is important to note, however, that several issues are likely to limit the widespread adoption of this compound. First, this agent is a controlled substance due to its abuse potential. Second, the short half-life of ã-hydroxybutyrate typically requires twice nightly administration, a dosing schedule that is likely to interrupt normal sleep architecture. Finally, the low potency of this compound (6 grams were used per night in the above trial) makes controlled-release dosage forms more difficult, as the drug is most practically formulated as a liquid.

Muscle Relaxants

Cyclobenzaprine is a muscle relaxant originally shown to be of some benefit in the management of fibromyalgia in the mid-1980s.[188] Although typically classified as a muscle relaxant, cyclobenzaprine shares structural and pharmacological similarities with TCAs.[193] The mechanism of action underlying cyclobenzaprine's muscle relaxing action is unclear, though it may be mediated by blockade of 5-HT_2 receptors.[193] Data generally support its use in FMS, particularly in treating sleep and pain, and there are some data suggesting synergism when cyclobenzaprine is used with fluoxetine.[188,269] The major problems patients report with cyclobenzaprine are morning "hangover" and dry mouth. These issues may be alleviated to some degree by the use of lower doses of cyclobenzaprine (1 mg to 4 mg) which have recently been shown to improve pain, sleep, and fatigue in FMS patients.[270]

Tizanidine, an α2 adrenergic agonist, reduces muscle spasticity by increasing presynaptic inhibition of motor neurons, and has also demonstrated analgesic effects in animal pain models.[271,272] The anti-nociceptive properties of the α2 agonists are not surprising when one considers the multiple sites of α2 adrenergic receptors within both the ascending and descending pathways . For instance, α2 stimulation reduces activation of PAF terminals, thereby reducing Glu and SP release. Increased α2 stimulation within the RVM may also activate the descending 5-HT system, providing further anti-nociception. These agents may also directly inhibit dorsal horn projection neurons. A recent 8-week, open-label study of 25 fibromyalgia patients receiving a total daily dose of tizanidine of 4-24 mg reported significant improvements in several parameters, in cluding sleep, pain, and measures of quality of life.[273] Of particular interest is the demonstration that treatment with tizanidine results in a reduction in substance P(SP) levels within the cerebrospinal fluid (CSF) of patients with FMS.

Baclofen is a GABAB agonist also approved as an anti-spasticity agent and likewise documented to be aneffective adjuvant analgesic in the management of various types of neuropathic pain.[274-276] While its mode of action is not fully characterized, its analgesic effects may be due to suppression of dorsal horn neuronal activity. There are currently no data pertaining to the use of baclofen in patients with FMS.

Opiates

Typical opiateagonists such as morphine act at various combinations of the mu, delta, and kappa opiate receptors. These receptors are located thoughout the CNS with all three receptors appearing to play a role in analgesia.[193] A recent study reported reduced levels of b-endorphin in peripheral blood mononuclear cells of fibromyalgia patients, implicating the possibility of a suboptimal endogenous in fibromyalgia patients.[277] Morphine and morphine-like compounds are widely used in many chronic pain states, including TMJD[278] and subsets of CLBP.[274] A survey of academic medical centers in the US reported that opiates were used in about 14% of FMS (mainly tertiary care) patients.[244]

There have been only a few controlled clinical trials of these agents in FMS. Interestingly, acutely administered intravenous morphine was not found to be effective in treating FMS pain.[280] Tramadol is another widely used analgesic that has a unique mechanism of action involving weak

mu agonist activity combined with 5-HT/NE reuptake inhibition.[187] Three double-blind studies have demonstrated the efficacy and tolerability of tramadol in the management of fibromyalgia pain, as an isolated compound[281,282] and in fixed-dose combination with acetaminophen (ie, "Ultracet").[278]

Miscellaneous Agents

5-T3 receptor antagonists (such as ondansetron and tropesitron), which are best known for their anti-emetic properties, also have analgesic effects.[284] Animal models have demonstrated that blockade of 5-HT_3 receptors has both nociceptive and anti-nociceptive effects, and clinical trials in settings of chronic pain have repeatedly revealed a bellshaped dose response curve, suggesting that optimal analgesic effect may involve a dose-dependent balancing act between these opposing activities. This duality of effect may be due in part to the presence of 5-HT_3 receptors on both PAF terminals and inhibitory dorsal horn interneurons.[284-287] This is an appropriate reminder of the complex nature by which the myriad 5-HT (and other) receptors interact throughout the pain pathways.

