

Cannabis in Multiple Sclerosis: Women's Health Concerns

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SUMMARY. Women's health has received greater attention with the recognition of significant differences in disease expression and drug action in men and women. Multiple sclerosis is a neurological disorder with important gender differences. MS patients have employed cannabis to treat a number of symptoms associated with the disease including spasticity, pain, tremor, fatigue, and autonomic dysfunction. The scientific literature includes supportive case reports, single-patient (N-of-1) trials and randomized clinical trials. Large-scale clinical trials are underway to answer questions concerning the efficacy and safety of cannabis in patients with MS. While these studies will answer important questions concerning the actions of cannabinoids on the nervous system, additional studies in female MS patients will be needed to address issues such as gender-specific actions on symptoms such as pain and autonomic dysfunction along with studies in menopausal and post-menopausal women. Since the drug-drug interactions have been reported with cannabinoids, the effects of cannabis on the actions of other centrally-acting drugs should be explored. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <<http://www.HaworthPress.com>> © 2002 by The Haworth Press, Inc. All rights reserved.]

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INTRODUCTION

Women's health issues have received attention as gender differences in disease expression and drug action are discovered. A gender-based approach recognizes the fundamental physiologic differences between men and women. The areas of difference between men and women in the nervous system are extensive including anatomy, cell numbers, neurotransmitter systems, response to hormones, sensation threshold and disease frequencies. Gender and multiple sclerosis (MS) has been the subject of several excellent reviews (Olek and Khoury 2000; Coyle 2000). Specific disorders such as migraine headache, depression and motor neuron disease also show clear gender preferences.

Multiple sclerosis is a disorder with important gender-associated differences in expression. Cannabis also interacts with the endocrine and immune systems of males and females with distinctions. As therapeutic cannabis use among MS patients has increased over the past generation, a review of the subject with attention to women's health concerns is warranted.

Multiple sclerosis is the most common cause of chronic neurological disability in young adults (Rusk and Plum 1998), and is more likely seen in women and in those who grew up in northern latitudes. In a summary of 30 incidence/prevalence studies, the cumulative female-to-male ratio was 1.77:1.00 (Irizarry 1997). With 350,000 MS patients in the United States, the number of female MS patients is approximately 225,000. Gender is clearly a determinant of susceptibility to MS. The increased female incidence in MS is similar to other autoimmune diseases with onset of symptoms in adulthood such as myasthenia gravis, Hashimoto's thyroiditis, Sjögren's syndrome and systemic lupus erythematosus. The female preponderance in MS lessens in those in whom presentation occurs later in life. MS attacks are less frequent during pregnancy while the postpartum period is one of higher risk (Whitaker 1998). While the postpartum increase in risk for MS attacks may discourage child-bearing, women who have borne a child fare better in the long term than those women who have not (Runmarker and Anderson 1995). Interestingly, the occurrence of a first pregnancy may lead to some permanent change in immune status.

Recognizing that current MS treatment is less than optimal, the use of cannabis offers an opportunity to demonstrate the therapeutic potential of cannabinoids on a number of neurological symptoms. In a survey of health care in 471 people with MS in the United Kingdom, use of cannabis was acknowledged by 8% (Somerset et al. 2001). Extrapolating to the 60,000 MS patients in the UK provides an estimate of 4,800 MS patients who employ cannabis in the UK and 28,000 in the United States. In a publication commenting on the use of cannabis in South Africa, James (1994) reported the experiences of a female MS patient (p. 369):

A few years ago I had started to eat small quantities of marijuana . . . the effects were immediate and remarkable. Control of bladder functioning which was a humiliating problem is restored to normal and has been a liberating influence in my life-style. I can now go out shopping, to the theater, etc., without anticipation of dread and panic. Painful and disturbing attacks of spasticity are relieved and now restful patterns of sleep are ensured where previously sleep was disrupted by urinary frequency or pain and discomfort not least I can laugh and giggle, have marvelous sex and forget that I have this awful, incurable, intractable disease.

