

Complementary Medicine and MS

November, 2006

Complementary Medicine

- Survey of Halifax MS Clinic, 1998: 219 MS patients responded
 - 67% using some complementary medicine at current time
 - 85% had at some time
 - Most common treatments: evening primrose oil, vitamins and diets
 - Most common therapists: chiropractors, massage and acupuncture
- 34% of Americans visit complementary practitioners
- Statistics Canada, 1998: 3.3 million Canadians paid over 1 billion dollars for chiropractic, naturopathic, homeopathic and Chinese therapies not covered by Health Plans
- Market for herbal remedies ~ \$175,000,000 per year

Why this Growth in Complementary Medicine?

- The message (and sometimes the messenger) in conventional medicine
- Focus on enhancing body's healing mechanisms and not just agents to eradicate disease
- The need to become an active participant and decision maker
- The human need for hope

General Comments

- Although most of these complementary therapies have reasonable safety records, **don't assume that natural = safe**
- Some of the world's most potent poisons are natural substances
- Some examples of risks: allergic reactions to bee stings;
rare stroke with chiropractic manipulation;
worsening hypertension with ginseng;
interaction of St. John's Wort with antidepressants.

General Comments

- The distinction between natural substances and pharmacologic treatments (or drugs) is very artificial
- Digoxin for the heart started out as digitalis, prepared from the plant foxglove
- Quinine for malaria and cramps started out as cinchona bark
- Feverfew is an herb recommended for headaches; now available as a prescription drug, Tanacet, for migraine

General Comments

- Drugs do have the advantage of better documentation of side effects through experience in clinical trials
- Herbs seldom have been used in large trials; but they do generally have the track record of many users over time, and generally a reasonable safety record.
- One concern with herbal remedies is knowing what the brand you buy contains: there are variable concentrations and purities

General Comments

- Vitamins are also generally quite safe in recommended amounts. Big doses of water-soluble vitamins (eg B, C, E) end up in urine.
- But large doses of fat-soluble vitamins (A, D, K) can be toxic
 - A can cause headaches and raised intracranial pressure
 - D can cause kidney stones
 - K interacts with blood clotting and the drug, coumadin
- Vitamin E can interfere with blood thinners

Need for Controlled Studies

- Why does the medical establishment insist on clinical studies to evaluate new treatments?
- MS is very variable over time and between different people with the same illness. Hence need to study a large number over a period of time.

Need for Controlled Studies

- People can undergo remissions even without any intervention. Hence need to randomize treatment allocation, and to have a placebo group (no active drug).
- Many MS symptoms are very subjective in nature, such as fatigue, numbness and pain. Patients and physicians may be swayed in how they report these things in a study if they truly believe that the treatment is going to help. Hence need to blind patients (or at least evaluators) as to which treatment they are receiving.

Need for Controlled Studies

- Testimonial evidence or 'before versus after' comparisons are fraught with danger. It may be unrelated factors or natural history at work.
- Preliminary reports about good outcomes can suggest ideas and treatments worth studying, but do not constitute proof without replication in an adequate number of people, preferably with blinded observers, and random allocation of treatments. Usually you need a placebo control as well.

Placebo Responses

- Response to an inactive treatment (eg sugar pill)
- Possible reasons for this:
 - Natural variability of the response
 - Concept of regression to the mean. ie if you pick subjects on the basis that they have been doing worse than average lately, they may improve to more average activity even without any treatment.
 - General improvements that occur when someone enters a study, and gets good follow-up and general care.
 - Possible effect of the mind when we feel we are doing positive things and getting better.

- Dr. Andrew Weil, on the placebo response:
“I regard the placebo response as a pure example of healing elicited by the mind; far from being a nuisance, it is, potentially, the greatest therapeutic ally doctors can find in their efforts to mitigate disease. I believe the art of medicine is in the selection of treatments and their presentation to patients in ways that increase their effectiveness through the activation of placebo responses.”