Members of the German Fibromyalgia Study Group extensively studied tropesitron in patients with FMS.[288-292] In addition to several small, open-label evaluations, a single randomized placebo-controlled doubleblind trial investigated the effectiveness of 5 mg, 10 mg, or 15 mg tropesitron given once daily for 10 days to 418 FMS patients. The results from this study suggest modest but statistically and clinically significant reductions in pain, but only in those patients treated with 5 mg tropisetron, consistent with the earlier described bell-shaped dose response curve. Constipation and other GI complaints were commonly reported, as is common with other 5-HT_3 blockers.

As mentioned above, certain TCAs are known to be NMDA receptor antagonists, though their activity in this regard is relatively weak (ie, they are low affinity agents).[193] Three studies have demonstrated high-level NMDA receptor blockades (imparted by the use of high affinity agents or large doses of low affinity compounds) can improve pain symptoms in FMS patients.[280,294,295] However, such high-level blockades are associated with significant cognitive side-effects, thus potentially limiting the utility of this approach.While the search continues for agents with more tolerable side effect profiles, NMDA receptor antagonists may ultimately prove to be most beneficial as adjunctive therapies when used concomitantly with other analgesics.[290]

Considering the observation that SP levels within the CSF of patients with FMS are routinely elevated, drugs designed specifically as SP or NK1 receptor antagonists are theoretically attractive . Indeed, a doubleblind, placebo-controlled, randomized 8-week crossover study was conducted in 1994 to evaluate the use of a selective NK1 antagonist, CJ-119794, in the treatment of FMS.[296] In short , the results were disappointing; treatment with CJ-119794 resulted in no significant improvements in pain, sleep, or affective endpoints. Unfortunately, this result is rather consistent with NK1 antagonists in a variety of clinical settings, despite promising preclinical results.[97] The only notable exception to this general trend has been within the antiemetic indication, for which aripretant—also known as MK-0869—has recently received approval in the US.

Bennett et al. conducted a randomized , placebo-controlled , doubleblind study of the clinical effects of growth horm one (GH) therapy in 50 women with FMS and pre-determined low IGF-1 levels.[297] Patients we rerandomized to self-inject daily either GH or placebo (reconstituted excipient only) for 9 months. The dose of GH was adjusted to maintain blood IGF-1 levels at approximately 250 mg/ml. The GH-treated group achieved a significant improvement in pain, sleep, and fatigue scores at 9 months compared to baseline, whereas no significant improvement was observed in the placebo group. Patients' responses tended to lag behind the initiation of GH therapy by approximately 6 months, although measurable improvements in muscle strength and exercise performance were discernible after 3 months with progressive improvement there after.

Since GH is known to raise energy levels, increase exercise capacity, build muscle strength, and improve cognitive function in other patient groups with decreased basal GH levels,[298-301] the improvements seen in this trial may merely reflect the general metabolic effects of GH and not be representative of a syndrome-specific response. Moreover, while GH therapy would appear to offer this subgroup of patients some symptomatic improvement, financial considerations limit the viability of GH as a long-term therapy in this population.

Non-Pharmacological Treatment Strategies

The two best studied non-pharmacological therapies are cognitive behavioral therapy (CBT) and exercise. Both of these therapies have been shown to be efficacious in the treatment of FMS, and excellent reviews of these treatments are referenced.[27,46,302] Both of these treatments can lead to sustained (eg, greater than one year) improvements and are very effective in compliant individuals. The challenge for new studies examining these treatments is to improve long-term adherence and compliance, and to move toward using modalities such as the Internet, or telemedicine, that will allow a larger number of patients access to these therapies. Also, new studies need to address the optimal manner in which to combine pharmacologic and non-pharmacologic therapies.

Discussion

The FMS landscape has changed markedly over the past 2 years since the preceding review was written.[38] In summary, FMS has moved much closer to the mainstream, gaining authenticity in many circles as a legitimate, treatable condition. Such a vast change in attitude would have been inconceivable just a few short years ago. The next few years promise to be equally exciting, as FMS garners more research interest and as drugs specifically indicated for FMS enter the market.

In the preceding review, we presented a conceptual view of FMS that attempted to integrate the various clinical and laboratory findings seen in FMS patients (Figure 4).[38] To summarize, we proposed that in susceptible individuals, all of the symptoms and findings are reciprocally interconnected, and abnormalities in one element would ultimately result in perturbations in the others. Equally important is the fact that no distinctions were made nor hierarchy presumed between the primary insult and secondary symptoms. From a therapeutic perspective, this model has an important implication: an attempt to treat a single symptom in isolation will not be effective in treating the syndrome.We suggest that trial data for zopiclone and amitriptyline support this hypothesis. The former compound is a sedative/hypnotic with no demonstrable efficacy against affective disorders, pain, etc. As predicted by the model, zopiclone's therapeutic benefits are limited to sleep in FMS patients. Amitriptyline, on the other hand, can theoretically benefit all of the elements in Figure 4, and this agent's global effectiveness is borne out by trial data.

