A survey of current fibromyalgia treatment approaches together with an overview and case studies of a new “old” treatment approach.

By Gordon Ko, MD, CCFP(EM), FRCPC and William Wine, PhD, DSc(toxicology)

[Editor’s note: Practical Pain Management recognizes the many controversies that surround cannabinoids, yet one cannabinoid is already on the commercial market (Marinol®) and has a significant following for its FDA-labeled use of nausea. Additionally, we are aware of a plethora of research and development activities to produce legitimate commercial, cannabinoid products. To this end, it is appropriate to educate physicians regarding the pharmacology as well as potential, legitimate, legal uses of cannabinoids. The publication of this article on cannabinoids is not to be construed that Practical Pain Management endorses the illegal use of marijuana, and we urge all physicians to know and follow their state and federal laws regarding marijuana and cannabinoid products.]

According to the American College of Rheumatology (ACR) definition, fibromyalgia is a syndrome of widespread muscle pain (over 3 months) and stiffness with 11 or more characteristic tender points on palpation (see Figure 1). It affects 2% of the population, predominantly females, with the most common age at presentation of 40 to 50 years. Symptoms in the fibromyalgia syndrome (FMS) include:

1) musculoskeletal complaints: “hurt all over,” stiffness, swollen feeling in tissues;
2) nonmusculoskeletal: fatigue, poor sleep (with reduced stages 3/4 slow wave sleep), and paresthesia; and
3) associated syndromes such as irritable bowel syndrome (IBS; 41.8% of FMS patients), dysmenorrhea, female urethral syndrome, endometriosis, noncardiac chest pain, plantar heel pain, migraine headache (45%), temporomandibular joint pain, sinusitis, and Sjogren’s syndrome. A higher incidence of carpal tunnel syndrome and Raynaud’s syndrome may explain some of the paresthesia complaints.

Characteristic Tender Points of Fibromyalgia

Eleven out of 18 tender points is required to make a diagnosis of fibromyalgia according to criteria established by the American College of Rheumatology.1

- suboccipital muscle insertions
- anterior aspect of C5-7 intertransverse spaces
- midpoint of upper trapezius muscles
- supraspinatus origin above spine of scapula
- second rib lateral to costochondral junction
- extensor muscle: 2 cm distal to lat. epicondyle
- gluteal: upper outer quadrant of buttock
- posterior to greater trochanter prominence
- medial fat pad of knee: proximal to joint line

FIGURE 1. Characteristic tender points of fibromyalgia.
Higher anxiety (63.8%) and depression have also been reported. The economic impact of this syndrome is significant. Chronic musculoskeletal pain is the number one cause of disability (under age 45) in North America, the number two cause for visits to the primary care physician and for workplace absences and the number three cause for hospitalizations in the USA. It is estimated that the direct medical cost of FMS to the U.S. economy is in excess of $16 billion annually. Despite such costs, effective long-term treatment remains elusive.

Etiology of Fibromyalgia

Postulated risk factors for the development of FMS include a family history of this condition, a family history of depression and/or alcoholism in first-degree relatives, childhood physical and sexual abuse, eating disorders, drug abuse, hypermobile joint syndrome. FMS has also been documented after physical trauma and whiplash, but the causal relationship has not been established in a consensus report on FMS and disability. A review on psychosocial aspects concluded that the view that FMS is caused by stress or abuse is unproven and that there is no evidence that communicating such a diagnosis causes iatrogenic consequences.

It has also been postulated that viral infections may play an etiologic role. 70% of FMS patients meet the Centers for Disease Control and Prevention criteria for chronic fatigue syndrome (CFS) and 70% of CFS patients meet the ACR criteria for FMS. The usual routine laboratory tests such as basic hematology, ESR, muscle enzymes, rheumatoid factor and ANA are all normal. CFS researchers suggest that deregulation of the 2.5A synthetase Rnase L antiviral pathway may be the pathophysiological reason. Muscle biopsy studies which are controlled have proven to be non-diagnostic. More recent electron microscopy suggests ultra-structural changes including increased DNA fragmentation (possibly due to persistent focal muscle contractions). Reduced growth hormone secretion; and elevated CSF substance P.

