

Pain in MS

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Pain Syndromes in MS

- **Prevalence - >65%[§]**
 - 18% claim it's among the top 3 worst symptoms of MS
- **Pain types*:**
 - Acute – 9%
 - Chronic - 48%
 - Mixed (acute on chronic) – 55%

[§]Kerns (2002) J Rehab Res Dev 39:225

*Moulin (1988) Neurology 38:1830

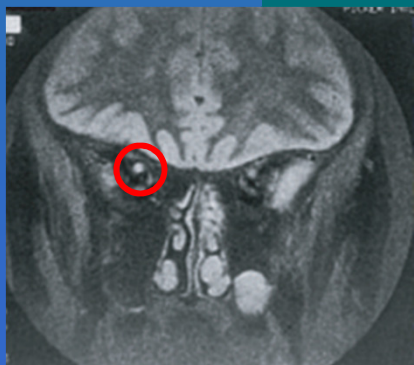
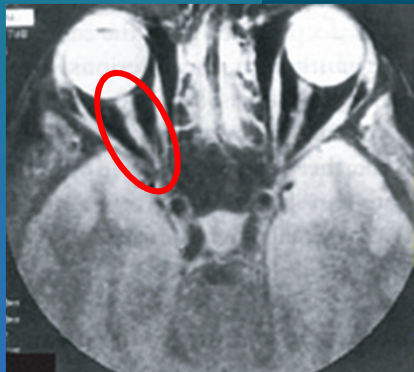
Prevalence and Impact of Pain

	Moulin (1988)	Indaco (1994)	Archibald (1994)	Ehde (2003)	Svendsen (2003)	Beiske (2004)
Pain	55%	57%	55%	44%	79.4%	65% (74% w sensory)
Tx			65%		24.4% daily	33%
Acute	9%	Neuralgia Lhermitte's				Neuralgia
Chronic	48%	70%	17% continuous		38.1% dysesthesia 36.5% allodynia 39.6% muscle 41.9% joint	Paresthesia
Other features		Dysesthesia Spasm	76% multiple	27% severe		Fatigue
Impact			↓ mental health, function	20% severe	Significant	40% significant

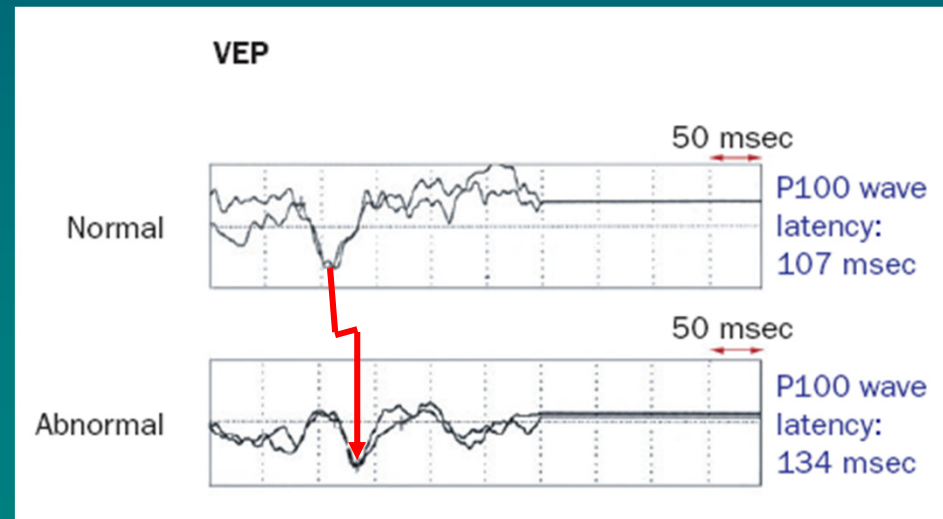
Acute Pain Syndromes in MS

- Pain associated with optic neuritis
- Trigeminal neuralgia
- Lhermitte's
- Paroxysmal burning pain
- Painful tonic *seizures* or spasms

Optic Neuritis



Site	Symptoms	Signs	Treatment	Established efficacy	Equivocal efficacy	Speculative
Optic nerve	Unilateral painful loss of vision	Scotoma, reduced visual acuity, colour vision, and relative afferent pupillary defect	Low vision aids	–	–	–



