Safety and Risk-Benefit Ratio of Cannabinoids in Fibromyalgia

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Disclosure Information

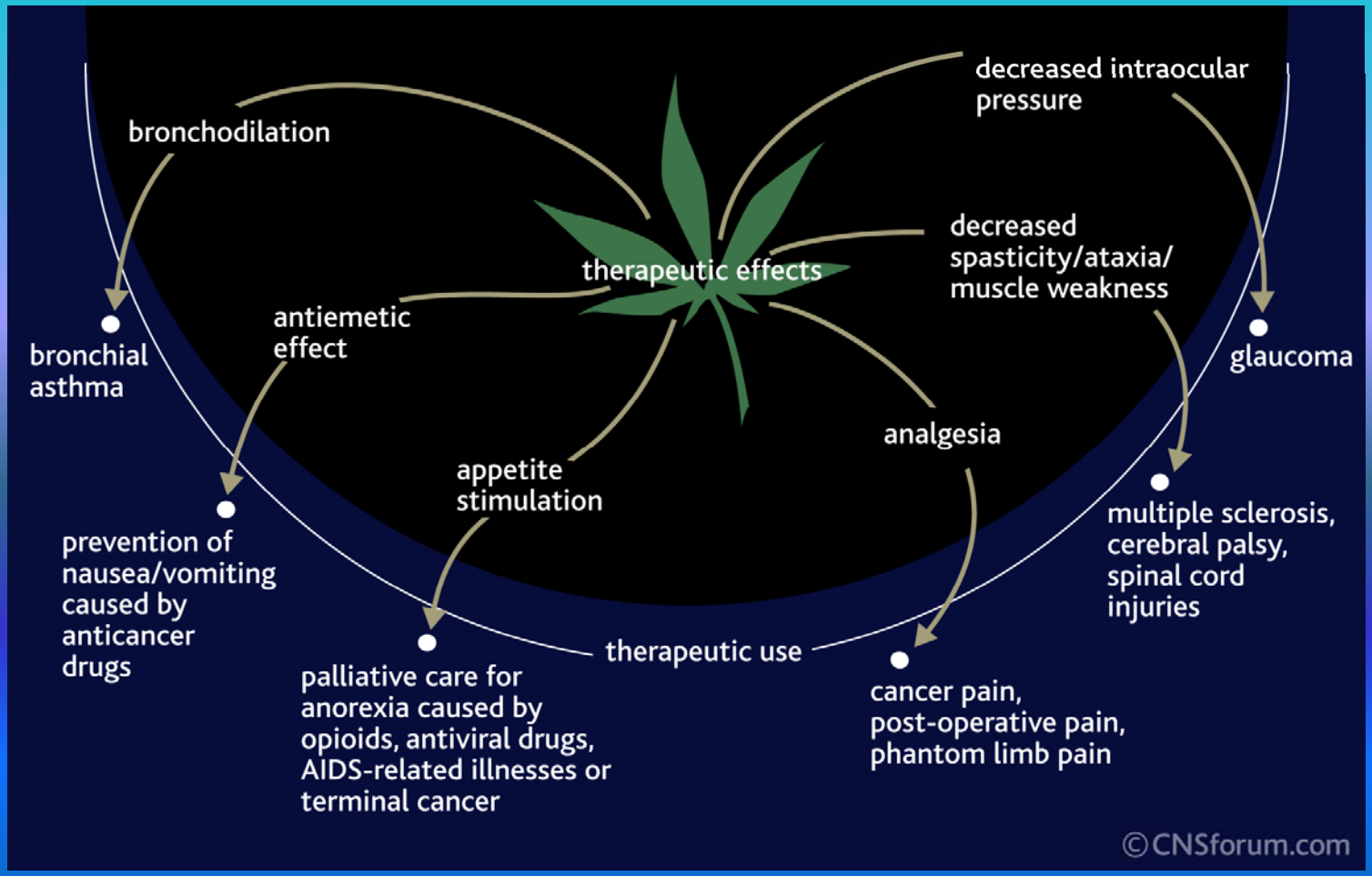
Valeant Canada Limited

- Research Grant

Objectives

- Adverse effects of cannabinoids
- A systematic review of safety studies of medical cannabinoids.
- To evaluate the risk-benefit ratio of cannabinoids in fibromyalgia treatment.

Cannabinoids: Medical Uses



Canadian Society of Addiction Medicine Statement:

"Cannabis is chemically classified in the hallucinogen category of psychoactive substances. The regular use of cannabis products is known to cause harmful health effects, including addiction, with its associated consequences to individuals, communities & society, among those that are susceptible.

Currently, available scientific information and clinical practice experience indicate that overall, there is more risk than benefit, in the use of cannabis products for medicinal purposes.

Ongoing well-designed clinical research into the possible medicinal uses of cannabis products is essential, using the same rigorous standards that are applied to any therapeutic agent prior to its introduction into general clinical practice."

Adverse Effects of Cannabis

- Reports and systematic reviews have found cannabis to be a risk factor for psychosis, cancer and neurocognitive effects
- All reports were focused on the recreational use of cannabis

Ware MA,et al.Pain Res Manag 2005;10 Suppl A:31A-37A

Kalant H, Prog Neuropsychpharmacol Biol Psychiatry 2004;28:849-63

Hall W,et al. Lancet 1998: 352:1611-6

Ashton CH, Br J Anaesth 1999;83:637-49

Campbell FA, et al. BMJ 2001;323:13-6

Russo E, et al. J Cannabis Ther 2002;2:3-57

Moore TH, et al. Lancet 2007;370:319-28

Hashibe M, et al. Alcohol 2005;35:265-75

Grant I, et al. J Int Neuropsychol SOC 2003;9:679-89

Side Effects

Symptom / Effect		Most common	Common	Rare
CNS	Sedation	√		
	Dizziness	√		
	Somnolence	√		
	Euphoria / high		√	
	Blurred vision		√	
	Anxiety			√
	Panic			√
	Paranoia			√
	Psychosis			√
	Depression			√
	Ataxia			√
	Asthenia			√
	Cognitive effects			√
Cardiovascular	Postural Hypotension		√	
	Vasodilation (red eyes)		√	
	Tachycardia			√
	Palpitations			√
Others	Dry mouth	√		
	Headache		√	

*If smoked - Respiratory effect such as bronchitis, COPD, lung infection.