Survey of Fibromyalgia Treatments

The most studied medications to date are the tricyclic derivatives such as amitriptyline and cyclobenzaprine. Randomized controlled trials (RCT) of these and other treatments as outlined in Tables 1 and 2 below, only demonstrate short-term improvement in symptoms. Only the most recent or most comprehensive RCTs are referenced.

One recent review on pharmacological therapies concluded that the best supported medications to date are the low dose tricyclic antidepressants, but that the benefits are short-term and have not been shown to be superior to placebo in 6 months of study. FMS patients are high consumers of nonphysician and complementary alternative medical (CAM) interventions. One study comparing those using such services found no differences in level of pain and functional impairment. Another study of 111 FMS subjects found that 98% had used at least one complementary medical strategy in the preceding 6 months and that such use was correlated with lower age, higher pain and higher disability. Use of complementary therapies was seen in patients of a higher socioeconomic status and a longer duration of fibromyalgia. The most popular therapy was oral supplementation and the most popular source of advice was from magazines (40%). Table 2 presents alternative medicine therapies reported as being helpful for FMS pain.

In the first author’s survey of 116 physiatrists (rehabilitation medicine specialists) in Ontario, Canada, 55% of respondents agreed that FMS is a “real disabling condition.” When asked what type of alternative therapy works, 14 different types were mentioned with the top three being acupuncture, biofeedback and chiropractic. It would appear that there is presently no standard therapy that is highly effective for treating FMS. Perhaps, this is the reason why so many of these patients pursue CAM modalities.

Promising new studies indicate that an
effective treatment of FMS may be achieved with cannabinoids. Following is an overview of cannabinoids followed by case studies of treatment outcomes.

Cannabinoids Overview
Cannabinoids are derived from the cannabis sativa plant (marijuana) and have been used over the past three thousand years to treat many physical conditions, including pain (see Table 3).

Scientific research (see Table 4) has begun to elucidate the mechanisms of action of THC (tetrahydrocannabinol, the main psychoactive component). To date, two important cannabinoid receptors have been identified in the human body: CB1 and CB2. The former is mainly confined to the central nervous system (CNS) and the latter in the peripheral immune system (tonsils, spleen, mast cells, lymphocytes). Importantly, few CB1 receptors are found in the cardiorespiratory area of the brainstem which makes cannabinoids safe in overdose.129,130 Further laboratory studies have demonstrated effects on several endogenous systems including:

1) Endorphinergic (specifically the periaqueductal gray matter).131,133
2) Serotonergic (stimulates 5-HT synthesis and inhibits 5-HT3 receptors that mediate pain, nausea).134
3) Dopaminergic (inhibit dopamine D1 receptors and activate dopamine D2 receptors, both via CB1 receptors).135,136
4) Glutamatergic (act presynaptically via CB1 receptor to reduce glutamate transmission via NMDA receptors without blockade).137 Glutamate is an important mediator of neurogenic inflammation (neuropathic pain).
5) Anti-inflammatory (inhibit prostaglandins E-2 synthesis and may bind and activate a not-yet characterized CB2-like receptor).138
6) Increases corticosteroid secretion.139 Its effect on inhibiting neuronal injury was recently shown to be independent of this.140
7) Improves sleep: In humans, Delta9-THC increase stage 4, or deep, sleep and reduce the duration of REM itself.140-145 Delta9-THC was found to signifi-
cantly decrease the time it takes to fall asleep in physically healthy insomniacs. It also tended to be associated with some decrease in awakenings in the first half of the night.146

A direct effect stimulation of melatonin secretion by Delta9-THC may play a role.148

At the recent Canadian/American Pain Society meeting in Vancouver (May 2004), over 20 clinical papers on cannabinoids were presented. Several were N of 1 trials. Larger randomized trials are described in Table 5.

