Published in final edited form as:

Curr Opin Anaesthesiol. 2011 October ; 24(5): 532–539. doi:10.1097/ACO.0b013e32834a1091.

Fibromyalgia: A Primer for the Anesthesia Community

Chad M. Brummett, M.D. [Assistant Professor, Director of Pain Research] and
Department of Anesthesiology, University of Michigan Health System, Ann Arbor, MI

Daniel J. Clauw, M.D. [Director] [Professor]
Chronic Pain and Fatigue Research Center

Departments of Anesthesiology, Internal Medicine (Rheumatology), and Psychiatry, University of Michigan Health System, Ann Arbor, MI

Abstract

Purpose of the Review—The present review is intended to give an overview of fibromyalgia for the anesthesiologist. While the basics of the treatment of fibromyalgia are included, the intent is to provide context to discuss the potential implications in perioperative management.

Recent Findings—One of the most important changes in the last year is the new criteria established by the American College of Rheumatology for the diagnosis of fibromyalgia. Instead of a combination of self-report and a tender point examination, there is a new self-report questionnaire that is now used to diagnose fibromyalgia. This tool incorporates aspects of widespread body pain and some of the known comorbid symptoms. A score of 0-31 is given, which allows for the disease to be viewed as a continuum of sensitivity and symptomatology, instead of as a binary diagnosis. This continuum has been termed “fibromyalgia-ness.” This article also reviews the advances in understanding of the pathophysiology and emerging therapies. Little is known about the impact of fibromyalgia in the perioperative period.

Summary—The impact of fibromyalgia on anesthesia care is not known. Years of quality research have clearly demonstrated multiple pathophysiologic changes that could impact anesthesia care and future study is needed.

Keywords

fibromyalgia; treatment; anesthesiology; postoperative pain; chronic post-surgical pain

Introduction

After years of skepticism and questioning, fibromyalgia is now a widely accepted medical disorder with many years of research identifying the augmented pain and sensory processing and distinct clinical phenotype. As there is no definitive test, biomarker or physical exam to ensure the presence of fibromyalgia, the diagnosis is given to a patient with widespread pain

Corresponding Author: Chad M. Brummett, M.D. University Hospital Department of Anesthesiology 1500 East Medical Center Drive 1H247 Box 5048 Ann Arbor, MI 48109 Phone: 734-936-4280 Fax: 734-936-9091 cbrummet@umich.edu.

Disclosures: Dr. Brummett has no relevant disclosures. Dr. Clauw is a consultant for Pfizer, Inc (New York, NY); Johnson and Johnson (New Brunswick, NJ), Forest Pharmaceuticals (New York, NY); Merck (Whitehouse Station, NJ); Nuvo Research, Inc. (Mississauga, Ontario); Eli Lilly, Inc. (Indianapolis, IN); Grunenthal Pharma Ltd. (Dublin, Ireland); Jazz Pharmaceuticals, Inc. (Palo Alto, CA). Dr. Clauw also receives research funding from Pfizer Pharmaceuticals and Forest Pharmaceuticals.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and co-morbid symptomatology. While accepted as an independent diagnosis by many clinicians, perhaps the most important new knowledge regarding this condition is to think of it as a metaphor or construct rather than a discrete diagnosis that best applies to some individuals with prominent central nervous system contributions to their chronic pain.(1) For several decades fibromyalgia has been known to frequently occur as a co-morbidity with a group of conditions such as irritable bowel syndrome, tension headaches, temporomandibular joint disorder, and interstitial cystitis.(2) However, more recent work has shown that the same central nervous system contributions to pain occur in subsets of individuals with nearly any type of chronic pain, including low back pain, osteoarthritis, and even inflammatory pain states such as rheumatoid arthritis.(3-6) Furthermore, this phenomenon is now understood to occur over a continuum rather than being present or absent, and has been termed “fibromyalginess” by Wolfe, who has demonstrated that the degree of fibromyalgia predicts pain and disability across all rheumatic disorders.(7, 8)

There are a multitude of recent reviews that focus on the epidemiology, pathophysiology, diagnosis, and treatment of fibromyalgia.(1, 9) This article will review the basics of fibromyalgia, but special attention will be paid to the implications for the anesthesiologist, especially regarding future research directions for the importance of assessing fibromyalginess (or the CNS contributions to pain) in both acute and chronic pain settings.