Source: Clark A.J. Cannabinoids for Pain Management. Pain Management & Research, Volume 10 Suppl A, Autumn 2005

Safety – Acute Effects

Mood effects	- Euphoria, Altered time perception and Relaxation
Toxicity	- Do not cause respiratory depression
Cardiac/Vascular effects	- Increased heart rate - Cause postural hypotension and tachycardia
Cognitive function	- Decreased motor coordination
Driving	- May have effects, but exaggerated with alcohol

Source: Ware M & Tawfik. Gourlay D. Cannabinoids for Pain Management. Pain Research & Management Journal. Vol 10 Supplement A – Automn 2005

Safety – Long term Effects

Dependency

- Lower risk than alcohol and tobacco
- Rare with therapeutic use only (unlike opioids)
- Withdrawal symptoms in heavy chronic users

Cognitive

- Impaired in heavy chronic users (resolve after 30 days of abstinence)

Psychosis & schizophrenia

- Higher risk to develop symptoms in young people
- May precipitate in predisposed people

Immunity

- Unknown

Pregnancy

- low birth rate, prematurity and intrauterine growth retardation

Source: Ware M & Tawfik. Gourlay D. Cannabinoids for Pain Management. Pain Research & Management Journal. Vol 10 Supplement A – Automn 2005

Addiction – Cannabinoids

	Nabilone	**Dronabinol**	**THC:CBD**
Source	Synthetic analog to THC	Synthetic THC	Cannabis extracts
Form	Oral, pulvule	Oral, gel capsule	Spray
Content	Crystalline powder	In sesame seed oil	Mixed with Ethanol
Clinical experience	1981	1990	2005
EMIT Assay	Negative	Positive	Positive
Abuse potential	**Lowest of all cannabinoids**	**Lower than natural THC**	**Not enough data available yet**
	Slower onset of action	Slow onset of action	Moderate onset of action
	No reinforcing effect	Low reinforcing effect	Ethanol content
	No volatilization / combustion via pulmonary route	lack of titratability	As needed drug
	Less euphoria & tachycardia		

Source: Gourlay D. Cannabinoids for Pain Management. Pain Research & Management Journal. Vol 10 Supplement A – Automn 2005

Metabolism

Nahas 1999, Guy 2004

	Nabilone (Cesamet®)	Dronabinol (Marinol®)	Sativex®
Source	THC analog	THC	THC + cannabinoL
Metabolites	Carbinol (RRS + SSS)	Hydroxy-11-THC + many other metabolites	Hydroxy-11-THC; 7-hydroxy-CBD + many other metabolites
CYP 450	Mainly 2C9, 3A4, inhibitor to 3A4 unknown	Mainly 2C9, 3A4, inhibito to 3A4	Mainly 2C9, 3A4 & 2D6 Inhibitor to 3A4 & 2D6
Receptors Involved	High affinity to CB1 and CB2	High affinity to CB1 and CB2	High affinity to CB1 and CB2
Urine Test (EMIT)	Negative	Positive	Positive

Pharmacokinetics

Néron 2001, CPS 2003

	Nabilone (Cesar®)t	Dronabinol (Mari®)l	Sative®
Source	Synthetic cannabinoid (TI analog)	Synthetic cannabinoi (THC)	THC + cannabinoL
Number of metabolites	2	>21	> 21
Distribution volume	Liposoluble (very large)	Liposoluble (very large)	Liposoluble (very large)
Onset of Action	60-90 minutes	30-60 minutes	30-150 minutes
T_{max}	2 hours	1-4 hours	1-4 hours
Duration of Action	8-12 hours	4-6 hours	12-24 hours
Half-life: □ Plasma □ Metabolites	 2 hours 35 hours	 19-56 hours 49-53 hours	 > 24 hours