Fat and MS

- Geographic distribution of MS suggested possible role of dietary fat and risk of MS. But there are alternative explanations for this, and some populations with high fat have low risk (eg. South Africans and Inuit).
- A recent review of dietary factors and the risk of developing MS, concluded that there is a fairly good consensus that animal fat, animal protein, and meat from non-marine sources all correlate with higher risk for MS. The 3 are so closely linked that individual effects of the 3 can not be isolated. There is a smaller inverse relationship for vegetable and fish intake and MS (ie protective).

Fat and MS

- But not complete agreement!
- Nurses Health Study (1 and 2) followed 92,422 women for 14 yrs and 95,389 women for 4 yrs.
- 195 new cases of MS occurred
- Compared risk for MS in those whose intake was in the top 20% vs those with intake in lowest 20%
- Found no statistical association of risk with intake of total fat, animal fat, saturated fat, vegetable fat, n-6 polyunsaturated fats or monounsaturated fat

Polyunsaturated Fatty Acids

- Reports of MS patients having lower serum levels of linoleic acid. This has been reproduced, but inconsistently.
- Also reports of altered proportions of omega-6 polyunsaturated fatty acids in the lecithin fraction of cerebral myelin.
- 3 randomized controlled and blinded clinical trials of linoleic acid plus or minus gamma-linolenic acid in relapsing-remitting MS. Also a negative study of them in progressive MS.

Polyunsaturated Fatty Acids

- Putting all this together, conclude there may well be a modest beneficial effect, at least early in the disease.
- Quite safe. But consider cost and calories. Also, large doses can cause diarrhea and vit E deficiency.
- Efamol or evening primrose oil (linoleic plus gamma-linolenic acid)
Sunflower oil (linoleic acid)
No studies comparing different doses.

Polyunsaturated Fatty Acids

- More recent interest in omega-3 and omega-6 fatty acids. These are essential polyunsaturated fats. 6 is in evening primrose oil, sunflower oil, soybean oil, wheatgerm oil. 3 is mainly in fish oils. Flaxseed oil contains both.
- A meta-analysis of 3 trials of omega-6 showed that large doses (20-25 g/d) decreased severity of relapses and limited disability mildly in early cases. No effect on long-term disability.
- A single trial of omega-3 using 2-3 g/d showed a marginal effect when added to a regimen with omega-6. Also a positive trial with fish oils alone.

Low Fat Diet

- Swank studied very restrictive diet aiming for less than 15 g animal fat per day, plus 15 g vegetable oil or fish oil daily.
- 1970 reported on 146 enrolled between 1948 and 1954, and followed for 14-20 yrs (mean of 17 yrs). Diet evolved over first few yrs.

Low Fat Diet

- Patients generally lost weight.
- Risk of MS attacks seemed to drop precipitously.
- Retrospective estimate of rate was 1.3/yr in year before diet, and 0.8/yr in each of 2 yrs before that.
- Attack rate in 1st yr on diet was 0.3/yr and subsequently dropped even lower.
- Fewer attacks than 2 historical control groups reported from ~ 1950.
- Mortality rate 1.2%/yr, again less than historical controls. It was 1.1% for good dieters and 1.7% for poor dieters.

Low Fat Diet

Critique: Historical controls are from ~ 20 yrs before. No randomized matched controls.

Retrospective attack rates are always somewhat suspect.

During entry period, 108 were seen and soon lost to follow-up; it is possible this group dropped out because they were not doing as well and reporting results without these cases favour good outcomes.

Death rates are really not lower than more recent studies. Also, most deaths not a direct result of MS.

Low Fat Diet

- 1990 reported on same subjects, now followed for 34 yrs. This time compared group who adhered to diet strictly and consumed < 20 g saturated fat per day (good dieters) vs group that consumed > 20 g per day (poor dieters).
- Table shows change in grade on a 6 point disability scale, and (number in group):

	Good Dieters	Poor Dieters
Minor disability at entry	0.9 (23)	4.3 (6)
Moderate disability	1.6 (25)	3.4 (33)
Severe at entry	0.8 (24)	2.4 (33)

Low Fat Diet

- Also reported lower death rates in good dieters. Did best if they were mild at time of starting diet and they started early in the illness.