The challenge for physicians is to evaluate patient observations using scientific methodology. Many authors have described individual patient experiences of therapeutic use of cannabis to treat symptoms of MS (Grinspoon and Bakalar 1997; Brown 1998; Iversen 2000). Additional support has been provided by single-patient clinical trials (N-of-1) and prospective double-blind placebo-controlled studies.

TREATMENT OPTIONS: ACUTE EPISODES, DISEASE MODIFICATION AND SYMPTOM MANAGEMENT

Management of an acute episode of demyelination in MS is sometimes achieved to a limited extent with corticosteroids. Disease modification is difficult to assess because MS is a chronic, unpredictable disorder in which the burden of white matter involvement is highly variable and the clinical response to drug treatment is modest. Five drugs have been approved by regulatory authorities to modify the clinical course of MS. Avonex[®] (interferon-beta-1a), Betaseron[®] (interferon-beta-1b), Copaxone[®] (glatiramer acetate/copolymer 1), and Rebif[®] (interferon beta 1a) have demonstrated efficacy in relapsing-remitting MS and may slow the course of secondary progressive MS. Novantrone[®] (mitoxantrone) is approved for secondary progressive and progressive relapsing MS. Immunosuppressants such as corticosteroids, methotrexate, and cyclophosphamide have been used to alter the natural history of MS with some success.

CANNABIS IN ACUTE TREATMENT AND DISEASE MODIFICATION

While patients may claim that cannabis can alter the natural history of MS, no clinical trials have been conducted in either acute treatment or disease modification. Data from animal research supports cannabinoids as a potential disease modifying treatment for MS. The immune-mediated disease, experi-

mental autoimmune encephalomyelitis (EAE), is considered the laboratory model of MS. In a study in the Lewis rat and guinea pig, Lyman and colleagues (1989) demonstrated that the oral administration of Δ -9-tetrahydrocannabinol (THC) was effective in the prevention and suppression of EAE. The authors suggested that Δ -9-THC might prove to be a new and relatively innocuous agent for the treatment of immune-mediated diseases such as MS. Since Δ -9-THC is the cannabinoid associated with negative psychotropic actions, investigators used other cannabinoids to assess actions in EAE. Wirguin and colleagues (1994) studied the effect of Δ -8-THC on EAE in the rat. Orally administered Δ -8-THC significantly reduced the incidence and severity of neurological deficit while parenteral administration was not effective. The difference can be explained on first-pass metabolism in the liver, which produces the active metabolite. Additional support for beneficial effects of cannabinoids in EAE was reported by Achiron and co-investigators (2000) using a synthetic non-psychotropic cannabinoid, dexanabinol (HU-211). The authors suggested that dexanabinol may provide an alternate treatment of acute exacerbations of MS. Finally, Guzman, Sanchez and Galve-Roperh (2001) reviewed the experimental evidence showing the protective effects of cannabinoids from toxic insults such as glutamatergic over-stimulation, ischemia and oxidative damage. The authors described the potential of cannabinoids to downregulate inflammatory cytokine production.

If cannabinoid drugs are to be used in acute treatment of MS or in disease modification, then studies in female patients will be needed. These studies involve assessment of drug effects on fertility, pregnancy and in nursing mothers. Since inclusion of women in early clinical trials is usually insufficient to identify gender-based differences in response, animal models are used to identify potential pharmacologic and toxicological effects (Christian 2001). Unfortunately, current animal models do not consistently demonstrate gender-based differences seen in humans. The cannabinoid Δ -9-THC is marketed in the United States as Marinol[®] and information concerning use in women is provided in the Physicians' Desk Reference (2002). Marinol is included in Category C (FDA designation for drugs with animal data showing harm to the fetus with no controlled human studies). The drug labeling states that Marinol should be used only if the potential benefit justifies the potential risk to the fetus. Likewise, its use in nursing mothers is not recommended since Marinol is concentrated in and secreted in human breast milk and is absorbed by the nursing baby.