Diagnostic Criteria for Fibromyalgia

The diagnosis of fibromyalgia has been a source of confusion and frustration for clinicians for many years. Traditional teaching required assessment of “tender points” with a diagnosis of fibromyalgia being made when the patient reported 11 or more of the 18 discrete points during physical examination.(10) Although most patients with fibromyalgia satisfy the tender point criteria, it is common that patients describe other areas of pain and tenderness, along with other comorbid symptoms and diagnoses. As such, the American College of Rheumatology (ACR) has created new diagnostic criteria for fibromyalgia that replace the tender point evaluation with a self-report measure of widespread body pain and comorbid symptomatology (fatigue, trouble thinking, waking up tired, depression, abdominal pain/cramps, and headache; Fig. 1).(11)

Epidemiology

Epidemiologic approaches to the fibromyalgia population have enhanced the understanding of the disorder and led to further hypothesis generation and ongoing research. The historical component of fibromyalgia, i.e. chronic widespread pain, is remarkably constant in different countries and cultures, afflicting approximately 8% of men and 12 % of women.(12) The older ACR criteria for fibromyalgia had unintendedly transformed a condition that affected slightly more women than men into one that almost exclusively affected women by also requiring that individuals have 11 or greater tender points – it was not until well after this criteria had been published that it became clear that women are much more tender than men, and that this element of the original criteria was biasing the criteria towards only identifying women with the condition.(13) There is a strong family predisposition for developing fibromyalgia, but again now this is more broadly understood to occur across chronic pain conditions.(14) The first degree relatives of fibromyalgia patients have 8x the risk of developing fibromyalgia and much higher risks of developing any type of chronic pain, and are much more tender, than the first degree relatives of controls.(15)

Altered Sensory Perception and Central Neurotransmission

Pain is the most common complaint of fibromyalgia patients. Patients with fibromyalgia demonstrate altered thresholds for virtually every type of sensory testing, including

nociception, proprioception, and even auditory perception.(16, 17) Many experts describe the sensory differences as altered volume control---essentially, the volume or gain on sensory processing is turned up in these patients. Although there are a number of ways to detect pain sensitivity, many experts agree that pressure pain testing (i.e. assessing mechanical rather than thermal or cold pain threshold) is the most reliable and reproducible method. These findings of augmented sensory processing noted by quantitative sensory have been corroborated by many functional neuroimaging studies that likewise demonstrate augmented pain processing, showing clear “objective” evidence of abnormal CNS pain processing in this condition.(18) In addition, approximately 80% of fibromyalgia patients, and comparable proportions of individuals with other chronic pain syndromes with prominent CNS contributions, demonstrate abnormal or absent descending analgesic activity.(19) Of note, although historically some have questioned whether fibromyalgia is fundamentally a psychiatric disorder with pathophysiology similar to depression, neither diffuse pain sensitivity nor decreased descending analgesic activity are found in individuals with depression.(20, 21)

A more complete understanding of the pathophysiology of fibromyalgia can be gleaned by examining the aggregate data regarding altered levels of central nervous system neurotransmitters. These findings correlate with the mood (see “Comorbid Psychopathology” section below) and pain complaints. Fibromyalgia patients have higher levels of CNS neurotransmitters associated with facilitation of pain when compared with controls, including glutamate and substance P.(22) Although most of these studies have examined cerebrospinal fluid (CSF) levels of neurotransmitters, Harris has performed a series of studies using proton spectroscopy to demonstrate that glutamate levels are elevated in the insula of individuals with FIBROMYALGIA (a finding also noted in CSF), and insular glutamate levels are closely related to pain sensitivity *in both fibromyalgia patients and controls*.(23, 24) These studies add additional biological support to the “fibromyalgia-ness” construct, because the relationship between insular glutamate was the same in both fibromyalgia and controls, but the fibromyalgia group was more pain sensitive because their mean glutamate levels were higher (Figure 2). Neurotransmitters associated with down-regulation of pain tend to be lower, including norepinephrine, serotonin (5HT_{1a,b}), and GABA. Endogenous opioid levels (and PET derived mu-opioid receptor occupancy) tend to be paradoxically elevated with decreased opioid receptor availability, perhaps explaining why individuals with fibromyalgia and other “central” pain states do not seem to respond to opioids.(25, 26) Thus, despite the lack of a definitive clinical biomarker or test for fibromyalgia, these findings have largely validated the complaints and symptoms of fibromyalgia patients, altered the treatment recommendations (See “Treatment of Fibromyalgia” section below), and led to an explosion in new pain research.