Agent	Possible use	Side effects,	Dose	Cost 30d
Dronabinol MARINOL χ⊗ -synthetic THC 2.5,5,10mg cap(seasame oil)	Treat severe **N&V** from cancer chemo Treat AIDS related **anorexia** {Oral form – little abuse potential}	N&V, ataxia, confusion, coordination problems, dizziness, somnolence, vertigo, red eyes, ↑ or↓ BP, palpitations, ↑HR, flushing, panic rx, delusion of persecution, depersonalization, depression, disturbance in thinking & euphoria :pregnant,breast feeding, ?Sz,psyc hx : ↑ SE: disulfiram, ethanol, fluoxetine, sleep meds. Theophylline↓theo level	2.5-5mg po TID-QID chemo N&V (~5mg/m2) ---2.5mg bid ac lunch & supper to ↑ appetite AIDS 3 ---**Start**: 2.5mg po HS Max 20mg/d	$120-133 $83 $45
Marijuana 4 χ⊗ (Banji, Cannabissativa, Grass, Pot,Weed etc… Cost ~$10-20/g)Contains: Delta-9-THC esp flowers & leaves ~10-20%THC, Delta-8-THC, cannabinol & CBD	An euphoriant. Possibly effective: ↑ appetite AIDS , ↓ pressure for glaucoma & treating MS, tics 20 Unknown: dandruff, hemorrhoids, obesity, asthma, urinary infections, leprosy, preventing rejection after kidney transplants …	Dry mouth, N&V, red eyes; heart, lung & BP dx, ↓mental fx, panic rx, ↑ weight, hallucinations, flashbacks, sedation, ?depression & sexual problems : pregnant, breast feeding, ?seizures, ?psych hx : ↑ SE: disulfiram, ethanol, fluoxetine, sleep meds. Theophylline↓theo level potency/purity concern if unregulated	1-3 grains (65-195mg) for smoking; Hashish plant resin1 grain (16-65mg)	HealthCanada (~12.5%THC) $5/gram 1-866-337-7705 endorsed grow ops & possession-Dose as a proposed daily amount eg. ≤ 5g/day 10
Nabilone W **CESAMET** 0.5,1mg cap (compound for low-dose e.g. simple syrup 5mg/50ml)	Treat severe **N&V** from cancer chemo _ EDS Sask.=nausea/anorexia in AIDS {Oral form – little abuse potential}	Drowsiness, vertigo, psych high/euphoria, dry mouth, depression, ataxia, blurred vision, hallucinations, sedation, headache : pregnant, breast feeding, ?seizures : ↑ SE: disulfiram, ethanol, fluoxetine, sleep meds. Theophylline↓theo level	1-2mg BID chemo N&V --- Start 0.25-0.5mg po HS ↑ by 0.5mg q2days Max 6mg/d	$430-840 $110-230
Tetranabinex/nabidiole x 11 **SATIVEX** χ⊗ Buccal spray soln 5.5ml= ~51 spraysNatural extract contains: Delta-9-THC 2.7mg & CBD 2.5mg/spray	Adjunctive symptomatic relief of **neuropathic pain** in **MS** pts >18yrs (Trial n=**66** 5wk aided approval for this indication18; but product studied in 5 short trials with a total of 368 pts) Approved as a narcotic April05 with CONDITIONS (promising evidence must be further confirmed) Canada **first** country in the world to approve its use.	mouth irritation~20% ,dizziness, euphoric mood, changes in mood & concentration, drowsiness, bad taste, vertigo, reaction time : allergy cannabinoids, propylene glycol, ethanol or pepermint oil, pts with severe heart, liver or kidney impairment, pregnant; ? psyc hx : ↑ SE: disulfiram, ethanol, fluoxetine, sleep meds. Theophylline↓theo level	Buccal 1 spray q4h directed below the tongue (often use 4 or **5** sprays/day) Initial: 1 spray/day; ↑ q2d Max ~12 sprays/day Prime: 2-3 times initially Unopened: Refrigerate Room temp: stable for 28days	$527 per 4 bottles (~200doses or ~40 days)

Overdose

The overall acute toxicity of THC is low

"Acute studies show that it is virtually impossible to die from acute administration of THC alone" Dr. Beaulieu

"There are low levels of CB1 receptors in brainstem cardiopulmonary centers, which probably accounts for the high margin of the cannabinoids" Dr. Lynch

Source: Lynch M & Beaulieu P. Gourlay D. Cannabinoids for Pain Management. Pain Research & Management Journal. Vol 10 Supplement A – Automn 2005

Contraindications/Precautions

- Contraindications
  - Suspected or known allergy
  - Significant hepatic or renal impairment
  - Serious cardiovascular disease
  - History of psychosis
  - Age <18 years
  - Reproductive: pregnancy, nursing, intention to conceive
- Warnings and precautions
  - Activities requiring judgment and coordination
  - Epilepsy or recurrent seizures
  - Potentiation of CNS depressant effects
  - THC has abuse potential
    - Not recommended in patients with addiction and drug abuse liability

Adverse Effects of Medical Cannabinoids : a systematic review

Wang et al. CMAJ 2008;178(13):1669-78

- 31 studies (23 randomized controlled trials and 8 observational studies of medical cannabis use)
- In the 23 randomized controlled trials, the median duration of cannabinoid exposure was 2 weeks (range 8 hours-12 months).

Adverse Effects of Medical Cannabinoids : a systematic review

Wang et al. CMAJ 2008;178(13):1669-78

- Adverse events: observed total of 4779
- Not serious AE's 4615 or 96.6%
- Serious AE's 164

  -Relapse of multiple sclerosis was the most common with 21 events12.8%

  -Vomiting 16 events or 9.8%

  -Urinary tract infection 15 or 9.1%

Adverse Effects of Medical Cannabinoids : a systematic review

Wang et al. CMAJ 2008;178(13):1669-78

- The rate of non serious adverse events was higher among the medical cannabinoids assigned participants than among controls .

- The most commonly reported non serious adverse event was dizziness 714 events or 15.5% among people exposed to cannabinoids.

Adverse Effects of Medical Cannabinoids : a systematic review

Wang et al. CMAJ 2008;178(13):1669-78

- It appears that short term use of existing medical cannabinoids increases the risk of non serious adverse events.

- The long term use risks were poorly characterized in published clinical trials and observational studies.

Nabilone Adverse Effects

Drowsiness (66%), vertigo (58.8%), psychological high(38.8), dry mouth(21.6%), depression(14%), ataxia(12.8%), blurred vision(12.8), sensation disturbance(12.4), anorexia(7,6), asthenia(7.6), headache(7.2), orthostatic hypotension(5.2), euphoria(4.0) and hallucinations(2.0)

Less than 1%: tachycardia, tremor, syncope, nightmares, distortion in perception of time, confusion, dysphoria, psychotic reactions and seizures.

Case Series Of FMS Patients Improved With Oral Cannabinoid Nabilone

Ko G, Wine W.Cronic Pain and Cannabinoids.Practical Pain Management,2005

Improvement on FIQ, VAS, Average TePs pain threshold

Conclusion: **Nabilone appears helpful as an adjuvant pain medication for carefully pre-screened FMS patients**

Nabilone for the Treatment of Pain in Fibromyalgia

Skrabek RQ, Galimova L, J Pain 2008;9:164-73.