<table>
<thead>
<tr>
<th>PHYSICAL THERAPIES</th>
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<tbody>
<tr>
<td>Aerobic exercise, when combined with flexibility and strength training, is superior to relaxation.</td>
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<tr>
<td>Pool exercise, Hydrotherapy, Low power laser therapy, Strengthening exercise, TENS (uncontrolled study).</td>
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<tr>
<th>PSYCHOLOGICAL THERAPIES</th>
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<tr>
<td>Cognitive Behavioral therapy, Group therapy, including relaxation and cognitive behavioral training, Hypnotherapy, Meditation-based stress reduction program.</td>
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<tr>
<th>ALTERNATIVE MEDICINE TREATMENTS WITH POSITIVE CLINICAL TRIALS</th>
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<tr>
<td>Biochemical: DHEA supplementation, Dietary indole supplementation (ascorbigen and broccoli powder), Dietary supplementation of coenzyme Q10 combined with Ginkgo biloba extract, Homeopathy, Multimodality approach including nutrition and hormone replacement, O24 essential oils, SAMe, p.o (improved VAS pain, not TPI during last week of 6 week study), Super Malic (malic acid 200mg and magnesium 50mg: 6 tablets bid), Vegan diet.</td>
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<tr>
<td>Electromagnetic (autonomic nervous system): Acupuncture, Copper wire bedsheets, Cranial electrotherapy stimulation, Static electromagnetic fields, Thermoflow garments.</td>
</tr>
<tr>
<td>Psychoemotional: Biofeedback — relaxation (combined with exercise best across years), Biofeedback — EMG, EEG-driven, Mind-body therapies.</td>
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<tr>
<td>Structural: Chiropractic therapy (4 weeks of spinal manipulation, soft tissue therapy, passive stretching), Osteopathy, Prolotherapy (75% pain improvement; unblinded study).</td>
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TABLE 2. Non-physician therapies reported helpful for pain in FMS.

Case Studies Of Cannabinoid Treatment Of FMS
Case #1. A 50 year old public health nurse, divorced mother of two, presented with longstanding FMS. This included neck pain x 26 years, low back pain x 23 years, migraines x 13 years. Predisposing childhood factors included: growing pains, eating disorders, depression (father died of Hodgkin’s). Associated syn-
dromes: costocondritis, plantar fascitis, tendonitis, menopause. Non-helpful treatments included mobicox, amitriptyline, glucosamine, fish oil, guaifenesin (naturopathy), massage, pool exercise, cognitive behavioral therapy and relaxation therapy. Temporary relief with toradol, robaxacet, acetaminophen, topical rubs, heating pad, chiropractic, osteopathy. She was allergic to meperidine, codeine. Cold made her worse.

She declined acupuncture and injections. For migraines, she used migral, zomig, fiorinal. L-tryptophan helped. For migraines, she used migranal, zomig, fiorinal. L-tryptophan helped.

TOS Doppler study. Beck depression score: 9/63. Other Observations

In general, it was noted that responders (to cannabinoid therapy) scored lower depression ratings (Beck score <21), had no previous adverse reaction (paranoia, psychosis) to marijuana use, and were employed or retired. It appeared also to work well in combination with opioids by amplifying analgesia and reducing nausea. The latter effect also helped in FMS patients with GI problems (irritable bowel, Crohn's). Poor responders included those with unstable psychiatric states, multiple chemical sensitivities, nondermatomal somatosensory deficits (conversion disorder), and those actively seeking disability claims.