Compston & Cole Lancet 2002;359:1221

Optic Neuritis

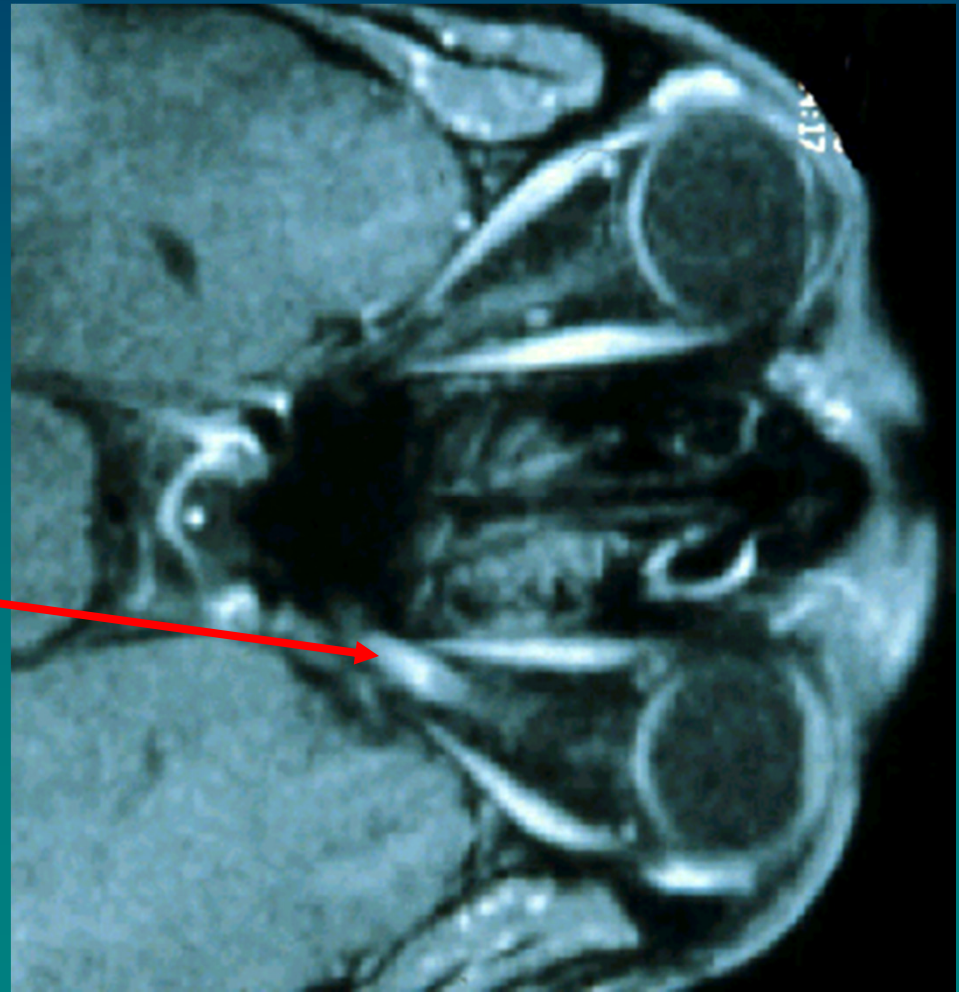
- Initial symptom in 16 - 30% of patients with MS
- Acute/subacute onset of monocular visual blurring or loss
- Maximal visual loss usually within the first 4 days
- Pain on eye movement is a frequent complaint
- May also have positive visual symptoms (e.g. photopsias)

Optic Neuritis Pain

- Typically appears at onset
- Tends to be severe, “boring” or “sudden, sharp and jabbing”
- Worse with eye movement
- Possibly due to stretching of meninges around the swollen optic nerve

Optic Neuritis - MRI

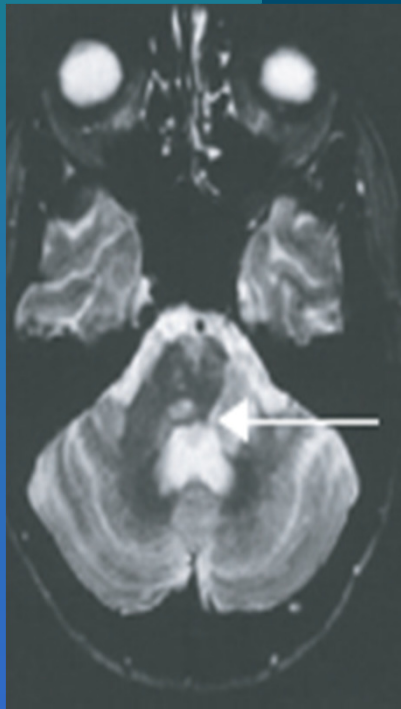
**Gadolinium
enhancement**



Optic Neuritis Pain

- Ocular pain reported in 92% of cases in ONTT, 87% worse with movement
- No apparent difference in patients with long vs. short involvement of the optic nerve (as defined by MRI)
- No data whatsoever on the effect of steroids in all studies to date

Brainstem Syndrome (Trigeminal Neuralgia)