A randomized double-blind placebo-controlled trial assessing the effect of the oral cannabinoid nabilone on pain and quality of life in patients with fibromyalgia

Nabilone for the Treatment of Pain in Fibromyalgia

Skrabek RQ, Galimova L, J Pain 2008;9:164-73.

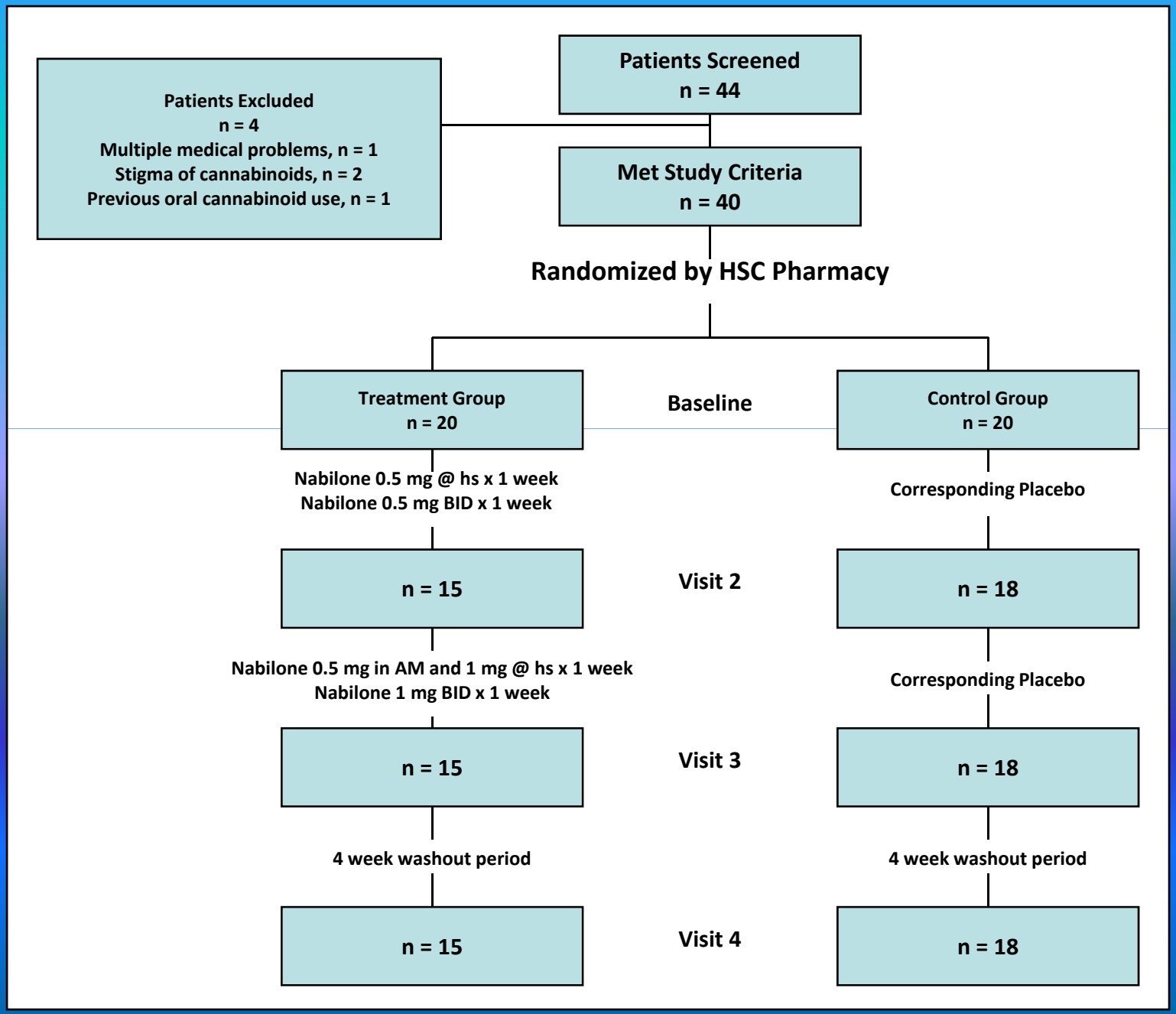
Hypothesis: Nabilone will significantly reduce pain and improve quality of life in patients with fibromyalgia, as evidenced by significant improvements in the outcome measures compared to the placebo group

Nabilone for the Treatment of Pain in Fibromyalgia

Skrabek RQ, Galimova L, J Pain 2008;9:164-73.

Methods: Patients were allowed to continue their current pain medications throughout the study

- Patients assessed at 0, 2, 4 and 8 week visits
- Primary outcome measure:
  - Visual analogue scale (VAS) for pain
- Secondary outcome measures:
  - Number of tender points
  - Average tender point pain threshold
  - Fibromyalgia Impact Questionnaire (FIQ)


Patients Screened
n = 44
Patients Excluded
n = 4
Multiple medical problems, n = 1
Stigma of cannabinoids, n = 2
Previous oral cannabinoid use, n = 1
Met Study Criteria
n = 40
Randomized by HSC Pharmacy
Treatment Group
n = 20
Baseline
Control Group
n = 20
Nabilone 0.5 mg @ hs x 1 week
Nabilone 0.5 mg BID x 1 week
Corresponding Placebo
n = 15
Visit 2
n = 18
Nabilone 0.5 mg in AM and 1 mg @ hs x 1 week
Nabilone 1 mg BID x 1 week
Corresponding Placebo
n = 15
Visit 3
n = 18
4 week washout period
4 week washout period
n = 15
Visit 4
n = 18

Nabilone for the Treatment of Pain in Fibromyalgia

Skrabek RQ, Galimova L, J Pain 2008;9:164-73.