Drug interaction studies would be needed to investigate the potential for significant interactions with drugs commonly used by women. Because cannabinoids are highly bound to plasma proteins and might displace other protein-bound drugs, dosage adjustment for other highly protein-bound drugs may be needed. In addition, drugs metabolized by hepatic mixed-function

oxidase enzymes may be inhibited by cannabinoids (Benowitz and Jones 1977). In the PDR drug interaction section for Marinol, specific precautions are included regarding potential interactions with a number of drugs including sympathomimetic agents, antihistamines, tricyclic antidepressants, muscle relaxants, barbiturates and theophylline. Other drugs which may be important in female patients include birth control drugs, hormones administered to treat symptoms associated with menopause, steroids, and drugs used in the treatment of osteoporosis.

The effects of inhaled cannabis on fetal development have been studied extensively. In a study of six one-year-old infants exposed daily to cannabis prenatally and through breastfeeding, no malformations were found in cannabis-exposed infants (Tennes et al. 1985). A prospective study of the effects of prenatal exposure to cigarettes and cannabis on growth from birth to adolescence found no significant effects on growth measures at birth although a smaller head circumference observed at all ages reached statistical significance among the adolescents born to heavy marijuana users (Fried et al. 1999). Finally, the relationship between maternal use of cannabis and pregnancy outcome was investigated in a study of 12,000 women in the UK (Fergusson et al. 2002). Five percent of mothers reported smoking cannabis before and/or during pregnancy. The use of cannabis during pregnancy was not associated with increased risk of perinatal mortality or morbidity. The babies of women who used cannabis weekly before and during pregnancy were lighter than those of non-users and had shorter birth lengths and smaller head circumferences. The findings of this study are consistent with earlier studies that have found an absence of statistical association between cannabis use and antenatal or perinatal morbidity and mortality. The reduced birth weight seen with regular or heavy cannabis use suggests that to optimize fetal growth and minimize the risk of an adverse pregnancy outcome, pregnant women should limit cannabis use during pregnancy. In female patients during the reproductive years, fertility and pregnancy are usually not affected by MS. While MS activity seems to decrease during pregnancy, exacerbation rates increase in the first 6 months postpartum (Birk and Rudick 1986). Since cannabinoids are secreted in human breast milk and absorbed by the nursing baby, cannabis use while breast-feeding should be avoided.

Special studies of cannabis in menopausal and post-menopausal women have been conducted. Mendelson and colleagues (1985) studied LH levels in menopausal women after marijuana smoking and found no significant difference in LH levels when compared to values for healthy menopausal women. In a study of the acute effects of marijuana smoking in post-menopausal women, Benedikt and colleagues (1986) noted statistically significant increases in pulse rate, intoxication levels and the confusion component of the Profile of Mood States Questionnaire (POMS). The finding of neuropsychological per-

formance impairment in post-menopausal women is not unlike the findings in moderate cannabis users (Pope et al. 2001) and in heavy cannabis users (Solowij et al. 2002). The degree of impairment in memory and attention are not surprising in chronic heavy users. Pope (2002) presents the consensus opinion that some cognitive deficits persist for hours or days after acute intoxication with cannabis has subsided. Since cognitive impairment is associated with MS, the potential for significant adverse effect on memory and attention in MS patients using therapeutic cannabis should be a subject of future clinical research.

CANNABIS IN SYMPTOM MANAGEMENT

Manifestations of MS are protean and depend on the location of persistent central nervous system lesions. Since MS lesions have a predilection for certain anatomic locations, recognizable clinical syndromes are common in MS. Surveys of symptoms in MS have been carried out with the most common symptoms including fatigue, balance impairment, muscle disturbances (weakness, stiffness, pain and spasm), and bowel and bladder impairment (Compston 1997). In chronic MS, signs and symptoms of motor dysfunction are found in at least 75 percent of patients (Miller 2000) with sensory impairment noted in 50 percent. Cerebellar abnormalities (ataxia, tremor, nystagmus or dysarthria) are found in at least a third of MS patients. Autonomic symptoms including bowel, bladder or sexual dysfunction are found in at least 50 percent of patients.