Site	Symptoms	Signs	Treatment		
			Established efficacy	Equivocal efficacy	Speculative
Brainstem	Diplopia, oscillopsia	Nystagmus, internuclear, and other complex ophthalmoplegias	–	–	Baclofen, gabapentin, isoniazid
	Vertigo		–	Prochlorperazine, cinnarizine	–
	Impaired speech and swallowing	Dysarthria and pseudo-bulbar palsy	Tricyclic anti-depressants	–	Speech therapy
	Paroxysmal symptoms		Carbamazepine, gabapentin	–	–

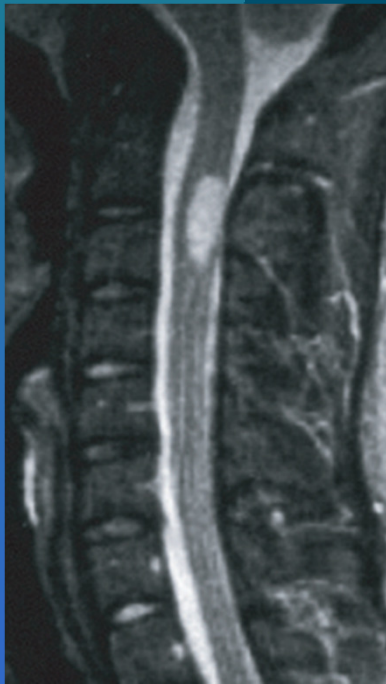
Trigeminal Neuralgia in MS

- **Features:**
 - Often difficult to differentiate from idiopathic TN
 - Patients tend to be younger
 - Tends to be bilateral
 - Can be very resistant to usual therapies

Lhermitte's Symptom

- Sensory symptom seen at onset in <5% of patients
- Most patients who present with Lhermitte's have MS
- Shock-like sensation down the spine with flexion of the neck
- Reliable indicator of cervical spinal cord disease and worth specific inquiry

Spinal Cord Syndrome



Site	Symptoms	Signs	Treatment		
			Established efficacy	Equivocal efficacy	Speculative
Spinal cord	Weakness	Upper motor neuron signs	–	–	–
	Stiffness and painful spasms	Spasticity	Tizanidine, baclofen, dantrolene, benzodiazepines, intrathecal baclofen	Botulinum toxin, IV corticosteroids	Cannabinoids
	Bladder dysfunction		Anticholinergics and intermittent self-catheterisation, suprapubic catheterisation	Desmopressin, intravesical capsaicin	Abdominal vibration, cranberry juice
	Erectile impotence		Sildenafil	–	–
	Constipation		Bulk laxatives, enemas	–	–
Other	Pain		Carbamazepine, gabapentin	Tricyclic anti-depressants, TENS	–
	Fatigue		Amantadine	Modafanil	4-aminopyridine, pemoline fluoxetine
	Temperature sensitivity and exercise intolerance		–	–	Cooling suit, 4-aminopyridine

Compston & Cole Lancet 2002;359:1221

Paroxysmal Burning Pain

- **Features:**
 - Often grouped with “paroxysmal symptoms” of MS
 - Many different qualities, though “aching”, “burning or searing” are regular descriptors
 - Can be associated with relapses

Chronic Pain Syndromes in MS

- **Dysesthetic extremity pain**
- **Back pain**
- **Painful leg spasms**

Chronic Pain Syndromes in MS

- **General Features:**
 - Most if not all associated with posterior column dysfunction
 - Tend to be worse nocturnally or with activity, heat and fatigue
 - Can be the most prominent symptom (more than weakness)

Dysaesthetic Extremity Pain

- **Commonest (29% Moulin series)**
- **Features:**
 - **Constant burning or “tight”**
 - **“Tightness” complaint easily misconstrued with spasticity**
 - **Tends to be symmetrical**
 - **Often seen with significant posterior column dysfunction but with relative preservation of spinothalamic tracts**

Back Pain (Mixed Neuropathic/Nociceptive)

- 14% of Moulin series
- Features:
 - Older usually more disabled patients
 - Typically, lower back
 - Radiation to hips, thighs but rarely below the knees
 - Worse with prolonged sitting/standing
 - Usually associated with degenerative changes on spine



Painful Leg Spasms

- **Less common but distinctive (13% of Moulin series)**
- **Features:**
 - Often overlap with back pain due to accompanying “spasticity”
 - Reported as “cramping” or “pulling”
 - Often worsened during relapses, hence tend to improve with steroids

Associated Pain Syndromes

- **Fibromyalgia**
- **Migraine/Headache**
- **Degenerative disc disease and radicular pain (e.g. sciatica)**
- **Osteoporosis (steroid accelerated)**
- **Osteopenia**
- **Skin breakdown (e.g. decubitus ulcer or “pressure sore”)**

Pain-Treatment

- **Treat the offending condition**
- **Medication**
 - Beware of interactions (e.g. fatigue)
- **Manual therapy**
 - Physiotherapy
 - Massage
- **Alternative therapies**
 - Acupuncture
- **Surgery**

Pain-Treatment (cont.)

