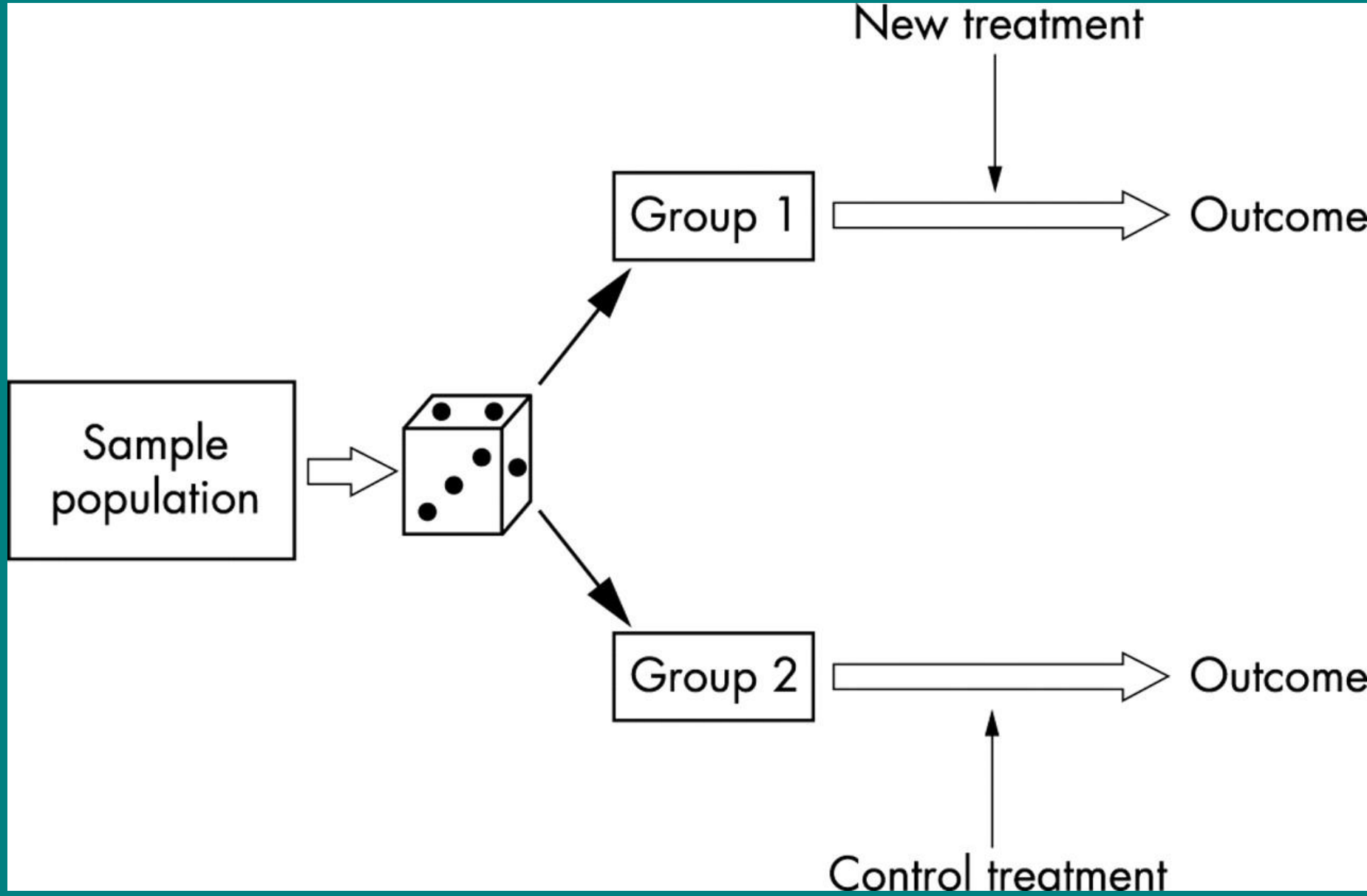
# Cannabis, the evidence

MCID minimally clinically important difference
VAS 1.5-2/10 or 30% reduction

# Randomised control trials



# Randomised Control Trials

- Often comparing two groups
- Placebo
- Randomised to reduce bias from chance