Comorbid Psychopathology

Psychological diagnoses, especially depression and anxiety, are common in the fibromyalgia population, as they are in any chronic pain condition. Although some have suggested that psychopathology is the “cause” of fibromyalgia, at any given time a minority of individuals with fibromyalgia will display an active Axis I or II psychiatric disorder, and psychological variables do not fully explain the widespread body pain and symptoms seen in this population. It is likely that some of the same neurotransmitter abnormalities that contribute to pain amplification (e.g., high Substance P and glutamate, low serotonin, norepinephrine and GABA) also contribute to the fatigue, sleep, memory, and mood symptoms experienced by individuals with fibromyalgia or fibromyalgia-ness.

Other Comorbid Conditions and Symptoms

While fibromyalgia remains an independent medical diagnosis, comorbid clusters of other pain conditions are often seen. These symptoms and conditions include headaches, temporomandibular joint pain, idiopathic low back pain, non-functional gastroenterological disorders, esophageal dysmotility, non-cardiac chest pain, interstitial cystitis, chronic prostatitis, vulvodynia, chronic fatigue, sleep disorders, memory disturbances, cognitive dysfunction, dry eyes, and “chemical sensitivity” (likely sensory sensitivity misnamed). Just as with any other disease, patients do not uniformly manifest all symptoms or disorders, and the pathophysiology behind the clustering is still an area of ongoing research.

Genetic Predisposition

Supporting the notion that there is a strong familial contribution to fibromyalgia, as well as more broadly chronic pain and tenderness, several genes have been identified that occur more commonly in fibromyalgia patients than controls. As is commonly seen in genetic studies, these genes are not found in all studies, but those involving regulation of serotonin and norepinephrine are the ones most commonly identified, including the serotonin receptor polymorphisms, and catechol-O-methyl transferase (COMT).(26, 27) Since some of these same genes that lead to decreased availability of serotonin or norepinephrine have also been shown to put individuals at risk for developing major depressive disorder, a better understanding is developing regarding why psychiatric conditions such as depression, post-traumatic stress disorder, obsessive compulsive disorder, and other disorder occur more commonly as co-morbidities in central pain states.

Treatment of Fibromyalgia

There are multiple recent reviews and meta-analyses that provide a more complete of the chronic management of fibromyalgia.(28-30) Although many clinicians assume that our treatments for fibromyalgia are less effective than those we use for other chronic pain conditions, data suggest otherwise, and overall efficacy of our current drugs for fibromyalgia is comparable to pharmacological therapy for other chronic pain states.(31) However, excluding chronic pain physicians, anesthesiologists and acute pain physicians are not normally directly involved in the chronic management of fibromyalgia patients. Therefore, the basics will be reviewed without detail to allow for context for most anesthesiologists.

Opioid and NSAID Therapy

Although NSAIDs and opioids are very effective analgesics for acute pain, and amongst the first line agents selected for many patients with long-standing pain, there is no evidence that either of these treatments is effective in fibromyalgia. These are among the many lines of evidence that suggest that chronic pain is not simply acute pain that has lasted too long, and it cannot be effectively treated as such. Despite the recommendation against the use of opioids in fibromyalgia, as well as the (largely anecdotal) concern that these patients may preferentially be at risk for opioid-induced hyperalgesia that would actually lead to worsening of their pain with these agents, their use in the condition is still widespread.

Antidepressants

Many of the recommended and Food and Drug Administration (FDA) approved drugs are in the antidepressant class, but it is important to recognize that not all antidepressants are effective in pain, or fibromyalgia. Duloxetine (Cymbalta, Eli Lilly Co, Indianapolis, IN) and milnacipran (Savella, Forest Pharmaceuticals, St. Louis, MO) are both in the class of serotonin-norepinephrine reuptake inhibitors (SNRIs), and have both been approved for use

in fibromyalgia. Prior to these FDA-approved drugs, tricyclic antidepressants (TCAs), such as amitriptyline, were the best studied and most commonly used class of drugs in fibromyalgia.(32) While this group does not carry official FDA approval, they also block the reuptake of serotonin and norepinephrine. The anti-cholinergic side-effects of TCAs often limit their tolerability, especially in older patients. The benefit of TCAs is that they are inexpensive and can also restore sleep cycles.

Two important clinical points bear emphasis. First, the efficacy of antidepressants in fibromyalgia and other chronic pain conditions seems to be independent of their antidepressant effects.(29) Moreover, it appears as though norepinephrine is the most important of the two neurotransmitters for relief of chronic pain, in that a pure norepinephrine reuptake inhibitor (es-reboxetine) has been shown to be quite effective in fibromyalgia (although it is not currently available in the US), whereas highly selective serotonin reuptake inhibitors (e.g. citalopram, es-citalopram) have not been shown to be effective in pre-clinical or clinical chronic pain conditions.(33)

Gabapentanoids

Another class of medications used in fibromyalgia are the gabapentanoids, or alpha-2-delta calcium channel ligands. The only medication in this class that carries FDA approval is pregabalin (Lyrica, Pfizer, New York, NY), but a randomized-controlled trial in fibromyalgia showed similar efficacy using gabapentin.(33, 34) While there may be some unique dosing and pharmacokinetic properties with pregabalin when compared with gabapentin, the efficacy and side effect profiles are not significantly different.