Low Fat Diet

Critique: Most extreme change is the 'Mild at entry' group and this is based on only 6 people in the poor dieter group.

No placebo control.

Poor dieters may have fallen off the wagon because they were doing poorly, not vice versa (a form of bias).

Death rates due to MS seems higher than that reported in more recent natural history studies.

Most of the reduction in deaths is due to cardiovascular death ... Can't dispute the effect of dietary fat on vascular disease.

Low Fat Diet

- Conclusion: diet could play a role in MS. It should be studied in a properly designed trial. There are many reasons, apart from MS, to limit saturated fat intake.

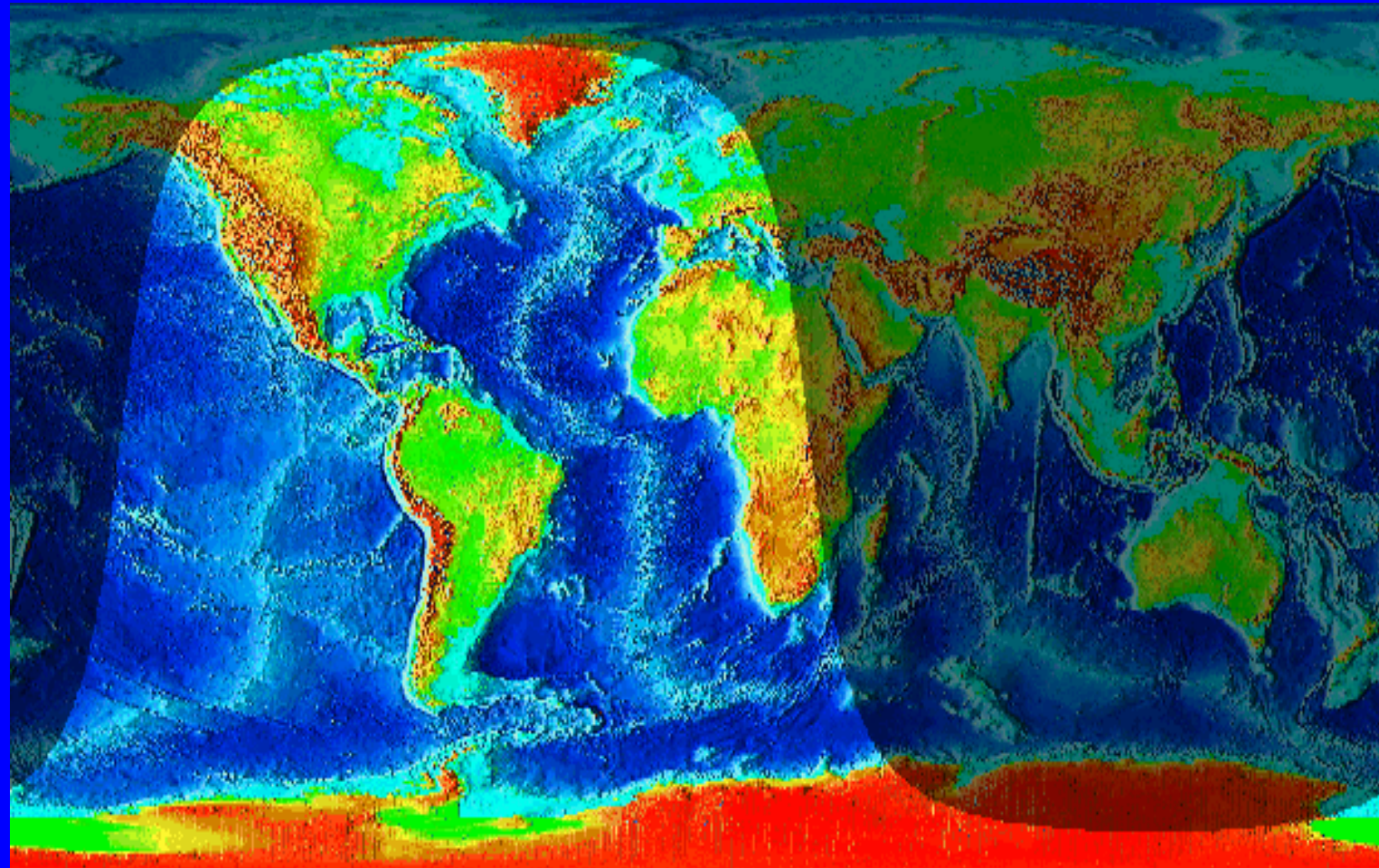
Vitamin D and MS

- Vitamin D is manufactured in our bodies by exposure to sunlight. We also ingest it. It plays a crucial role in calcium absorption and bone formation.
- Nieves measured vit. D levels in 52 women with MS, admitted to hospital... found 12 had vit. D deficiency and mean level overall in insufficient range.
- Early workers emphasized potential role in osteoporosis (higher risk in MS patients).
- Animal work Shows vit. D3 inhibits induction and progression of EAE (the animal model of MS)

Vitamin D and MS

- Hayes suggested hypothesis that it may play a role in causing MS and could explain geographic distribution of MS.

World-wide Incidence of MS



High

Medium

Low

Medium

High

Besides the role of latitude, it also would fit with lower rates at altitude in Switzerland, and along the coast in Norway.

Vitamin D and MS

- Nurse's Health Study (92,500 women followed from 1980 to 2000) and Nurse's Health Study 2 (95,300 women followed from 1990 to 2001)
- 173 cases of MS occurred
- Relative risk of MS if taking ≥ 400 IU per day was 0.59 (95% confidence interval 0.38 to 0.91)

Vitamin D and MS

- Another intriguing association of vit D with MS risk is the observation that there is a small but statistically significant variation in the month of birth and risk for subsequent development of MS. November babies have lowest risk and May babies have highest. Might this reflect the May baby being the result of a winter pregnancy and mom having less vitamin D?
- Plans to study vitamin D in controlled trial. If you choose to supplement your own intake, then do not take over 2000 IU per day. Higher doses can be toxic.