Patient Screening and Advising

The use of Nabilone is contraindicated in patients with known sensitivity to marijuana or other cannabinoid agents, and in those with a history of psychotic reactions. Since Nabilone can elevate heart rates and cause postural hypotension, it should be used with caution in the elderly and in patients with hypertension or heart disease. Nabilone is metabolized in the liver by the CYP 2C9 pathway and should be used with caution in patients with liver dysfunction. Due to the addi-
The evidence suggests that Nabilone (Cesamet), titrated in to obtain medical purposes.

• Listed in US Pharmacopoeia until 1941

Table 3. History of cannabinoid use.

tive effects, Nabilone should be used with caution in patients taking sedatives such as benzodiazepines, barbiturates, or excessive alcohol. When prescribing Nabilone, begin at a low dose and titrate up slowly.

Patients should be counseled on the most common adverse reactions:

• Drowsiness (reported in 66% of patients and therefore have them take initial doses prior to sleeping at night)
• Dysphoria/Euphoria — Mood alteration (reported in 30% of patients)
• Dry Mouth (reported in 22% of patients). Encourage patients with the knowledge that the adverse effects of Nabilone will decrease in 4-7 days.

Dosing

The recommended starting dose is 0.5mg QHS at bedtime. After 1-2 weeks the dose may be increased to 1mg QHS to enhance further analgesia. Some FMS patients are very sensitive to medications and may need to start at a lower dose of 0.25mg (in suspension).

Long-Term Management of Fibromyalgia

There is no universal "magic bullet" for the treatment of FMS. It is a syndrome and not a specific pathological disease entity. Diagnosis is made be exclusion (the usual lab tests are all negative). Symptoms may last on average 15 years.154 Review papers suggest that positive outcomes occur not only with age but also with an adequate physical activity level and coping skills. Excess major negative life events and permanent disability pensions were associated with a negative outcome. Younger age of onset and less sleep disturbance were associated with a more favorable outcome. Effective management is best with an interdisciplinary approach emphasizing lifestyle improvement ("TENSQ": Toxin elimination, Exercise, Nutrition, Sleep hygiene, Quiet "de-stress" time) and pain control. Perhaps oral and sublingual cannabinoids (without the stigma or pulmonary adverse effects of inhaled marijuana), used in an integrated approach will become an effective well-accepted standard therapy. These case studies backed by laboratory and clinical research indicated that it helps not only with pain but also with anxiety, irritable bowel and abnormal sleep.

Conclusions

One recent extensive FMS review paper listed 433 references. Out of this, there was no mention of cannabinoids. Our present review has summarized not only up-to-date published studies on chronic FMS pain management but also presented the first-ever reported case series of effective FMS treatment with cannabinoids.

The evidence suggests that Nabilone (Cesamet), titrated in low dosages is an extremely safe and effective pain medication for FMS patients. It also exhibits very little or no adverse drug interaction effects with concurrent analgesic or psychiatric medications. In fact, it appears to potentiate opioid medications, so that patients can taper doses to safer levels. All of this would support the contention that perhaps the most promising emerging treatment to date for pain control is the use of cannabinoids.

From an evidence-based perspective, there is an obvious need to do a randomized controlled double-blinded study for cannabinoids in FMS. It is hoped that this review will stimulate further research in this area and enhance the well-being and future use of cannabis.

Table 4. Medical cannabinoid key discoveries.