Emerging therapies

Because of the approval of three drugs for fibromyalgia, and the fact that the majority of trials that have been performed in the past decade in this condition have been “positive,” there has been significant work in developing even better therapies for fibromyalgia. Sodium oxybate (also known as gamma-hydroxybutyrate or GHB) is an example of a compound that has recently been shown to be very efficacious in fibromyalgia.(35) However, in spite of the strong efficacy data this drug was not approved by the FDA because of safety concerns. Nonetheless, the prominent simultaneous salutary effects on pain, sleep, and fatigue strongly suggest that low GABA is an important therapeutic target in fibromyalgia and related conditions. Similarly, although there are no cannabinoids approved for use in chronic pain in the US, this class of drugs has displayed efficacy in both fibromyalgia and in other chronic pain conditions.(36, 37) Another neurotransmitter system that is clearly involved in fibromyalgia and more broadly in pain is the glutamatergic system, as evidenced by the fact that an intravenous ketamine infusion seems to be predictive of subsequent responsiveness to dextromethorphan in fibromyalgia, but is not efficacious itself as long-term therapy.(38, 39)

Another exciting development in the pain field that is being partially led by work in fibromyalgia is the explosion of interest and knowledge in the use of central neurostimulatory therapies in fibromyalgia and related conditions.(40-43) These therapies, which include transcranial direct current stimulation and magnetic stimulation, have been shown to have impressive effects on pain and a number of other domains in fibromyalgia, and in some cases the effect of therapy has lasted well after the cessation of treatment.

Non-Pharmacological Therapies

Non-pharmacological therapies should be a key component to the overall treatment of fibromyalgia as well as any other chronic pain condition, but are often under-utilized in clinical practice. The treatments in this regard with the most consistent effects include

patient education, cognitive behavioral therapies, and exercise.(44) While the treatment of depression and anxiety seems obvious to most clinicians, cognitive behavioral therapy (CBT) and biofeedback are specific techniques that demonstrate effect sizes that are often greater than many of the pharmacologic treatments. These techniques are unique to standard methods of counseling and are not offered by all psychiatrists and psychologists. Despite the documented efficacy of CBT and exercise, many patients cannot find trained providers in their local communities, and more commonly insurance providers do not pay for the service. Because of this, many groups are moving towards showing that internet-based programs that incorporate education, CBT and exercise can be quite effective in fibromyalgia and other chronic pain states.(45) The content of these programs is also being scrutinized and refined as studies are demonstrating that even becoming more active (in contrast to formal exercise) can be beneficial in fibromyalgia, and that CBT that encourages individuals to identify stressful early life events and “disclose” and work through these events might actually cure some individuals with chronic pain, instead of palliation as occurs with typical CBT.(46-48)

Implications for the Anesthesiologist

Whereas much has been learned about the chronic management of fibromyalgia, there are almost no data to guide the management of fibromyalgia patients in the perioperative setting.

Acute Pain Management

While an increased understanding of the pathophysiology of fibromyalgia has not led to a cure of the disease, years of intensive research have led to major changes in the ways that fibromyalgia patients are treated in the outpatient setting. In the chronic pain setting, fibromyalgia patients are not thought to derive analgesic benefit from opioids, likely due to the increased endogenous endorphin and enkephalin levels and decreased opioid receptor availability. As was previously noted, patients tend to respond better to medications targeting the altered central neurotransmitters, including serotonin and norepinephrine. Despite the changes in the outpatient treatment of fibromyalgia, anesthesiologists do not currently individualize care for fibromyalgia patients, much less reliably assess for the diagnosis. There are no data as to whether fibromyalgia patients are less likely to respond to opioids in the perioperative period or disproportionately manifest side effects from their use. The only recommended fibromyalgia medications used with any regularity in the perioperative period are gabapentin and pregabalin;(49, 50) however, these medications have been widely applied in the acute pain setting without regard to a particular responder profile.