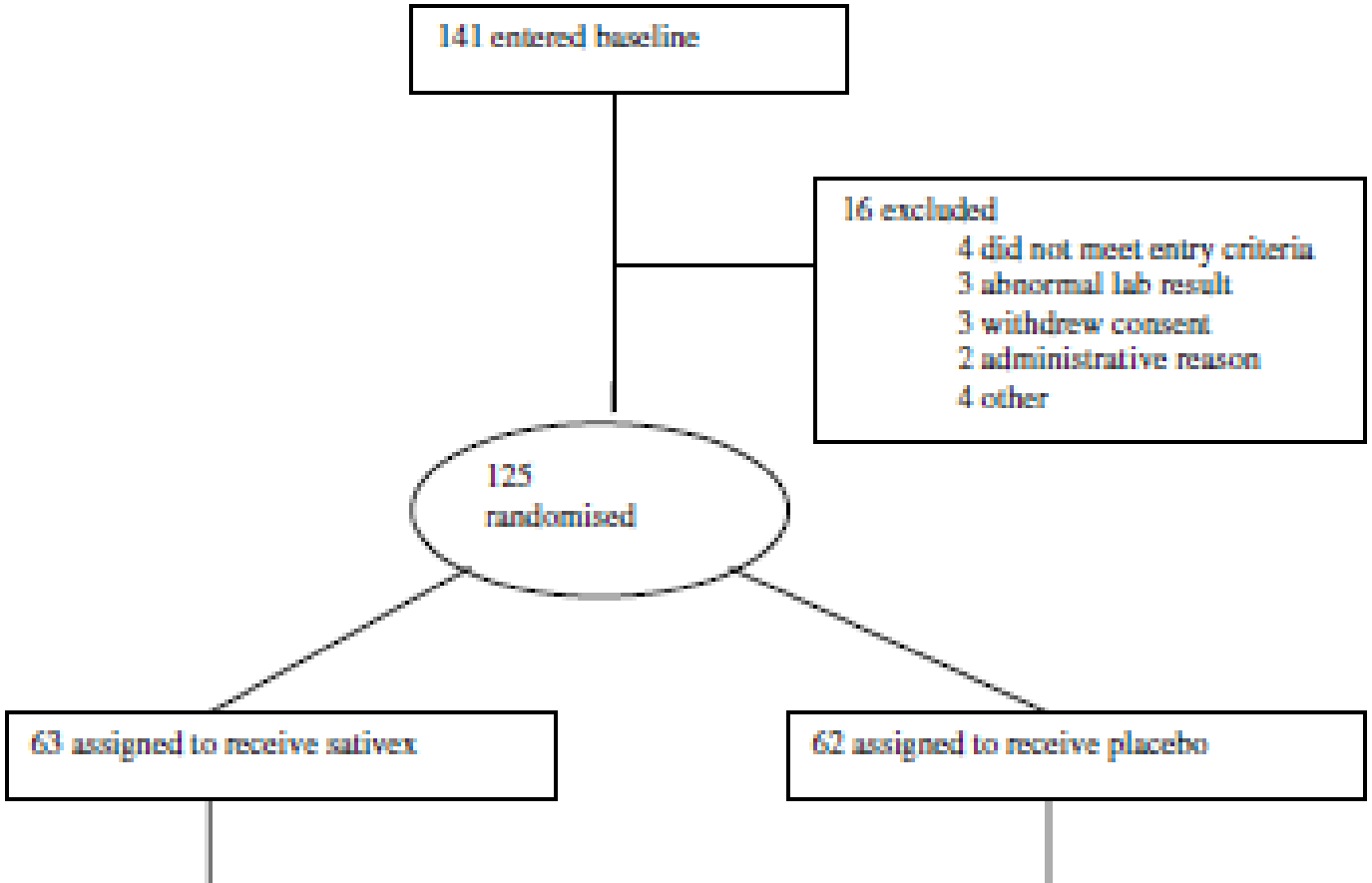
Pain 133 (2007) 210–220

PAIN

www.elsevier.com/locate/pain

# Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmikko [a,*], Mick G. Serpell [b], Barbara Hoggart [c], Peter J. Toomey [d], Bart J. Morlion [e], Derek Haines [f]