■ Medication

- Central pain modifiers
(e.g. Amitriptyline, Gabapentin)
- Neuralgic pain relievers
(e.g. Carbamazepine)
- Non-narcotic anti-inflammatories
(e.g. Naproxen, Toradol)
- Narcotics
(e.g. Codeine, Percocet, Tramadol)
- Cannabinoids

Cannabinoid Treatment in Multiple Sclerosis

Study	Treatment	Results
Petro et al (1981)	oral THC, placebo	reduced spasticity
Clifford (1983)	oral THC, placebo	improved coordination
Ungerleider et al (1987)	oral THC, placebo	reduced spasticity
Meinck et al (1989)	cigarette smoke marijuana	reduced spasticity and ataxia
Greenberg et al (1994)	cigarette smoke THC, placebo	impaired balance, posture
Martyn et al (1995)	oral nabilone, placebo	improved well-being, spasms, nocturia
Schon et al (1999)	oral THC, cigarette smoke	reduced nystagmus amplitude
Hamann et al (1999)	oral nabilone	complete pain relief
Killestein et al (2002)	oral THC, plant extract, placebo	worse or no improvement
Zajicek et al (2003)	oral THC, cannador, placebo	no effect on spasticity
Svendsen et al (2004)	oral THC, placebo	decrease pain intensity
Vaney et al (2004)	oral cannador, placebo	no improvement in spasticity
Rog et al (2005)	oral THC:CBD, placebo	significant reduction in pain and sleep disturbance

Treatment of Central Neuropathic Pain in MS using THC:CBD

■ Objective

- Compare efficacy and tolerability of THC:CBD 1:1 with placebo
- Adjunctive therapy in central neuropathic pain

■ Patient population

- Adult MS patients with central pain
 - ❖ Dysaesthesia, painful spasm
- 85 screened
- 66 randomized
 - ❖ THC:CBD 1:1 (n=34) and placebo (n=32)

Trial of THC:CBD in MS Neuropathic Pain (cont.)

■ Method

- Continuation of existing analgesics
- Self-titration of study medication to maximum 48 sprays daily
- 11-point numerical rating scale (NRS-11) to measure pain and sleep disturbance

■ Randomization

- Placebo and treatment groups comparable

■ Patient disposition

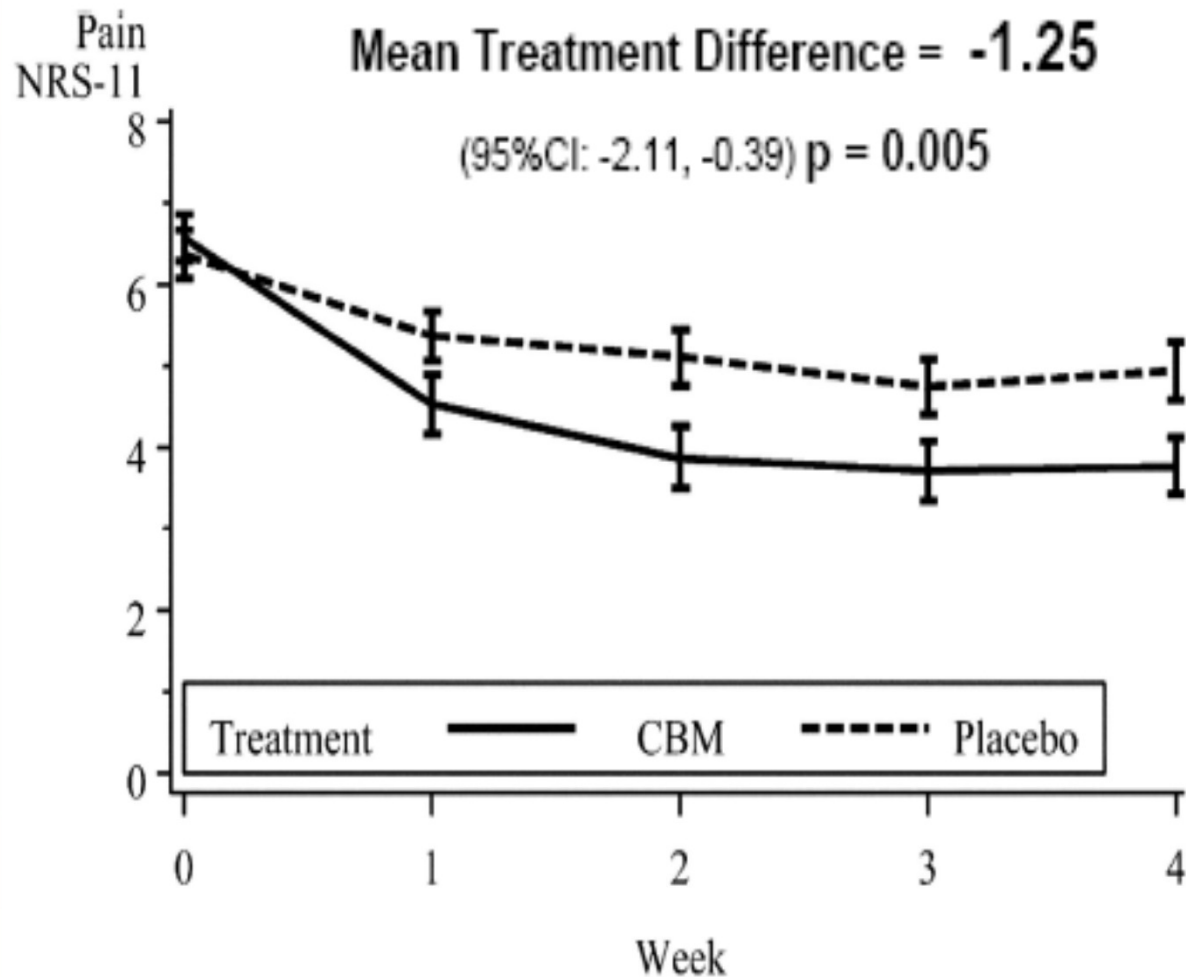
- 64 patients completed study
- 2 patients withdrew from treatment group