There are certainly limits to the degree to which an anesthetic can be “personalized” for a fibromyalgia patient, but attempts should be made to determine whether the lessons learned from the outpatient management of fibromyalgia can apply to the acute pain setting. It is important that we begin to create treatment algorithms that are specific to the patient instead of the surgical condition. Are there patients in whom opioids should be limited? Should gabapentin be included as a portion of every anesthetic for a fibromyalgia patient? Is regional anesthesia a preferred method for postoperative analgesia, even when it seems as though it is not necessary for the surgery being performed?

Chronic Post-Surgical Pain

Chronic post-surgical pain has been the focus of a number of editorials and intensive sessions at recent anesthesia conferences.(51, 52) Much of the focus has been in cases of new chronic post-surgical pain, as is seen in thoracic surgery, breast surgery, and amputation.(53) Unfortunately, the risk factors predisposing patients to chronic pain after

surgery and the transition from acute to chronic pain are still poorly understood. Many experts now believe that there is a “pain prone” phenotype (likely with corresponding genotypic alterations) that predisposes patients to chronic pain after an insult or stressful period. Research in the prevention of chronic post-surgical pain has been focused on aggressive treatment of acute pain due to the association between severe acute pain and the development of chronic pain. Acute pain management is likely warranted and continued research is reasonable; however, it is quite possible that the same patients that are prone to severe acute pain are also predisposed to chronic pain. Whereas a fibromyalgia phenotype may not explain all of the predisposed patients, it is logical to assume that the pathophysiologic alterations associated with fibromyalgia may also lead to chronic pain after surgery. Future research is needed to confirm this hypothesis.

There are also many surgeries done each year intended to treat a pain condition, such as lower extremity joint arthroplasty.(54) While these interventions do frequently improve pain, analyses of outliers clearly indicate that there is a subset of patients that fail to improve.(55-58) Such surgeries are intended to treat a peripheral condition (i.e. knee or hip osteoarthritis), while the etiology of the patients pain may actually be due to altered central pain processing. Whether preoperative fibromyalgia actually predicts poor outcome is not known but is an area of ongoing research by our group. Previous studies of failure to respond to total knee arthroplasty paint a picture of a fibromyalgia patient--longer duration of pain, pain in other locations, and depression.(55, 58) Further understanding of how to predict failure could greatly improve patient care and physician satisfaction, while also saving enormous amounts of money. Certainly, if some patients are deemed not to be good candidates for surgery, non-operative management options will need to continue to be explored.

Future Directions

It is clear that there is a subset of the population that has altered pain and other sensory thresholds due to central nervous system factors. The fibromyalgia population seems like a logical starting point for the implementation of “personalized analgesia.” One of the key limitations in actualizing this type of personalized analgesia is the detection of patients with altered central pain processing. The anesthesia community is beginning to embrace the multiple domains that need to be included in pain research beyond a 0-10 number, such as physical function and psychological measures. The use of well-constructed self-report questionnaires allows us to get a phenotype. Additional research is needed to understand the sensitivity and potential applications of self-report questionnaires. The use of point-of-care genotypic analyses as a portion of the preoperative assessment for pain sensitivity is also an area of a great deal of research. Hopefully, through a combination of genotype and phenotype, pain prone patients can be identified and anesthesia can be tailored to the individual.

Conclusion

Fibromyalgia is a disorder of widespread body pain and comorbid symptomatology that can significantly impact quality of life. Increased understanding of some of the mechanistic underpinnings of fibromyalgia has advanced care and research in the chronic pain setting. There are limited data regarding the impact of fibromyalgia in the acute pain and perioperative setting. While some of the lessons from the chronic management of fibromyalgia can be applied to acute pain, future studies are needed.