Reasons for withdrawal from study:

Control group 1- headache

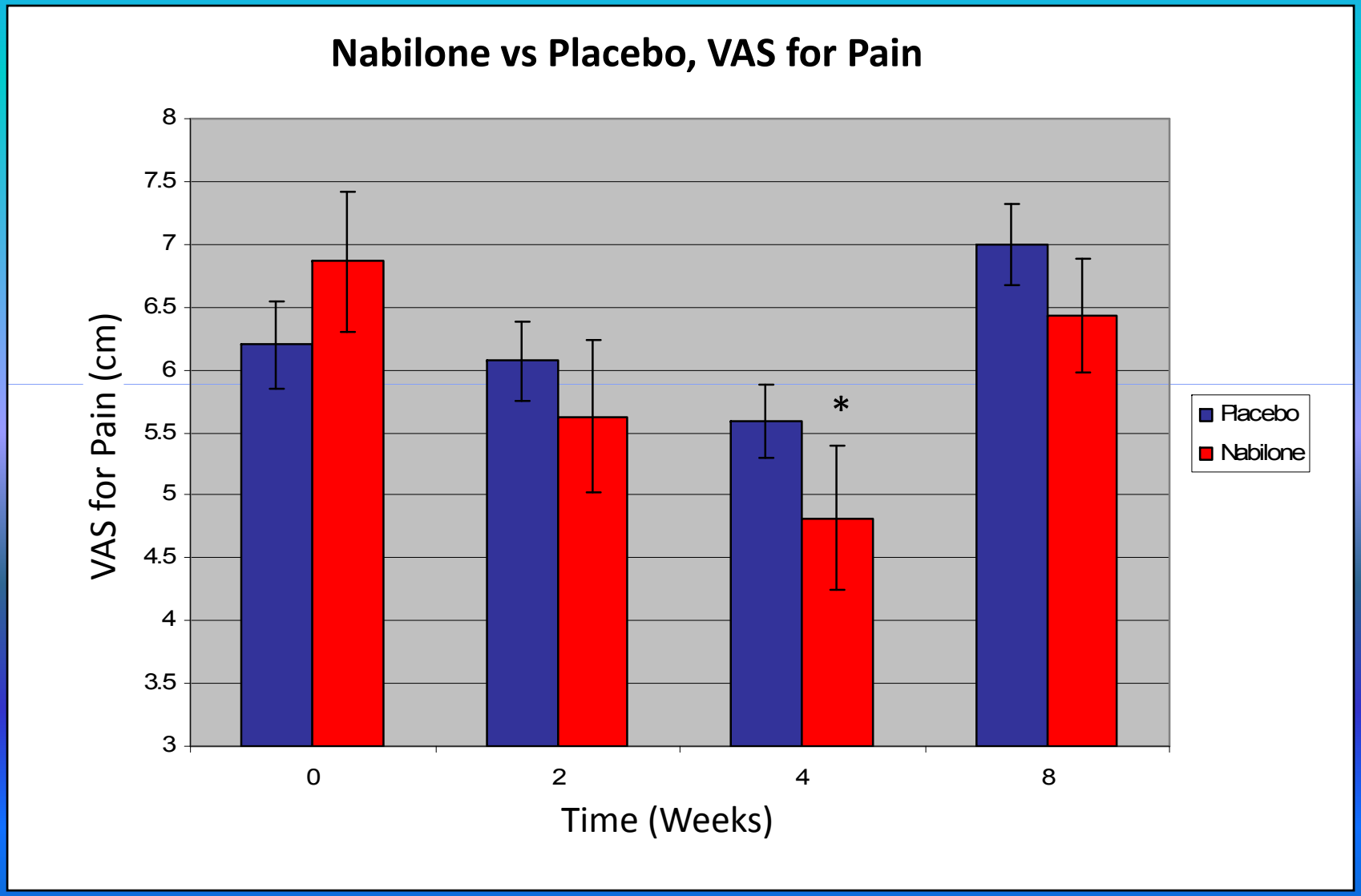
1- no reported reason or AE

Study group 2-no listed AE and no stated reason

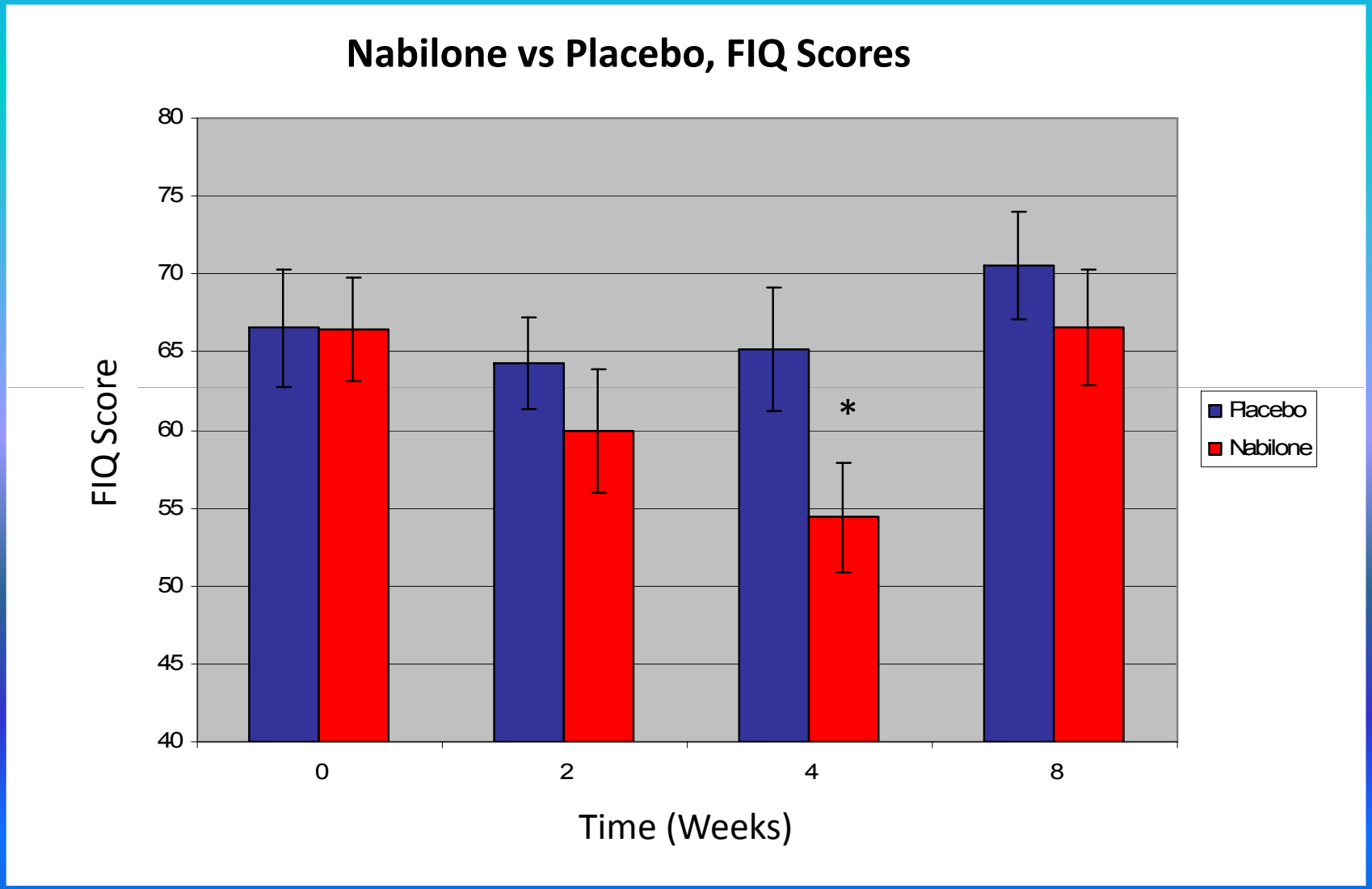
1- dizziness, disorientation, nausea