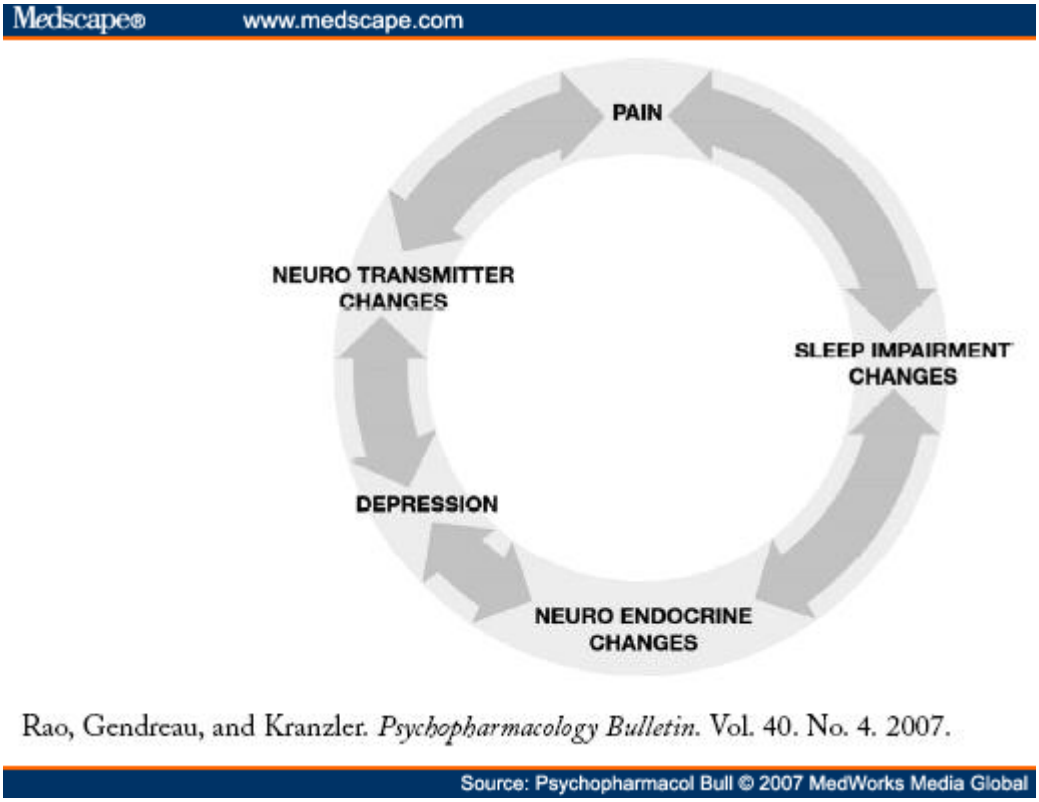

Figure 4.

A Model of Fibromyalgia as a Bidirectional Cycle

Based upon this model and available clinical trial data, we predict that three pharmacological classes of drugs likely to be of benefit to patients with FMS:

- Dual reuptake inhibitors
- Antiepileptic compounds
- NK1 antagonists

On the first two points, our predictions have been born out experimentally. Both milnacipran and duloxetine have demonstrated efficacy in FMS, and venlafaxine may be beneficial at higher doses.[192,228,234] Of note, the ranking of these compounds in order of decreasing efficacy—milnacipran, duloxetine, and venlafaxine—also corresponds to their relative activities on NE vs. 5-HT; a point that confirms the importance of NE to analgesia. Also of note is the marked dissociation in placebo (but not active) response rates seen in milnacipran trials; data which support the notion of pathophysiology underlying pain and depression are different.[303]

Pregabalin appears to be a very effective compound in the treatment of FMS, based upon the one of the largest double-blind, placebo-controlled, randomized trial performed in FMS to date. The major concern with respect to this compound is tolerability, as CNS side effects were extremely prevalent at the dose required for a statistically significant result. It should be noted,

however, that the data to date regarding pregabalin in FMS come from a monotherapy trial. One may speculate that a lower, more tolerable dose would be equally efficacious if combined with another effective drug, such as a DRI. Indeed, such a combination may be ideal, as the DRIs tend to cause a degree of insomnia; pregabalin dosed at night would, presumably, counter act this side effect.