Bee Venom and MS

- Popular in Far East and a number of MS pts in North America tried this.
- Bee venom contains several anti-inflammatory compounds, but not known if they penetrate CNS.
- Risk of anaphylactic reaction to sting. Allergy occurs in ~15% of hymenoptera stings, although more often wasps than bees.

NB: if you do try it, test for allergy first, and have an anaphylactic kit available.

- Most advocates suggest 2-3 sessions per week, 25-30 stings per Rx, for at least 6 months.

Bee Venom and MS

- Anecdotal reports of sudden energy and better sensory function, occasionally fewer muscle spasms.
- Controlled trial of venom injected into mice with EAE showed no benefit.
- Pilot study of 8 MS pts injected with several constituents of venom showed no benefit.
- 2005 Wesselius reported randomized cross-over trial of bee stings (20 bees, 3 times per week) for 24 weeks, and 24 weeks of no Rx.
- 26 pts with RR or secondary progressive with relapses

Bee Venom and MS

- Looked at MRI, attacks, disability (EDSS), fatigue and quality of life scales.
- No significant improvement in any of these.
- Conclusion: although the studies are small, I feel we can discourage people from trying this. The anecdotal reports are likely placebo responses!

Marijuana and MS

- Several ingredients are active in CNS. THC (tetra-hydro-cannabinol) and cannabidiol are 2 in highest concentrations. THC binds to CB1 and CB2 receptors that normally bind arachidonic acid derivatives. CB1 widespread in CNS and inhibits neurotransmitter release of monoamines and amino acid transmitters. CB2 expressed on some immune system cells.

Marijuana and MS

- 6 small case series or small brief randomized trials (really pilot studies) suggested it helps spasticity and pain in MS. Often limited by side effects.
- Killestein et al, Neurology, '02 reported randomized double-blind crossover study in 16 MS pts with severe spasticity.
6 had used cannabis before, but not in 2 mths.

Marijuana and MS

- Excluded any significant prior psych Hx, prior drug or alcohol abuse, and not allowed to drive.
- Received oral THC capsules (Marinol), or plant extract capsule or placebo.
- One psychotic reaction with extract.
- Other adverse effects generally mild, but more common in Rx groups (esp plant extract).