A survey of cannabis-using MS patients in the USA and UK by Consroe and colleagues (1997) reported improvements after cannabis use in spasticity, chronic pain, acute paroxysmal phenomena, tremor, emotional dysfunction, anorexia/weight loss, fatigue, diplopia, sexual dysfunction, bowel and bladder dysfunction, vision dimness, dysfunction of walking and balance, and memory loss (descending rank order). While the authors of this study discuss the potential shortcomings of the survey design, this report suggests that cannabis may significantly relieve signs and symptoms of MS such as spasticity and pain along with a number of other complaints.

IMPAIRED MOBILITY: SPASTICITY

In the 19th century, O'Shaughnessy (1842) used hemp extract in treating muscle spasms associated with tetanus and rabies. Reynolds (1890) reported using cannabis to treat muscle spasms, as well as for epilepsy, migraine, and other indications. While medicinal cannabis use continued in the years after the work of O'Shaughnessy and Reynolds, little was published concerning cannabis and spasticity until the 1970s. A survey of 10 spinal-cord injured

males was published in 1974 in which 5 patients reported reduced spasticity, 3 patients noted no effect and 2 patients did not have significant spasticity (Dunn and Davis 1974).

The use of cannabis to treat spasticity associated with MS has been reported by a number of investigators over the subsequent interval. Petro (1980) reported one patient with MS who used cannabis to treat nocturnal leg fatigue and spasms associated with spasticity. Petro and Ellenberger (1981) conducted a double-blind clinical trial that demonstrated statistically significant reduction in spasticity following the oral administration of Δ -9-THC in doses of 5 and 10 mg. Investigators have confirmed the observation using Δ -9-THC (Hanigan et al. 1985; Ungerleider et al. 1988; Maurer et al. 1990), cannabis (Meinck et al. 1989) and nabilone (Martyn et al. 1995). Additional preclinical support for the benefit from cannabis in spasticity was provided by the report of Baker and colleagues (2000). In this study, cannabinoid receptor agonism improved tremor and spasticity in mice with chronic relapsing experimental allergic encephalomyelitis (CREAE) and indicated that the endogenous cannabinoid system may be active in control of spasticity and tremor. Further support for cannabinoid receptor involvement was provided in an animal study in which cannabinoid receptor (CB_1) changes were found in regions of the brain involved in the control of motor symptoms (Berrendero et al. 2001). The role of the endocannabinoid system in spasticity was demonstrated in CREAE mice in a further study, which manipulated tone using cannabinoid receptor agonists and antagonists (Baker et al. 2001).

Since a considerable body of scientific evidence supports the efficacy of cannabinoids in spasticity, review articles (Gracies et al. 1997; Consroe 1999) and medical texts (Compston 1999; Compston 2001) include cannabis as a treatment option in spasticity. In *Brain's Diseases of the Nervous System Eleventh Edition* (Compston 2001), among the treatments for spasticity associated with MS, cannabinoids are listed along with baclofen, dantrium, benzodiazepines and tizanidine.

Gender issues are involved in MS-associated spasticity. Since females are more likely to experience demyelination at an earlier age than males, the burden of white matter disease over time may be greater in females. The earlier appearance of symptoms in females is somewhat counterbalanced by a greater prevalence of spinal MS seen in males and occurring later in life. The late occurring form of MS often involves progressive spinal lesions presenting with spasticity and pain.

TREMOR

Tremor in MS is treated with beta-blockers, anticonvulsants or, in rare cases, stereotactic procedures. Experimental evidence for benefit from canna-

bis is provided in a preclinical study by Baker and colleagues (2000) in which treatment with a CB₁ antagonist resulted in increased forelimb tremor. Since isolation of tremor from spasticity may be difficult in experimental animals, interpretation of such evidence may be questioned. In the survey of patients with MS by Consroe and associates (1997), 90% of subjects with tremor reported improvement after cannabis. In a study of 8 MS patients with tremor and ataxia, oral THC was effective in 2 of 8 subjects with both subjective and objective improvement (Clifford 1983).