1- poor coordination, dizziness, headache and nausea

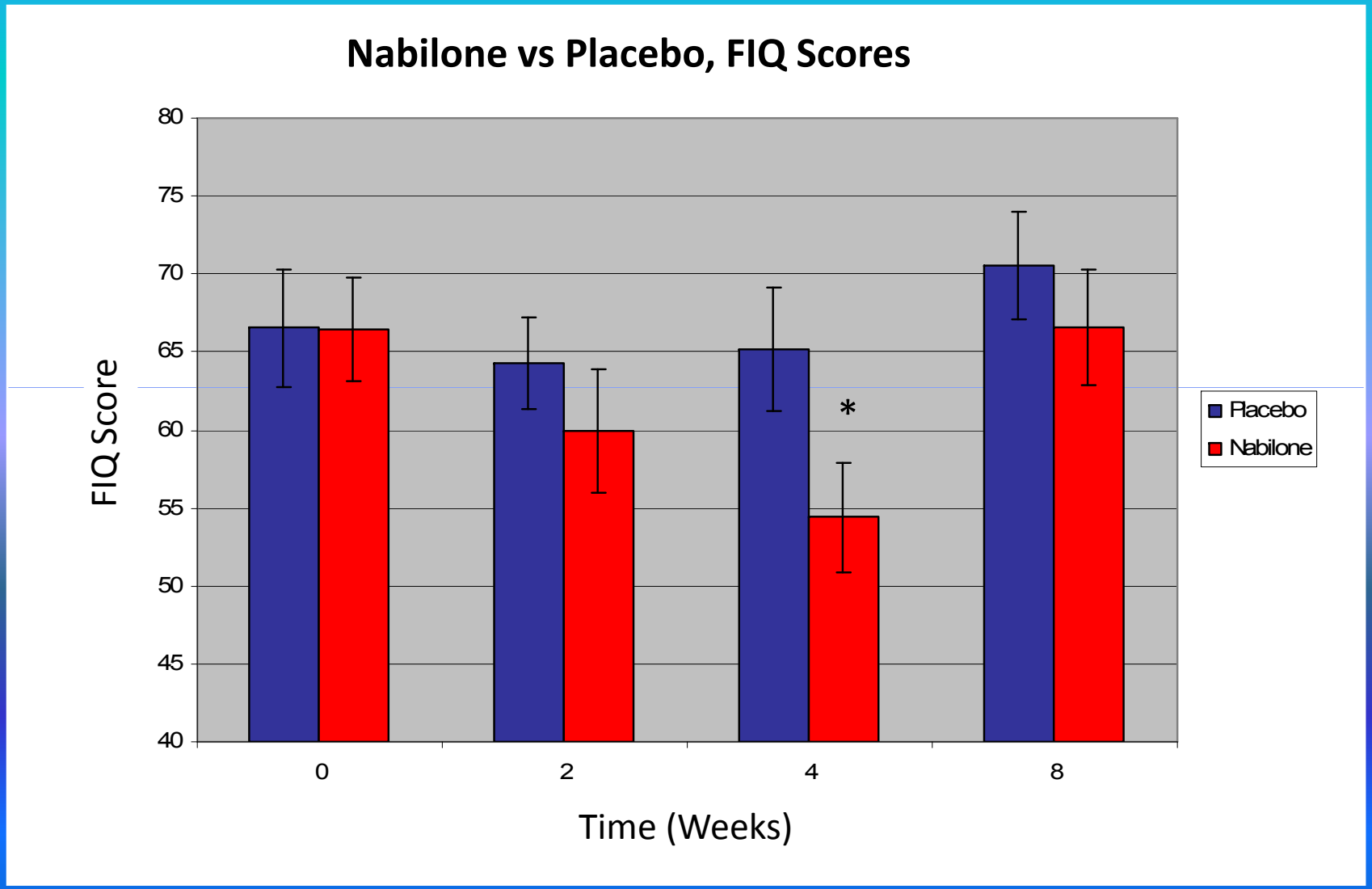
1-drawziness and fatigue


Nabilone vs Placebo, VAS for Pain
VAS for Pain (cm)
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
0
2
4
8
Time (Weeks)
*
Placebo
Nabilone