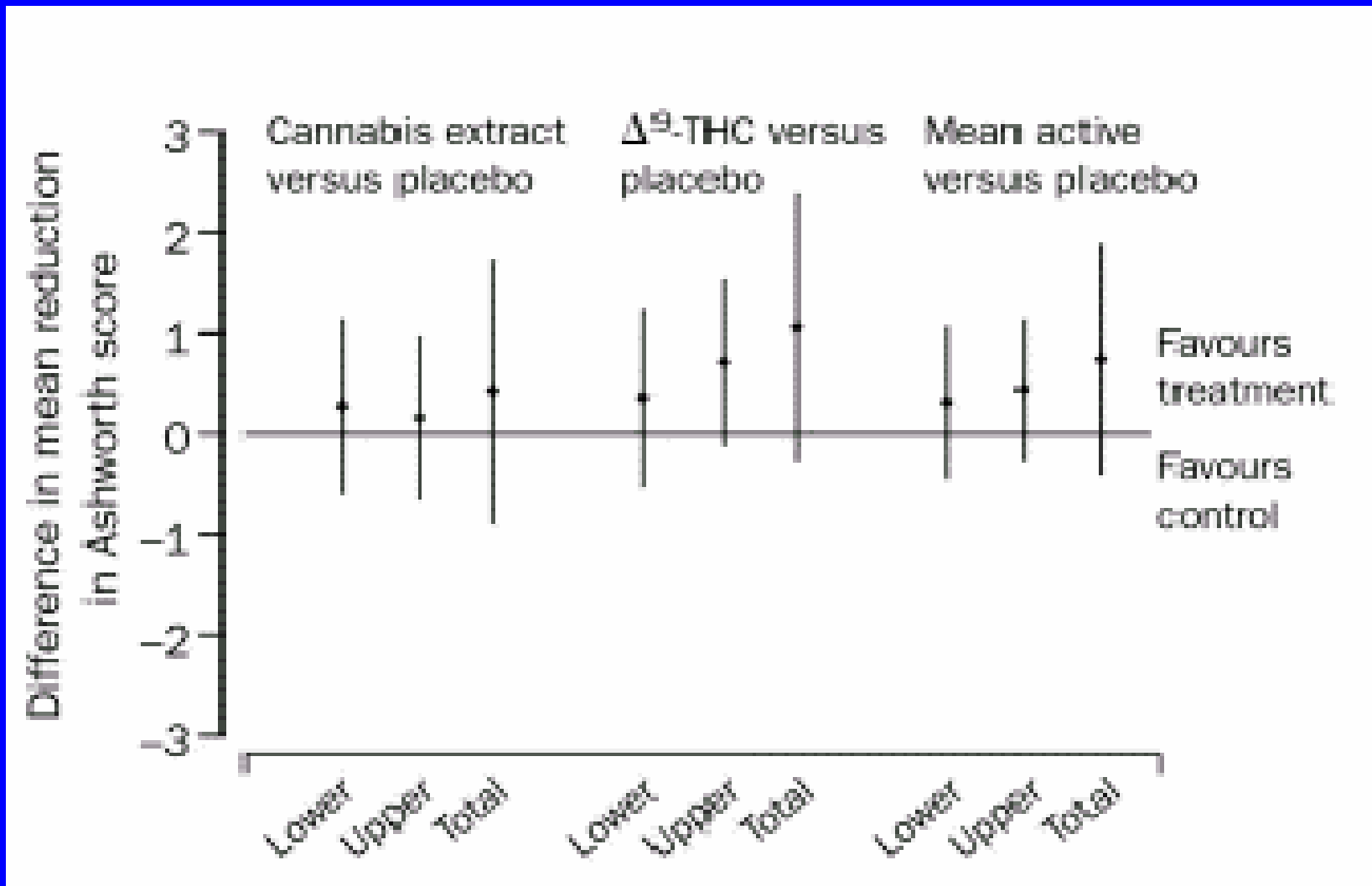
Marijuana and MS

- Spasticity did not improve by Ashworth scale.
Trend to worse MSFC with extract ($p=0.09$) and 9-hole Peg score (coordination) worse with THC ($p=0.02$)
With THC found improvement in 2 quality of life scales, but offset by pts. global impression that they were worse. Pain not measured.