Rog et al, Neurology 2005

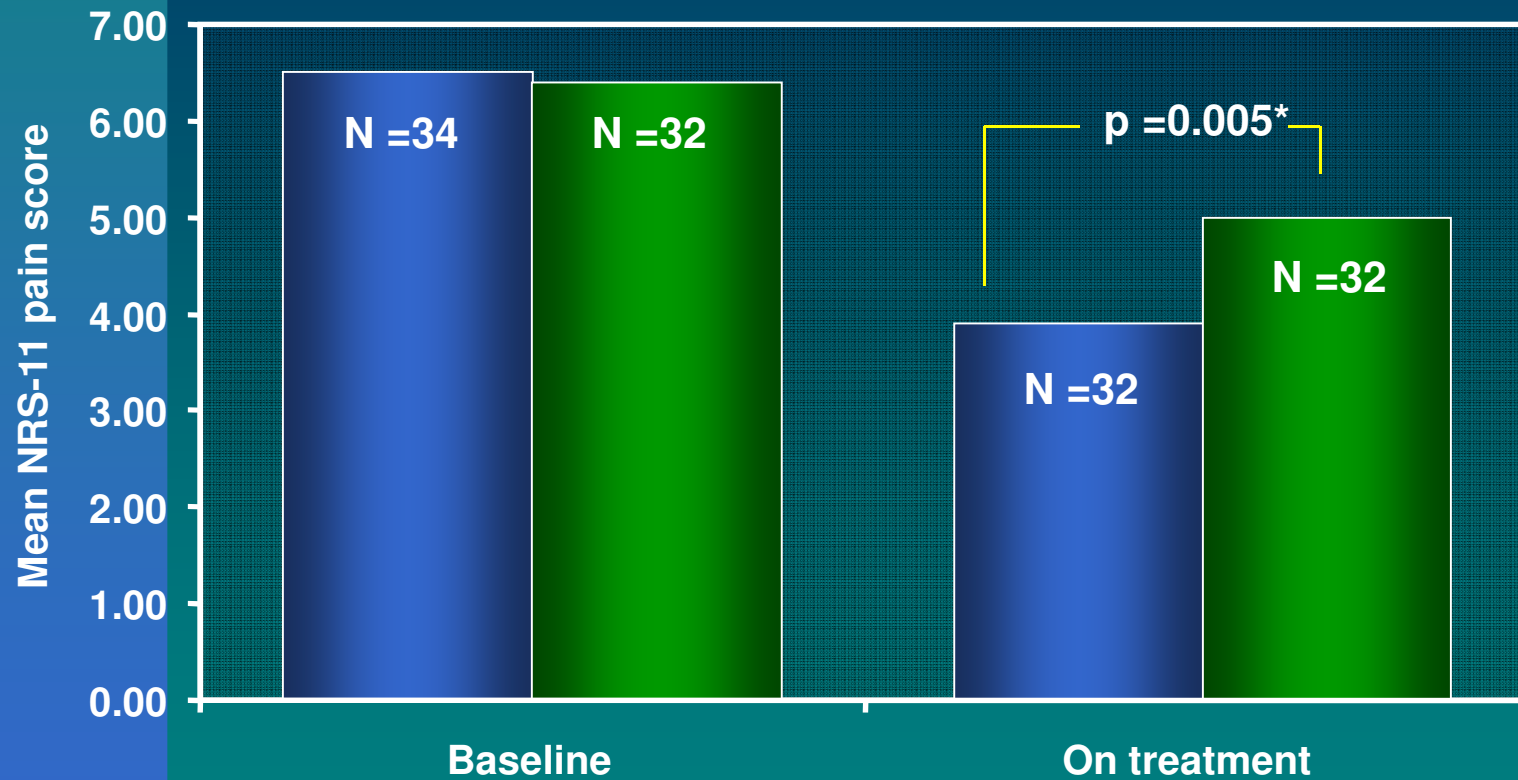
Trial of THC:CBD in MS Neuropathic Pain (cont.)