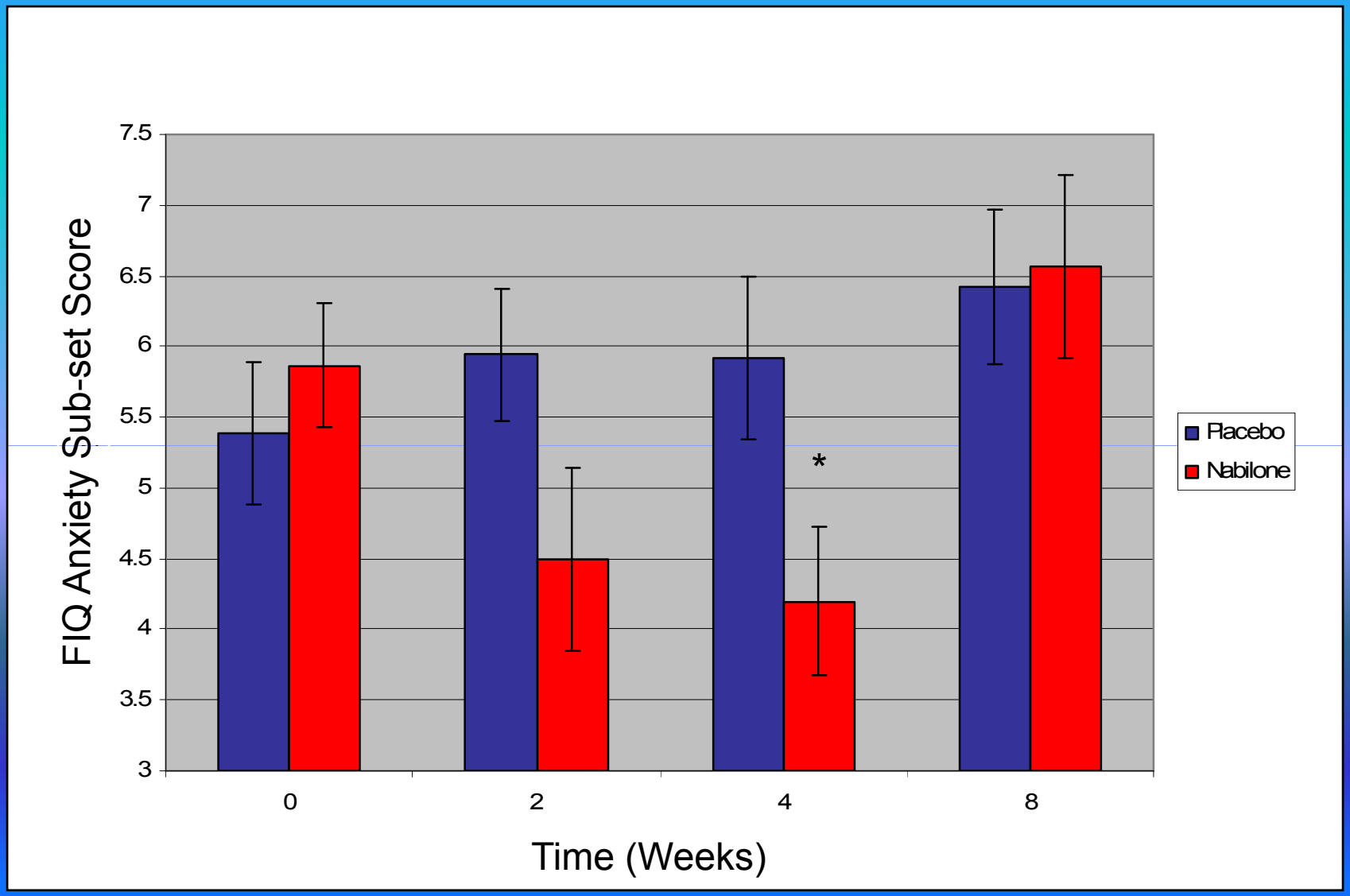
*(-2.04, p<0.02)


Nabilone vs Placebo, FIQ Scores
FIQ Score
80
75
70
65
60
55
50
45
40
0
2
4
8
Time (Weeks)
*
Placebo
Nabilone

*(-12.07, p<0.02)


Nabilone vs Placebo, FIQ Scores
FIQ Score
80
75
70
65
60
55
50
45
40
0
2
4
8
Time (Weeks)
*
Placebo
Nabilone

*(-12.07, p<0.02)


FIQ Anxiety Sub-set Score
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
0
2
4
8
Time (Weeks)
*
Placebo
Nabilone

***(-1.67, p<0.02)**

Results

- The treatment group experienced more side effects per person at 2 and 4 weeks (1.58, $p<0.02$ and 1.54, $p<0.05$) respectively
- Common side effects
  - drowsiness 7/15
  - dry mouth 5/15
  - vertigo 4/15
  - ataxia 3/15
- No serious adverse events occurred during the study

Conclusion

The first randomized control trial to demonstrate the benefit of nabilone in fibromyalgia

The significant reductions in VAS for pain, FIQ and FIQ anxiety scores seen in the treatment group, coupled with minimal side effects, suggest that nabilone is a beneficial, well tolerated, treatment option in patients with fibromyalgia

Follow-Up Study

- 6 month retrospective follow-up of Nabilone for the Treatment of Pain in Fibromyalgia
- A chart review of the 15 patients who continued taking nabilone at the conclusion of the last study
- Outcome measures:

  -VAS for pain

  -FIQ score

Follow-Up Study

- 3 patients were lost to follow-up and no further data to analyze
- Of 12 remaining patients, only 3 continued to use nabilone
- None of the patients continued the 1 mg BID dose
- 1 patient continued 0.5 mg @hs
- 2 patients continued 0.5 mg BID