Reference List

1. Ablin K, Clauw DJ. From fibrositis to functional somatic syndromes to a bell-shaped curve of pain and sensory sensitivity: evolution of a clinical construct. *Rheum Dis Clin North Am*. May; 2009 35(2):233–51. [PubMed: 19647139]
2. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med*. Jan 24; 2000 160(2): 221–7. [PubMed: 10647761]
3. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum*. Feb; 2004 50(2):613–23. [PubMed: 14872506]
4. Gwilym SE, Keltner JR, Warnaby CE, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum*. Sep 15; 2009 61(9):1226–34. [PubMed: 19714588]
5. Lee YC, Chibnik LB, Lu B, et al. The relationship between disease activity, sleep, psychiatric distress and pain sensitivity in rheumatoid arthritis: a cross-sectional study. *Arthritis Res Ther*. 2009; 11(5):R160. [PubMed: 19874580]
6. Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther*. Apr 28.2011 13(2):211. [PubMed: 21542893]
7. Wolfe F. Fibromyalgianess. *Arthritis Rheum*. Jun 15; 2009 61(6):715–6. [PubMed: 19479689]
8. Wolfe F, Michaud K. Outcome and predictor relationships in fibromyalgia and rheumatoid arthritis: evidence concerning the continuum versus discrete disorder hypothesis. *J Rheumatol*. Apr; 2009 36(4):831–6. [PubMed: 19228653]
9. Arnold LM, Clauw DJ. Fibromyalgia syndrome: practical strategies for improving diagnosis and patient outcomes. *Am J Med*. Jun.2010 123(6):S2. [PubMed: 20569735]
10. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. Feb; 1990 33(2):160–72. [PubMed: 2306288]
11. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*. May; 2010 62(5):600–10. [PubMed: 20461783] **Summary- The American College of Rheumatology criteria for the diagnosis of fibromyalgia have been modified and no longer require a physical examination. Instead, a new self-report questionnaire has been developed for the diagnosis and now allows for the calculation of a “fibromyalgia-ness” scale.
12. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol*. Jun; 2007 21(3):403–25. [PubMed: 17602991]
13. Wolfe F, Ross K, Anderson J, et al. Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. *J Rheumatol*. Jan; 1995 22(1):151–6. [PubMed: 7699662]
14. Diatchenko L, Nackley AG, Tchivileva IE, et al. Genetic architecture of human pain perception. *Trends Genet*. Dec; 2007 23(12):605–13. [PubMed: 18023497]
15. Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. *Arthritis Rheum*. Mar; 2004 50(3):944–52. [PubMed: 15022338]
16. Geisser ME, Glass JM, Rajcevska LD, et al. A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. *J Pain*. May; 2008 9(5):417–22. [PubMed: 18280211]
17. Geisser ME, Donnell C Strader, Petzke F, et al. Comorbid somatic symptoms and functional status in patients with fibromyalgia and chronic fatigue syndrome: sensory amplification as a common mechanism. *Psychosomatics*. May-Jun;2008 49(3):235–42. [PubMed: 18448779]
18. Nebel MB, Gracely RH. Neuroimaging of fibromyalgia. *Rheum Dis Clin North Am*. May; 2009 35(2):313–27. [PubMed: 19647145]
19. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol*. Oct; 2010 23(5):611–5. [PubMed: 20543676]

20. Giesecke T, Gracely RH, Williams DA, et al. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis Rheum.* May; 2005 52(5):1577–84. [PubMed: 15880832]
21. Paul-Savoie E, Potvin S, Daigle K, et al. A Deficit in Peripheral Serotonin Levels in Major Depressive Disorder but not in Chronic Widespread Pain. *Clin J Pain.* Mar 16.2011 *Summary- Serotonin levels were compared between fibromyalgia patients, patients with major depressive disorder, and healthy controls. Compared with fibromyalgia patients and healthy controls, patients with depression had lower serotonin levels, thereby indicating that serotonin levels are not necessarily lowered in fibromyalgia.
22. Dadabhoy D, Crofford LJ, Spaeth M, et al. Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome. *Arthritis Res Ther.* 2008; 10(4):211. [PubMed: 18768089]
23. Harris RE, Sundgren PC, Craig AD, et al. Elevated insular glutamate in fibromyalgia is associated with experimental pain. *Arthritis Rheum.* Oct; 2009 60(10):3146–52. [PubMed: 19790053]
24. Harris RE, Sundgren PC, Pang Y, et al. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. *Arthritis Rheum.* Mar; 2008 58(3):903–7. [PubMed: 18311814]
25. Harris RE, Clauw DJ, Scott DJ, et al. Decreased central mu-opioid receptor availability in fibromyalgia. *J Neurosci.* Sep 12; 2007 27(37):10000–6. [PubMed: 17855614]
26. Xiao Y, He W, Russell IJ. Genetic Polymorphisms of the {beta}2-Adrenergic Receptor Relate to Guanosine Protein-coupled Stimulator Receptor Dysfunction in Fibromyalgia Syndrome. *J Rheumatol.* Mar 16.2011
27. Lee YH, Choi SJ, Ji JD, et al. Candidate gene studies of fibromyalgia: a systematic review and meta-analysis. *Rheumatol Int.* Dec 1.2010
28. Arnold LM, Clauw DJ, McCarberg BH. Improving the Recognition and Diagnosis of Fibromyalgia. *Mayo Clin Proc.* May; 2011 86(5):457–64. [PubMed: 21531887]
29. Hauser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA.* Jan 14; 2009 301(2):198–209. [PubMed: 19141768]
30. Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. *J Pain.* Jun; 2010 11(6):505–21. [PubMed: 20418173]
31. Clauw DJ. Pain management: Fibromyalgia drugs are ‘as good as it gets’ in chronic pain. *Nat Rev Rheumatol.* Aug; 2010 6(8):439–40. [PubMed: 20676122]
32. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics.* Mar-Apr;2000 41(2):104–13. [PubMed: 10749947]
33. Hauser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with gabapentin and pregabalin--a meta-analysis of randomized controlled trials. *Pain.* Sep; 2009 145(1-2):69–81. [PubMed: 19539427]
34. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* Apr; 2007 56(4):1336–44. [PubMed: 17393438]
35. Russell IJ, Holman AJ, Swick TJ, et al. Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: Results from a 14-week, randomized, double-blind, placebo-controlled study. *Pain.* May; 2011 152(5):1007–17. [PubMed: 21397402]
** Summary- Sodium oxybate, a GABA derivative, given to fibromyalgia patients improved pain, fatigue, sleep, and function when compared to placebo. While not approved for use in the U.S., it is a novel concept for future research.
36. Lynch ME, Campbell F. Cannabinoids for Treatment of Chronic Non-Cancer Pain; a Systematic Review of Randomized Trials. *Br J Clin Pharmacol.* Mar 23.2011
37. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. *J Pain.* Feb; 2008 9(2):164–73. [PubMed: 17974490]
38. Cohen SP, Verdolin MH, Chang AS, et al. The intravenous ketamine test predicts subsequent response to an oral dextromethorphan treatment regimen in fibromyalgia patients. *J Pain.* Jun; 2006 7(6):391–8. [PubMed: 16750795]
39. Noppers I, Niesters M, Swartjes M, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: A randomized, prospective, double blind, active