- Mean daily sprays
 - THC:CBD 1:1 = 9.6
 - Placebo = 19.1
- Outcomes
 - Primary:
 - ❖ Change in neuropathic pain severity (NRS-11)
 - Secondary:
 - ❖ Change in sleep disturbance due to pain (NRS-11)
 - ❖ Patients' global impression of change (PGIC)

RESULTS: Pain Scores



RESULTS: Pain Scores



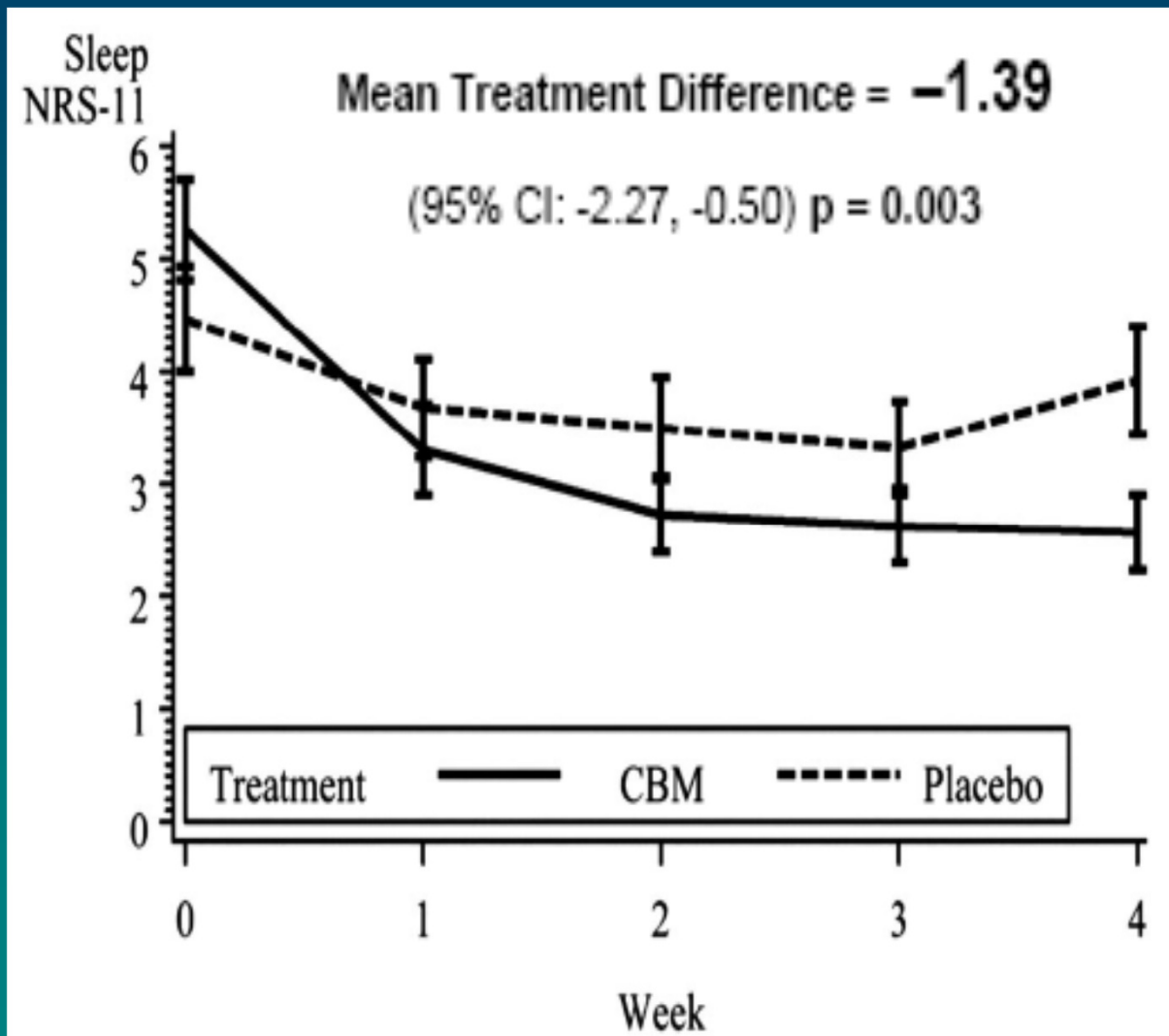
Scale
0 = No pain
10 = Worst possible pain