NYSTAGMUS

Nystagmus is an eye movement abnormality often associated with MS. In an N-of-1 clinical trial, a 52-year-old man with MS and pendular nystagmus was studied in the United Kingdom over 3 months before and after cannabis in the form of cigarettes, nabilone and cannabis oil-containing capsules (Schon et al. 1998). The investigators demonstrated improved visual acuity and suppression of the patient's pendular nystagmus after inhaled cannabis and were able to correlate the therapeutic effect with acute changes in serum cannabinoid levels. Nabilone and orally administered cannabis oil capsules had no effect. Because of the anatomical relationships involved in eye movement control, the authors suggest an effect at the level of the dorsal pontine tegmentum. In support of action at the level of the deep brain stem is the benefit seen with cannabis in intractable hiccups (Gilson and Busalacchi 1998) and evidence supporting cannabinoid analgesic actions mediated in the rostral ventromedial medulla (Meng et al. 1998). Responding to the report of benefit in nystagmus associated with MS, Dell'Osso (2000) reported an individual with congenital nystagmus whose oscillations dampened after smoking cannabis. Dell'Osso commented that while he had seen similar reports from patients, cannabis research is discouraged in the United States.

POSTURAL REGULATION

The complex integration of sensory and motor function required for postural regulation is impaired in many patients with MS. Impairment of posture is most disabling for patients, distressing for caregivers, and frustrating for physicians. Lesions of spinal, cerebral and cerebellar pathways result in loss of balance. In a study of 10 MS patients, inhaled cannabis caused increased postural tracking error both in MS patients and in normal control subjects (Greenberg et al. 1994). The authors admitted in their publication that dynamic posturography "is not a measure of spasticity." Some authors have reported incorrectly that this study is a negative study in spasticity. Since cerebellar dys-

function is a common finding in MS seen in a third to 80 percent of patients, one can anticipate that many MS patients with both motor and cerebellar symptoms may find improved spasticity and impaired balance. Cannabinoids should be used with caution in patients with the combination of corticospinal (spasticity) and cerebellar (balance) deficits.

FATIGUE

Fatigue is one of the most frequently reported symptoms in MS and is clearly distinct from fatigue experienced in an otherwise healthy individual. The mechanism for fatigue in MS is unknown. No differences have been found in the level of MS-associated fatigue between men and women. Clinical trials have demonstrated that amantadine may be beneficial; however, the supporting evidence is weak (Branas et al. 2000). In a single-blind trial of modafinil in patients with MS (Rammohan et al. 2002), fatigue scores were improved during treatment (200 mg/day). In the only study addressing the effect of cannabis on fatigue, Consroe (1997) reported survey data which showed from 60 to 70% of subjects reported cannabis reduced fatigue states (tiredness, leg weakness). No controlled clinical trials of cannabinoids have investigated this condition.

PAIN

Because of the nature of MS as a disruption of transmission of nerve impulses, paroxysmal manifestations are commonly seen including tonic brainstem attacks, trigeminal neuralgia, and spasticity. Anticonvulsants and antidepressants are commonly used in MS pain syndromes, with some benefit. Cannabinoids have not been studied extensively in MS-associated pain. In other pain models, cannabinoids have demonstrated efficacy comparable to potent analgesics, such as the opioids (Campbell et al. 2001). Gender differences can affect pain via biological differences in the nociceptive and perceptual systems. In humans, women are, in general, more sensitive to painful stimuli when compared to men (LeResche 2001). The prevalence of pain syndromes in female patients with MS has not been studied.

BLADDER DYSFUNCTION

Bladder impairment in MS is seen in up to 80% of patients at some time during the course of the disease and can vary from slight inconvenience to potentially life-threatening when renal function is compromised. The complex interaction between bladder detrusor and sphincter function is disrupted with

spinal cord lesions in MS. Drugs used in the treatment of spasticity such as baclofen and diazepam are effective in treating bladder symptoms in many MS patients by inhibiting the urethral sphincter. MS patients, as the example of the female patient from South Africa described earlier (James, 1994), report improvements in bladder function after cannabinoid use. Based on the observations of improved urinary tract function, an open-label pilot study of cannabis based medicinal extract (CBME) has been reported by Brady and colleagues (2001). In this study sublingual CBME improved lower urinary tract function in 10 patients with advanced MS and refractory urinary tract dysfunction over 8 weeks of treatment.