placebo-controlled trial. *Eur J Pain*. Apr 9.2011 * Summary- While ketamine provided short-term analgesia, the benefit was not present at the delayed time points in the weeks to follow. Therefore, there is not a role for periodic ketamine infusions in fibromyalgia patients.

40. Lefaucheur JP. Is rTMS a therapeutic option in chronic pain syndrome? Insights from the treatment of fibromyalgia. *Pain*. Mar 28.2011
41. Mhalla A, Baudic S, de Andrade DC, et al. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. *Pain*. Mar 10.2011 *Summary- When compared with a sham procedure, repetitive transcranial magnetic stimulation improved self-report of pain and quality of life measures.
42. Roizenblatt S, Fregni F, Gimenez R, et al. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. *Pain Pract*. Dec; 2007 7(4):297–306. [PubMed: 17986164]
43. Valle A, Roizenblatt S, Botte S, et al. Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. *J Pain Manag*. 2009; 2(3):353–61. [PubMed: 21170277]
44. Goldenberg DL. Multidisciplinary modalities in the treatment of fibromyalgia. *J Clin Psychiatry*. 2008; 69(Suppl 2):30–4. [PubMed: 18537461]
45. Williams DA, Kuper D, Segar M, et al. Internet-enhanced management of fibromyalgia: a randomized controlled trial. *Pain*. Dec; 2010 151(3):694–702. [PubMed: 20855168] ** Summary- Cognitive behavioral therapy has long been supported as an effective therapy in fibromyalgia and other chronic pain conditions, but access to care is often limited. Patients randomly assigned to a web-based behavioral self-management system showed significant improvements in pain, physical function and overall global improvement when compared with standard medical therapy for fibromyalgia. This extremely important study demonstrates the potential for the development of a web-based program to allow more patients to receive an effective therapy to which access is often limited.
46. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. *Arthritis Res Ther*. 2010; 12(2):R55. [PubMed: 20353551]
47. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity in adults with fibromyalgia: results at follow-up. *J Clin Rheumatol*. Mar; 2011 17(2):64–8. [PubMed: 21325963]
48. Hsu MC, Schubiner H, Lumley MA, et al. Sustained pain reduction through affective self-awareness in fibromyalgia: a randomized controlled trial. *J Gen Intern Med*. Oct; 2010 25(10):1064–70. [PubMed: 20532650]
49. Buvaendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol*. Oct; 2009 22(5):588–93. [PubMed: 19606021]
50. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. *Br J Anaesth*. Apr; 2011 106(4):454–62. [PubMed: 21357616]
51. Dworkin RH, McDermott MP, Raja SN. Preventing chronic postsurgical pain: how much of a difference makes a difference? *Anesthesiology*. Mar; 2010 112(3):516–8. [PubMed: 20124976]
52. Kehlet H, Rathmell JP. Persistent postsurgical pain: the path forward through better design of clinical studies. *Anesthesiology*. Mar; 2010 112(3):514–5. [PubMed: 20124977]
53. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. May 13; 2006 367(9522):1618–25. [PubMed: 16698416]
54. Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. Apr; 2007 89(4):780–5. [PubMed: 17403800]
55. Wylde V, Hewlett S, Learmonth ID, et al. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain*. Mar; 2011 152(3):566–72. [PubMed: 21239114] * Summary- Many patients fail to derive pain benefit following total knee replacement. In a study of patients 3–4 years after total knee arthroplasty, major depression and number of pain problems elsewhere were independent predictors of a poor outcome. Whereas these data do not directly implicate fibromyalgia as a risk factor for failure, the phenotype is consistent with high