■ THC:CBD 1:1 ■ Placebo

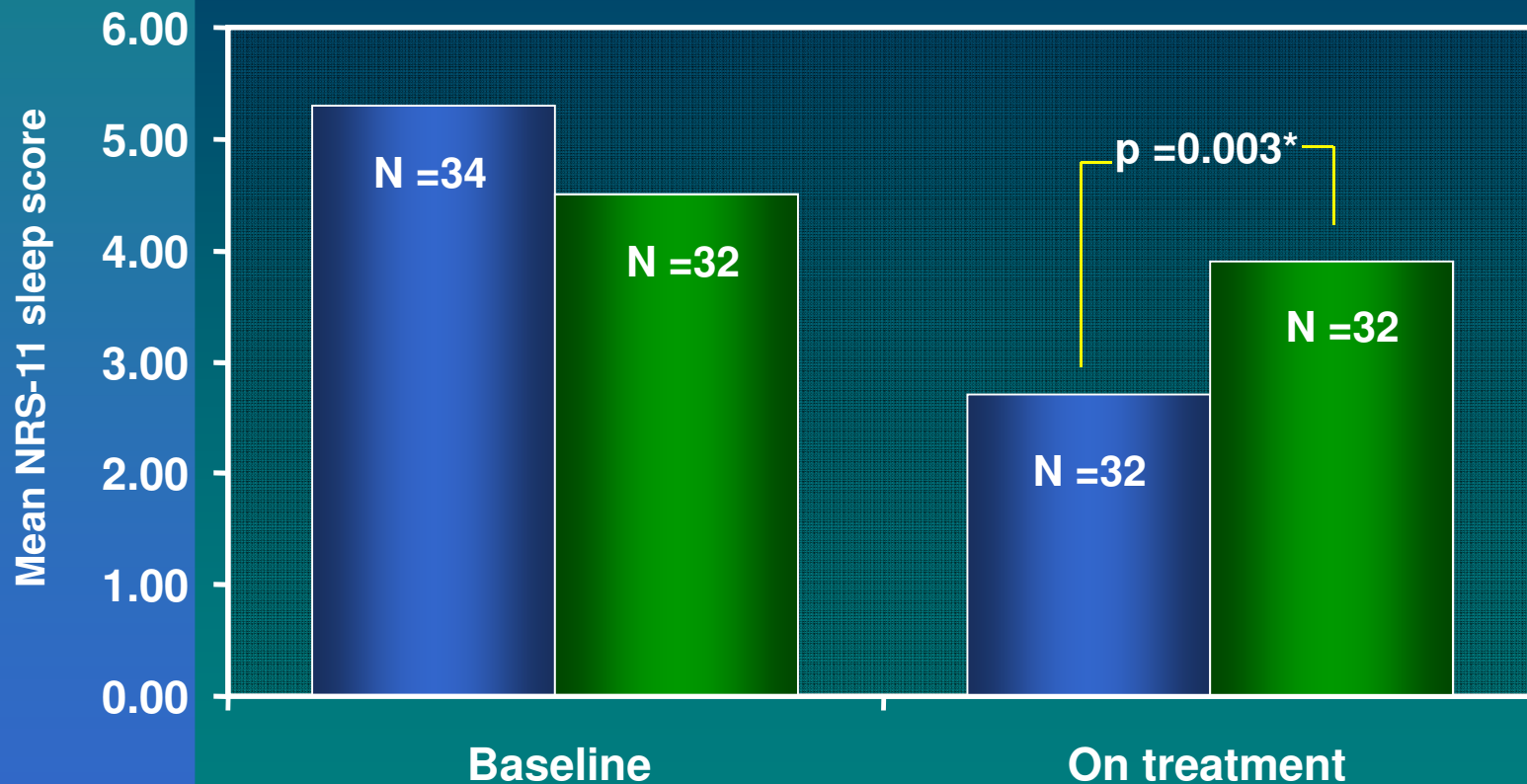
*Active vs placebo

Rog et al, Neurology 2005

RESULTS: Sleep Scores



RESULTS: Sleep Scores



*Active vs placebo

Scale

0 = Did not disrupt sleep

10 = Completely disrupts sleep, unable to sleep due to pain

■ THC:CBD 1:1 ■ Placebo

Rog et al, Neurology 2005

Initiating Therapy: Sativex[®]