<table>
<thead>
<tr>
<th>Year</th>
<th>Key Discovery</th>
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<tbody>
<tr>
<td>1964</td>
<td>Delta 9THC identified as the main psychoactive ingredient of cannabis (Gaoni &amp; Mechoulam)</td>
</tr>
<tr>
<td>1980</td>
<td>Synthetic Cannabinoids</td>
</tr>
<tr>
<td>1988</td>
<td>CB1 Receptor identified (Devane et al.)</td>
</tr>
<tr>
<td>1990</td>
<td>CB1 Receptor cloned (Matsuda et al.)</td>
</tr>
<tr>
<td>1992</td>
<td>CB2 Receptor (Kaminski et al) + Endogenous Ligands (anandamide) (Mechoulam et al) identified</td>
</tr>
<tr>
<td>1993</td>
<td>CB2 Receptor cloned (Munro et al.)</td>
</tr>
<tr>
<td>1994-7</td>
<td>Cannabinoid Receptor Antagonists developed: (SR141716A) (Rinaldi-Carmona et al)</td>
</tr>
<tr>
<td>1998</td>
<td>Endogenous Ligands proven analgesics</td>
</tr>
<tr>
<td>1999</td>
<td>'Knock out' receptor modified mice CB1 (Ledent et al., Zimmer et al.)</td>
</tr>
<tr>
<td>2000</td>
<td>'Knock out' receptor modified mice CB2 (Buckley et al.)</td>
</tr>
<tr>
<td>2000-1</td>
<td>Clinical use of cannabis initiated Canada is first industrialized nation to legalize the use of medicinal marijuana (Allan Rock, federal minister of health).</td>
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</table>
TABLE 5. Summary of randomized trials of cannabinoids.

<table>
<thead>
<tr>
<th>Conditions</th>
<th># Subj</th>
<th>Cannabinoid Drug</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative pain or trauma pain*</td>
<td>56</td>
<td>Levonatradol 1.5 to 3mg i.m.</td>
<td>Significant analgesic effects of each dose of levonatradol as compared to placebo</td>
</tr>
<tr>
<td>Chronic refractory pain (esp. MS and neuropathic pain)**</td>
<td>60</td>
<td>Nabilone 0.25mg to 3mg</td>
<td>30% obtained significant relief and beyond that, a decreased use of other analgesics and psychotropic medications</td>
</tr>
<tr>
<td>Neuropathic pain**</td>
<td>24</td>
<td>THC &amp; CBD (Cannabidiol)</td>
<td>Pain relief significantly superior to placebo. Improved bladder control, muscle spasms and spasticity were improved.</td>
</tr>
<tr>
<td>Chronic pain**</td>
<td>34</td>
<td>THC; CBD; THC:CBD 1:1 mixture</td>
<td>Extracts which contained THC proved most effective in symptom control</td>
</tr>
<tr>
<td>Neuropathic pain**</td>
<td>21</td>
<td>CT-3</td>
<td>Effective in reducing chronic neuropathic pain compared with placebo</td>
</tr>
</tbody>
</table>

*June 2005. Its on-label indication is for care of our chronic pain patients.
**2005. The sublingual cannabinoid spray marketed by Bayer pharmaceuticals will be launched in Canada in June 2005. Its on-label indication is for neuropathic pain associated with multiple sclerosis.

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Dr. William Wine, PhD, DSc (toxicology) is a Psychopharmacologist at the Canadian Centre for Integrative Medicine, Markham, Ontario, Canada.

References (High quality treatment trials are followed with an asterisk below)

43. Rege M, Andersson M, Abrahamsen L et al. Increased...
TABLE 6. Case Study #1 Outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Two months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS pain (average)</td>
<td>9/10</td>
<td>6/10</td>
</tr>
<tr>
<td>FQI</td>
<td>85.0</td>
<td>61.9</td>
</tr>
<tr>
<td>APT</td>
<td>0.6 kg (18/18)</td>
<td>1.3 kg (18/18)</td>
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</table>

TABLE 7. Case Study #2 Outcomes.

<table>
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<tr>
<th></th>
<th>Pre-treatment</th>
<th>Six weeks later</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS pain (average)</td>
<td>9/10</td>
<td>5/10</td>
</tr>
<tr>
<td>FQI</td>
<td>77.4</td>
<td>63.0</td>
</tr>
<tr>
<td>APT</td>
<td>1.98 kg (15/18)</td>
<td>2.62 kg (10/18)</td>
</tr>
</tbody>
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TABLE 8. Case Study #4 Outcomes.

Chronic Pain and Cannabinoids