Marijuana and MS

- CAMS study; Zajicek et al, Lancet, Nov '03
- UK study of 630 stable MS pts with spasticity. Excluded if prior psychosis, age >64, significant cognitive impairment, fixed contractures, use of beta-interferons, active infections. Not driving.
- Received synthetic THC 2.5 mg capsules (Marinol); or plant extract with 2.5 mg THC and 1.25 mg cannabidiol plus < 5% other cannabinoids; or placebo.
- Double blinded but often guessed Rx: guessed on active drug in 77% of THC pts, 77% of extract pts, and 50% of placebo pts.

Marijuana and MS



Changes in Ashworth scores from baseline to 13 weeks (95% CI)

Marijuana and MS

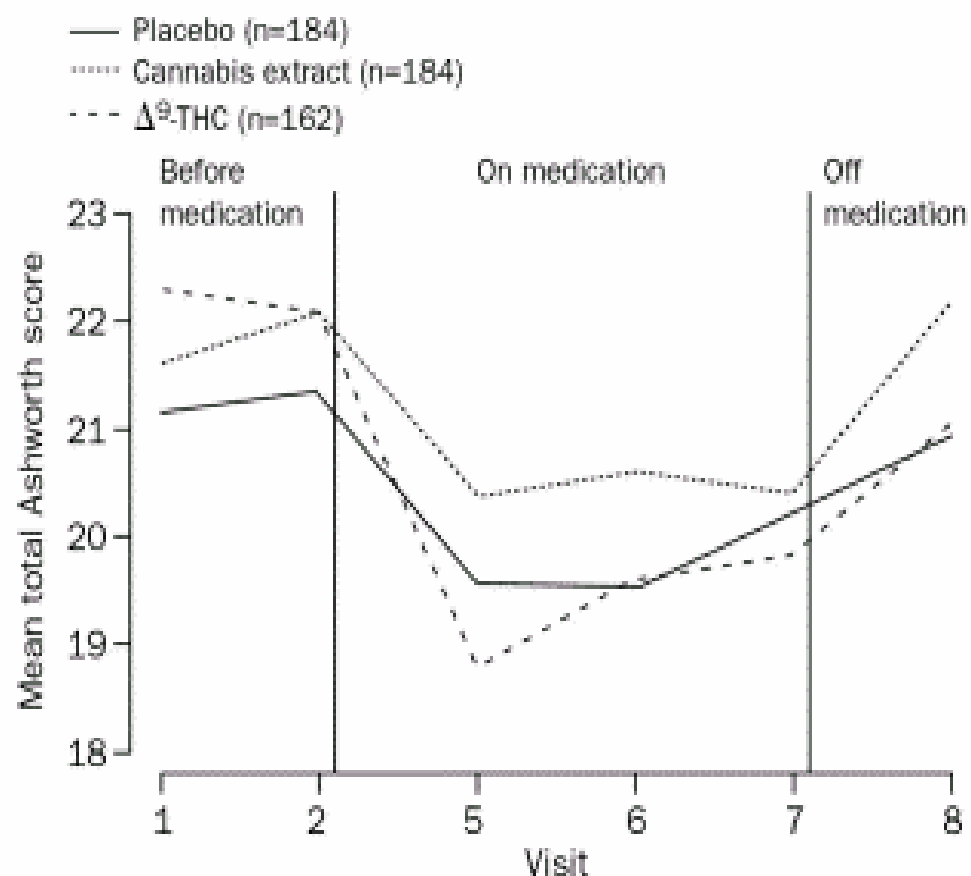


Figure 4. Changes in Ashworth scores by visit and treatment group Mean (95% CI)