Follow-Up Study

- Reasons for not continuing the use of nabilone included:

  -the medication was too expensive

  -they did not find the medication beneficial

  -they were already on too many medications

  -the medication was not offered to them after the study

Follow-Up Study

- VAS and FIQ scores were compared to the 8 week mark of the previous study, when the patients were last seen

Follow-Up Study Results

- None of the patients that stopped taking nabilone had a >50% benefit in their pain relief at 6 month follow-up
- 1 of the 3 patients who continued taking nabilone had >50% improvement in VAS for pain
- Difference in VAS for pain between groups at 6 months was 2.73, $p>0.15$
- None of the patients developed a tolerance to nabilone

Follow-Up Study Results

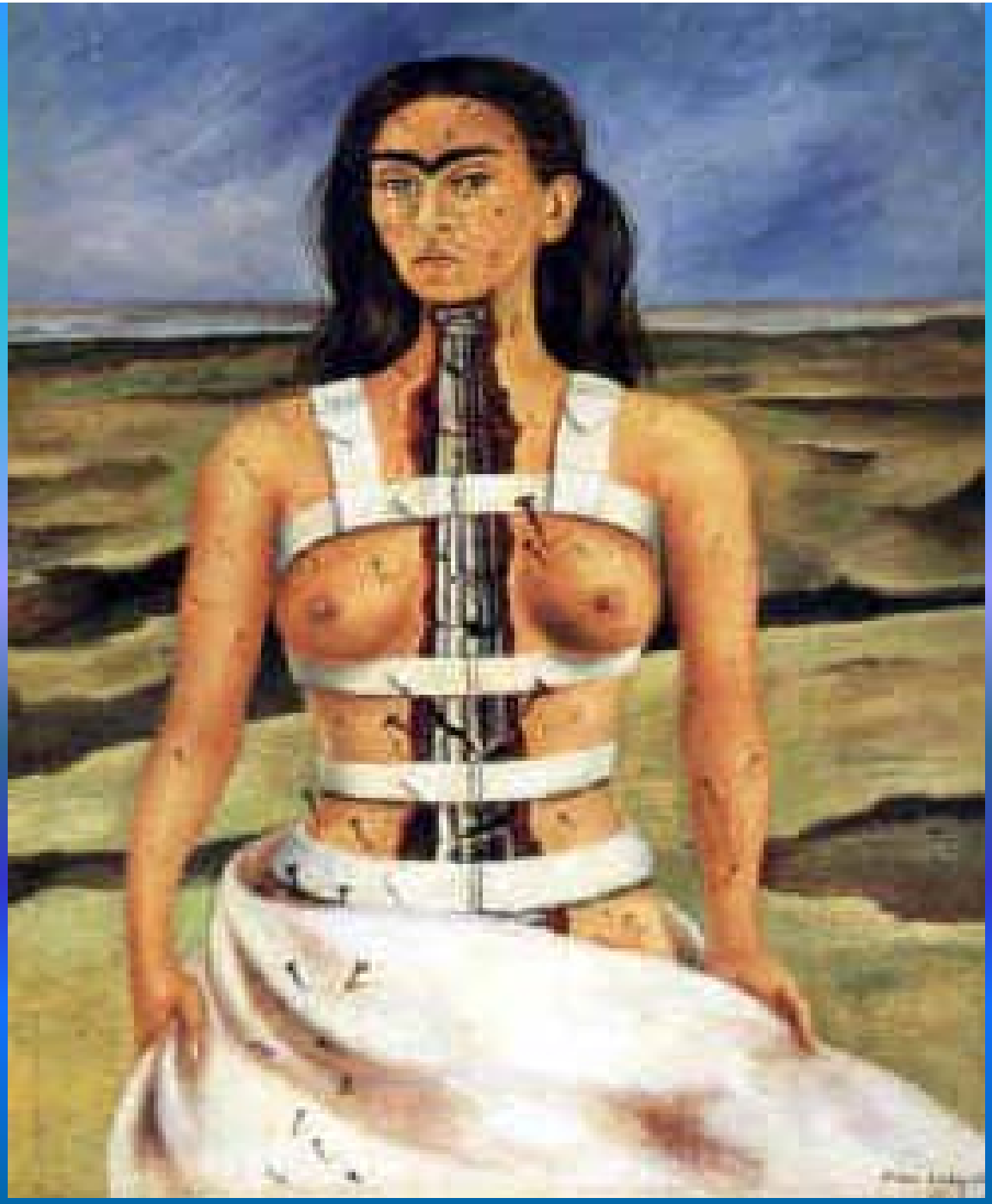
- 1 of the 9 patients who did not continue treatment with nabilone had a drop in their FIQ score of 22 points
- The remaining 8 patients had increase in their FIQ score ranging from 3.5 to 27 points, avg: 10.6, SD:14.3
- 2 of the 3 patients who continued treatment had drops in their FIQ score of -16.9 and -30.9 points. The last patient's score increased by 2.9, avg:-15.0, SD:17
- Difference in FIQ at 6 months between groups was 25.6, $p<0.10$

Follow-Up Study Conclusion

- The data suggests a trend towards a benefit in pain relief and quality of life improvement in patients with fibromyalgia who continued on nabilone
- This is too small study to make definitive conclusions about the long term use of nabilone in people with fibromyalgia

Conclusion

- Use of cannabinoids associated with numerous nonserious adverse effects (nervous system and psychiatric disorders are the most common).
- Only one RCT reviewed effects of a synthetic cannabinoid analog (Nabilone) in people with Fibromyalgia
- Reported adverse effects of Nabilone were generally mild. No serious adverse events were observed
- Future RCTs are necessary to assess long term benefit and safety of medical cannabinoids in people with fibromyalgia.



THANK YOU