SEXUAL DYSFUNCTION

Treatment of sexual dysfunction in male MS patients includes a range of options including pharmacological treatments such as sildenafil (Viagra[®]), papaverine or phentolamine. No treatment other than local administration of artificial lubrication is available for treatment of sexual dysfunction in females. In the Consroe survey of cannabis effects on MS signs and symptoms (1997), 51 subjects reported sexual dysfunction with 62.7% claiming improvement in sexual function after cannabis. No analysis by gender was reported. Based on previously reported survey data, the clinical study of cannabis as a treatment of sexual dysfunction in MS appears warranted.

DISCUSSION

Neurologists in practice in the 1970s noted two distinct patient groups using therapeutic cannabis. Military personnel injured in Vietnam claimed that cannabis was helpful in controlling symptoms associated with traumatic spinal injury. Female patients described beneficial effects from cannabis in treating spasticity, migraine headache or menstrual pain. These observations led to a number of small clinical trials supporting the claims of individual patients. Because of regulatory hurdles in conducting clinical research with cannabis, the total number of patients treated with cannabinoid drugs remains low.

Fortunately, interest in the subject has increased with the initiation of several large-scale cannabis studies in MS in the United Kingdom. The National Institute of Clinical Excellence (NICE), the UK regulatory authority, will assess the results of clinical trials scheduled to be completed by the end of 2002.

Over the years, many patients have asked questions concerning the efficacy and safety of cannabis as a therapeutic agent. While cannabis remains as a prohibited drug in the United States, Δ -9-THC is marketed as Marinol[®] without objection. One can contrast a potential package insert for cannabis with that for

the antispastic drug, Lioresal® Intrathecal. With the use of Lioresal via a spinal pump, the drug labeling states that in clinical trials “13 deaths occurring among the 438 patients treated with Lioresal Intrathecal in premarketing studies.” Interestingly, two MS patients died suddenly within 2 weeks of drug administration. Imagine the regulatory reaction if a single patient would die after cannabis use. A potential risk associated with cannabis is secondary to the inhalation of cannabis containing smoke. The evidence of significant health risk associated with cigarette smoking is overwhelming. While many patients avoid inhalation risks by using oral cannabis, the rapid action of an inhaled formulation is effective with symptoms such as flexor spasms or tonic brainstem attacks. One study noted an elevated risk of myocardial infarction (4.8 times baseline) in the 60 minutes after cannabis inhalation (Mittleman et al. 2001). While cannabis was considered a rare trigger of acute myocardial infarction, risk elevation was associated with obesity, current cigarette smoking and male gender.

Additional safety concerns associated with cannabis use in MS include the negative effects of cannabis on balance and cognition. While these negative effects may limit the potential usefulness of cannabis as a treatment of chronic symptoms in MS, many MS patients may yet benefit from cannabis.

While the interest in cannabis as a therapeutic agent for MS is high, many unanswered scientific questions remain including:

1. How does cannabis compare with current standard treatments for MS symptoms?
2. Can alternative delivery systems be developed to provide rapid onset of action with greater safety when compared to inhaled cannabis?
3. Can specific cannabinoids be used more effectively to stimulate or block cannabinoid system receptor activity?
4. Can the immune-modulating actions of cannabis be used to alter the natural history of MS?
5. Can the long-term risks and benefits of cannabis be quantified to determine a useful risk/benefit ratio in treating the life-long disability in MS?

CONCLUSIONS

Evidence in support of cannabis treatment for spasticity associated with MS includes animal studies and a small number of clinical trials using cannabinoid drugs. Clinical reports of benefit in tremor and nystagmus have been published in MS patients. Potential other signs and symptoms in MS, which may be improved with cannabis, include fatigue, pain, bladder disturbances and sexual dysfunction. Women are twice as likely as men to develop MS. Gender spe-

cific concerns in female patients include use of cannabis during pregnancy, potential effects on the fetus, and risks associated with breast-feeding. Large-scale clinical trials may provide some answers concerning the potential of cannabis in treatment of MS.

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