Marijuana and MS

Table 4. Assessment of treatment benefit at visit 8

	Treatment group			P
	Cannabis extract (n=197)	Δ^9 -THC (n=181)	Placebo (n=198)	
Symptom improvement				
Bladder				0.149
Yes	68 (44%)	67 (40%)	51 (33%)	
No	87 (56%)	97 (59%)	102 (67%)	
Pain				0.003
Yes	83 (57%)	64 (50%)	51 (37%)	*
No	63 (43%)	64 (50%)	86 (63%)	
Tremor				0.052
Yes	58 (48%)	44 (40%)	43 (33%)	
No	64 (52%)	67 (60%)	89 (67%)	
Spasticity				0.003
Yes	121 (61%)	108 (60%)	91 (46%)	*
No	76 (39%)	73 (40%)	107 (54%)	

Self-reporting

Marijuana and MS

- Sativex is a spray that contains the 2 major ingredients of cannabis (tetrahydro-cannabinol and cannabadiol)
- Rog et al studied this in a randomized double-blind placebo-controlled study in 66 MS pts with persistent pain. 59 had neuropathic pain and 7 had painful muscle spasms.
- One week to titrate sprays as required (1 to 48 allowed); then 4 weeks on Rx

Marijuana and MS

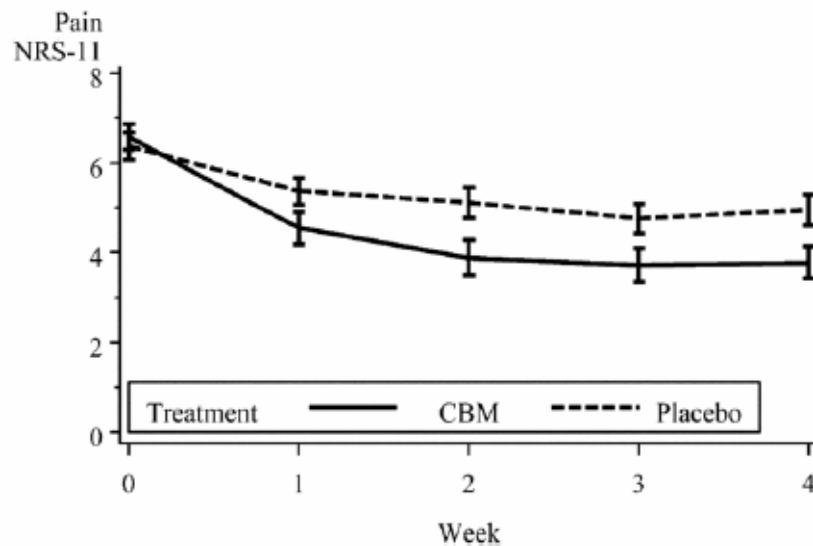


Figure 2. Mean 11-point numerical rating scale (NRS-11) pain scores (\pm SEM) for the cannabis-based medicine (CBM) ($n = 33$) and placebo group ($n = 32$). Week 0 refers to the run-in week. The patients were on test medication in weeks 1 to 4.