- **Start low and go slow**
- **Patient self titres starting with 2-3 daily doses**
- **Incremental increases over weeks to median dosing of ~5 sprays/day**
- **Titration against pain relief**
- **Strive for reducing concomitant pain meds (especially opiates) with successful pain relief**

Cannabinoid Drugs

■ **Sativex[®] (GW Pharmaceuticals-Bayer)**

- THC:CBD (cannabis-based medicinal extract) sublingual oromucosal spray (27 mg/mL THC and 25 mg/mL CBD)
- proposed analgesic in MS neuropathic pain predictable response (reduced individual variability in absorption)

■ **Marinol[®] (Solvay Pharma)**

- Dronabinol, synthetic THC oral capsule (2.5, 5, 10 mg)
- antiemetic in cancer chemotherapy and appetite stimulant in AIDS-related anorexia
- unpredictable response (high individual variability in absorption)

■ **Cesamet[®] (Valeant Pharmaceuticals)**

- Nabilone, synthetic THC analog oral capsule (0.5 mg, 1 mg)
- antiemetic in cancer chemotherapy unpredictable response (high individual variability in absorption)

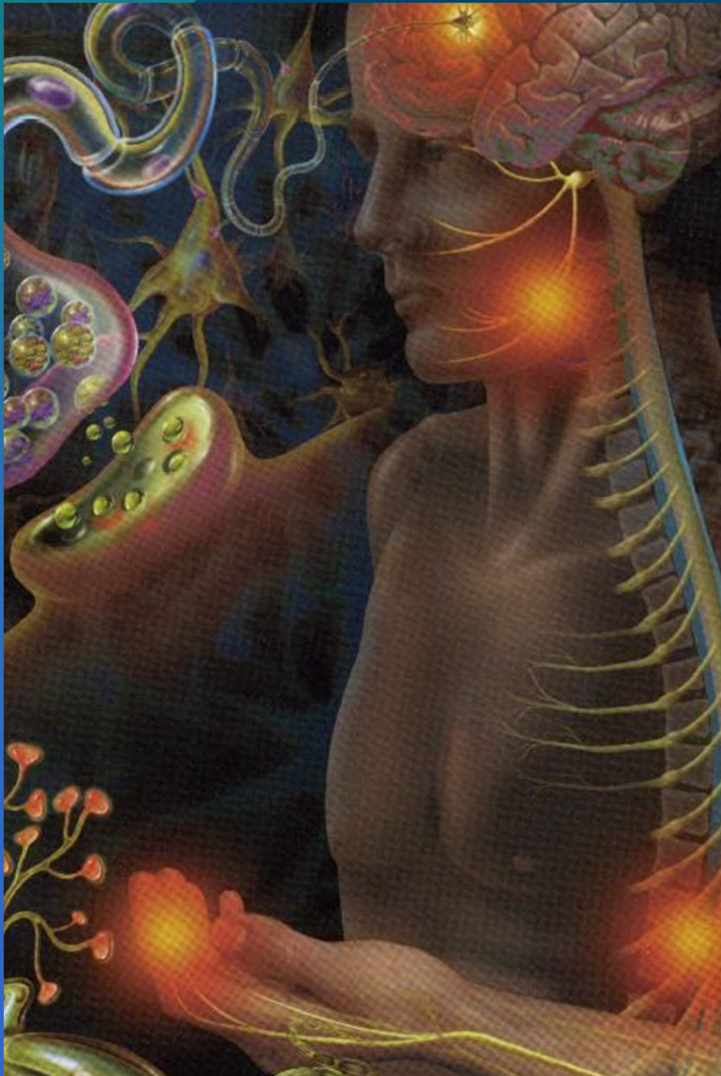
Pharmacokinetic Comparison of Available Cannabinoids

	Nabilone (Cesamet)	Dronabinol (Marinol)	THC:CBD (Sativex)
Source	Synthetic Cannabinoid (THC) Analog	Synthetic Cannabinoid (THC)	Cannabis extract
Formulation	Oral (capsule)	Oral (capsule)	Buccal spray
Onset of Action	60-90 min	30-60 min	30-150 min
T_{max}	2 hrs	1-4	1.5-4
Duration of Action	8-12	4-6	12-24

Other Approaches to Pain

- TENS
- Acupuncture
- Exercise
- Relaxation exercise
- Tai Chi
- Local injections
- Biofeedback
- OT
- Massage
- Heat or ice
- Stress management
- Visualization
- Meditation
- Hypnosis
- Dorsal column stimulation

Pain Management - Conclusions



- Many types of pain may be present in each patient
- Effective management often requires multiple medications and modalities