fibromyalgia-ness and indicates that preoperative assessment tools may be beneficial in either selecting patients for surgery and/or personalizing their perioperative analgesic regimen.

56. Wylde V, Dieppe P, Hewlett S, et al. Total knee replacement: is it really an effective procedure for all? *Knee*. Dec; 2007 14(6):417–23. [PubMed: 17596949]
57. Nikolajsen L, Kristensen AD, Thillemann TM, et al. Pain and somatosensory findings in patients 3 years after total hip arthroplasty. *Eur J Pain*. Aug 29.2008
58. Bourne RB, Chesworth BM, Davis AM, et al. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res*. Jan; 2010 468(1):57–63. [PubMed: 19844772]

Key Points

- Fibromyalgia is a disorder of widespread pain, which is due to augmentation of central pain processing.
- Comorbid symptoms such as depression, anxiety, fatigue, and difficulty thinking are common but not uniformly expressed in all patients.
- The American College of Rheumatology recently eliminated tender point examinations and have created a self-report questionnaire for the diagnosis of fibromyalgia.
- Improved understanding of the altered central neurotransmitter levels (i.e. low norepinephrine and serotonin) has helped direct treatment and research.
- Future research is needed to understand the impact of fibromyalgia in perioperative medicine, acute pain, and the development of chronic post-surgical pain.

Fibromyalgia Diagnostic Criteria

1) WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.

Put a Check to indicate a painful region.

☐ Shoulder, Lt. ☐ Shoulder, Rt.	☐ Upper Leg, Lt. ☐ Upper Leg, Rt.	☐ Lower Back ☐ Upper Back
☐ Hip, Lt. ☐ Hip, Rt.	☐ Lower Leg, Lt. ☐ Lower Leg, Rt.	☐ Neck
☐ Upper Arm, Lt. ☐ Upper Arm, Rt.	☐ Jaw, Lt. ☐ Jaw, Rt.	☐ No pain in any of these areas
☐ Lower Arm, Lt. ☐ Lower Arm, Rt.	☐ Chest ☐ Abdomen	

WPI score _____

2) SS scale score:

- ☐ Fatigue
☐ Waking unrefreshed
☐ Cognitive symptoms

For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:

- 0 = no problem
 1 = slight or mild problems, generally mild or intermittent
 2 = moderate, considerable problems, often present and/or at a moderate level
 3 = severe: pervasive, continuous, life-disturbing problems

Considering somatic symptoms in general, indicate whether the patient has:

- 0 = no symptoms
 1 = few symptoms
 2 = a moderate number of symptoms
 3 = a great deal of symptoms

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

SS Scale Score _____

Criteria

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

- 1) Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI 3–6 and SS scale score ≥ 9 .
- 2) Symptoms have been present at a similar level for at least 3 months.
- 3) The patient does not have a disorder that would otherwise explain the pain.

** Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.*

Figure 1. Updated American College of Rheumatology survey criteria for fibromyalgia
 The new ACR survey for FM with the 19 potential body areas and the symptom assessment. Scores can range from 0-31, and patients are asked whether the symptoms have been present at nearly the same level for the last 3 months or more. The presence of pain for 3 months or more with a score ≥ 13 meets the survey criteria for FM. (Adapted from Wolfe, F., et al., The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*, 2010. **62**(5): p. 600-10 with permission)

Figure 2. Glutamate levels in the posterior insula are negatively correlated with experimental pressure pain testing

Medium pressure thresholds from fibromyalgia patients (solid circles) and control patients (open circles) are displayed in this scatterplot, along with a regression line across both groups. Fibromyalgia patients demonstrated higher central glutamate levels and corresponding lower pain thresholds; however, the correlation between higher glutamate levels and lower pain thresholds was also demonstrated in the control group. Glx = glutamate (From Harris, R.E., et al., Elevated insular glutamate in fibromyalgia is associated with experimental pain. *Arthritis Rheum*, 2009. **60**(10): p. 3146-52 with permission)