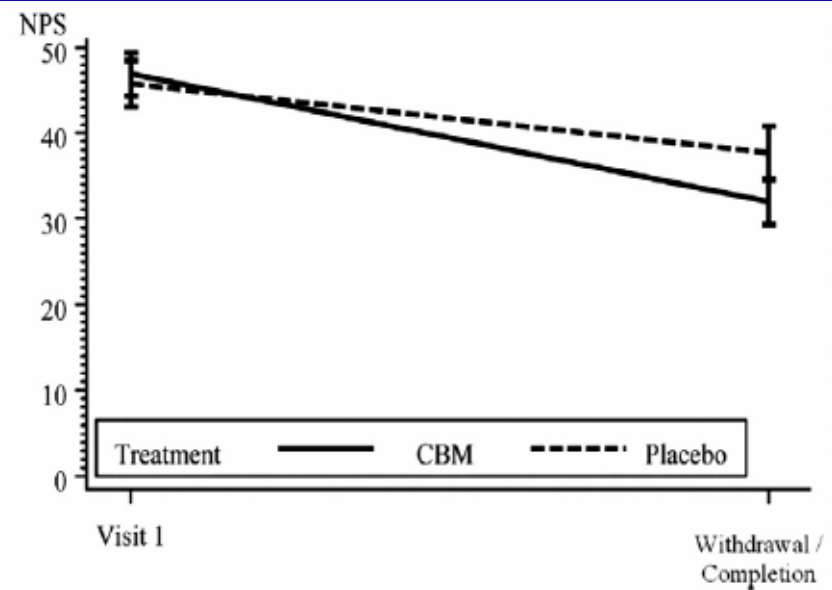


Figure 3. Mean neuropathic pain scale (NPS) scores (\pm standard error of mean) for the cannabis-based medicine (CBM) ($n = 33$) and placebo group ($n = 32$) at baseline (Visit 1) and end of treatment (Withdrawal/Completion).

Pain scores on Sativex (CBM) or placebo

Marijuana and MS

- The improvement in pain was moderate but statistically significant.
- Pts also reported improvement in sleep
- Average dose was 9.6 sprays per day
- Side effects included dry mouth, bad taste, long-term memory difficulties (5% difference in scores), somnolence (3 pts of 34), euphoria (2) and dizziness (18)

Marijuana and MS

- Conclusion: marijuana or ingredients as capsules (Marinol or Nabilone) or sprays (Sativex) can sometimes help neurogenic pain. Spasticity less clear, and objective evidence is rather modest. Not a first line treatment due to potential side effects.

Dental Amalgam

- Lay press has published articles suggesting a possible link between amalgam fillings and risk of MS. Many pts have had their fillings removed and replaced with porcelain.
- Mercury is neurotoxic. Large exposures can affect balance, cognitive function and peripheral nerves. Documented occupational exposures and intoxications have caused permanent damage.
- Trace amounts of mercury can leak out of these fillings.

Dental Amalgam

- But no evidence that trace amounts cause damage. Also, no extra mercury in MS plaques or normal portions of MS brains compared to controls.
- One retrospective survey by Siblingrud found 33% fewer attacks in MS pts who had not had amalgam fillings inserted in past year.
- Bangsi reported a case-control study in MS pts in Montreal. 143 cases and 128 controls.
- Pts had more fillings than controls; ie risk of MS higher if you had any fillings.
- But no trend towards more risk with more fillings or longer exposures!

Dental Amalgam

- Casetta reported case-control study from Italy (132 pts and 423 controls) and also found more cases with fillings, but no statistical association between number of fillings or exposure time and risk of MS.
- McGrother in England reported a case-control (39 female pts and 62 controls) and also found more MS pts with fillings. But no difference between groups in number of fillings or body mercury levels.
- No randomized trial of replacing amalgam fillings.

Dental Amalgam

- I have not seen any change in the course of my pts who have chosen to have this done.
- Conclusion: MS pts seem to have a higher chance of having any amalgam fillings, but there is no convincing evidence that this is causally related to their illness, or that the number of fillings adversely affects the course of their illness. I wouldn't personally recommend this to pts.

Other Modalities

- Yoga
 - Although studied, studies have limitations
 - Suggestion it may help anxiety, pain and stiffness
 - My patients who try it generally are favourably impressed
- Tai Chi
 - Small study in 19 pts reported improved emotional and social functions, less stiffness, improved walking speed
 - I hear favourable reports, even if it has nothing to do with balancing life energies and forces

Other Modalities

- Therapeutic touch and Reflexology
 - No good evidence in MS, and theory behind it is very implausible
 - May help relaxation, and placebo effects
- Magnets
 - 3 published studies in small number of pts (20, 30, 38) showing benefit in spasticity, pain, bladder function, fatigue. One was placebo-controlled.
 - High intensity fields have some risk
 - Worthy of further study, but only for symptom control

Advice When Considering Therapeutic Claims

1. Is it safe?
2. Is it expensive?
3. Is the information or “evidence” being presented by someone who profits from this?
4. Is there a plausible reason why this might help?
5. Are they citing studies and journals, or just giving testimonials and quoting individuals?
6. If it is good for everything, then it is probably too good to be true.