We recognized in the previous review that our prediction regarding the efficacy of NK1 antagonists in FMS was speculative.[38] In light of the generally poor clinical showing of this class of agents in general, perhaps the negative results seen with CJ-11974 in FMS are not surprising. 291 However, it may still be too early to condemn the entire class as issues with blood brain barrier penetration, affinity to human NK1 receptors, etc. have been noted with several early compounds.

It is important to note that none of the compounds presently in active development for FMS are considered traditional analgesics or antiinflammatories; all of them are thought to have their primary effects almost exclusively within the CNS. Thus, we hope this review will stimulate dialogue between the community of physicians who treat FMS patients and the scientific and clinical researchers studying brain physiology and pharmacology. Some of the ideas resulting from that dialogue will undoubtedly involve the use of pharmacologically active agents to further dissect the biology of FMS and/or determine clinical response. We expect our understanding of FMS, as well as the physiological links between mind and body in the "functional somatic disorders" in general, will advance rapidly as a result of such collaborative efforts.

Table 1. Fibromyalgia Pharmacotherapy: Summary of Randomized, Controlled Trials

Table 2. Comparison of in Vitro Monoamine Uptake Inhibitory Activity or Transporter Binding

CLASS	AGENT	NE (NM)	5-HT (NM)	TYPE OF DATA	SELECTIVITY RATIO (NE:5-HT)	REFERENCE
TCA	Amitriptyline	19	2.8	Ki*, transporter binding	7:1	Owens, M., et al., 1997
		35	4.3	KD, transporter binding	8:1	Tatsumi, M., et al., 1997
		24	39	IC50, uptake inhibition	1:1.6	Hyttel, J., 1994
		63	67	Ki, uptake inhibition	1:1.1	Vaishnavi, S.N., (In Press)
	Nortriptyline	1.8	15	Ki*, transporter binding	1:8	Owens, M., et al., 1997
		4.37	18	KD, transporter binding	1:4	Tatsumi, M., et al., 1997
		3.4	570	IC50, uptake inhibition	1:168	Hyttel, J., 1994
	Maprotiline	11.1	5800	KD, transporter binding	1:523	Tatsumi, M., et al., 1997
	Doxepin	29.5	68	KD, transporter binding	1:2.3	Tatsumi, M., et al., 1997
	Dothiepin	46	8.6	KD, transporter binding	5.3:1	Tatsumi, M., et al., 1997
	Imipramine	20	1.3	Ki*, transporter binding	15:1	Owens, M., et al., 1997
		37	1.4	KD, transporter binding	26:1	Tatsumi, M., et al., 1997
SSRI	Fluoxetine	777	0.9	Ki*, transporter binding	863:1	Owens, M., et al., 1997
		240	0.81	KD, transporter binding	296:1	Tatsumi, M., et al., 1997
	Citalopram	7865	1.5	Ki*, transporter binding	5243:1	Owens, M., et al., 1997
		4070	1.16	KD, transporter binding	3509:1	Tatsumi, M., et al., 1997
	Paroxetine	85	0.065	Ki*, transporter binding	1307:1	Owens, M., et al., 1997
		40	0.13	KD, transporter binding	308:1	Tatsumi, M., et al., 1997
	Sertraline	817	0.15	Ki*, transporter binding	5447:1	Owens, M., et al., 1997
		420	0.29	KD, transporter binding	1448:1	Tatsumi, M., et al., 1997
DRI	Milnacipran	4.3	14	IC50, uptake inhibition	1:3.3	Rao, S.G., 2002
		68	151	Ki, uptake inhibition	1:2.2	Vaishnavi, S.N., (In Press)
		100	203	IC50, uptake inhibition	1:2	Moret, C., et al., 1985
	Duloxetine	3.45	0.8	IC50, uptake inhibition	4.3:1	Rao, S.G., 2002
		20	3.7	Ki, uptake inhibition	5.4:1	Vaishnavi, S.N., (In Press)
	Venlafaxine	2269	7.5	Ki*, transporter binding	300:1	Owens, M., et al., 1997
		1060	8.9	KD, transporter binding	120:1	Tatsumi, M., et al., 1997
		1420	145	Ki, uptake inhibition	9.8:1	Vaishnavi, S.N., (In Press)
		1260	74	Ki#, transporter binding	17:1	Beique, J., et al., 1998

*compared to [3H]citalopram or [3H]nisoxetine in HEK-293 cells transfected with human SERT or NET.

#compared to [3H]cyanoimipramine and [3H]nisoxetin in rat brain membranes.

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