141 entered baseline
16 excluded
4 did not meet entry criteria
3 abnormal lab result
3 withdrew consent
2 administrative reason
4 other
125
randomised
63 assigned to receive sativex
62 assigned to receive placebo

Pain 133 (2007) 210–220

PAIN

www.elsevier.com/locate/pain

# Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmikko [a,*], Mick G. Serpell [b], Barbara Hoggart [c], Peter J. Toomey [d], Bart J. Morlion [e], Derek Haines [f]

## Table 2
## Patient characteristics

| | Sativex ($N = 63$) | Placebo ($N = 62$) |
|---|---|---|
| Age, yr mean (SD) | 52.4 (15.8) | 54.3 (15.2) |
| Women, *N* (%) | 35 (55.6) | 39 (62.9) |
| White, *N* (%) | 61 (97) | 60 (97) |
| Weight, kg mean (SD) | | |
| Men | 79.9 (16.7) | 86.8 (16.7) |
| Women | 72.0 (18.2) | 72.7 (17.3) |
| Duration of pain, yr mean (SD) | 6.4 (5.7) | 6.2 (6.4) |

Pain 133 (2007) 210–220

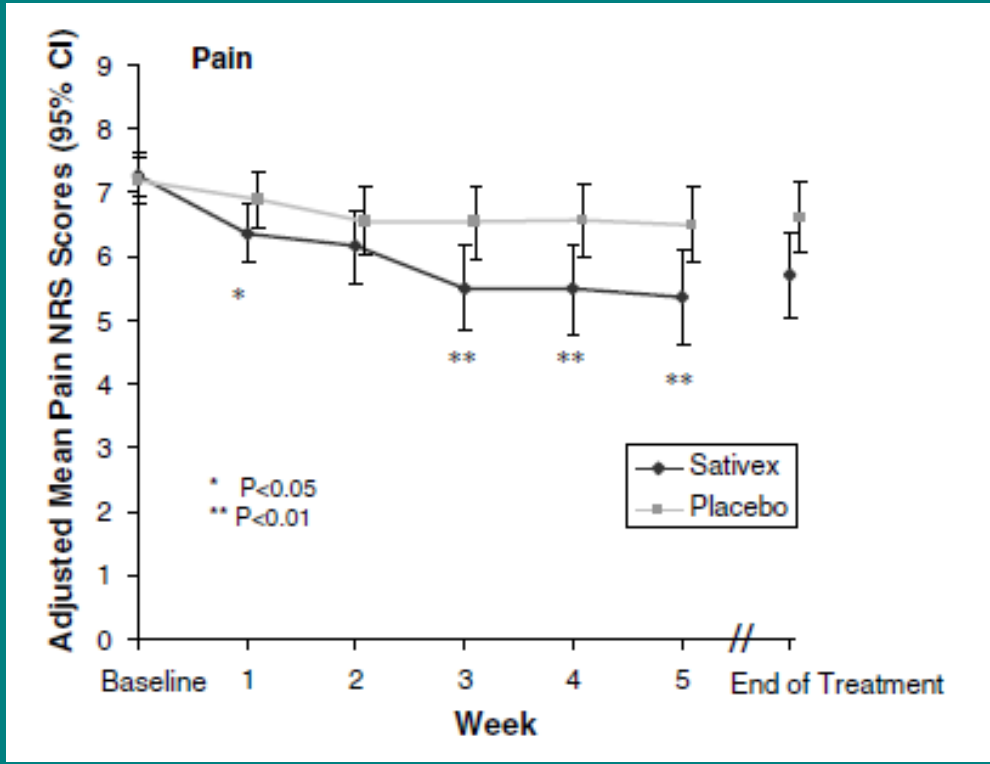
PAIN

www.elsevier.com/locate/pain

# Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmikko [a,*], Mick G. Serpell [b], Barbara Hoggart [c], Peter J. Toomey [d], Bart J. Morlion [e], Derek Haines [f]

N = 125
6.3 years duration of pain
Sativex -1.48
Placebo -0.52



# Randomised control trial pitfalls

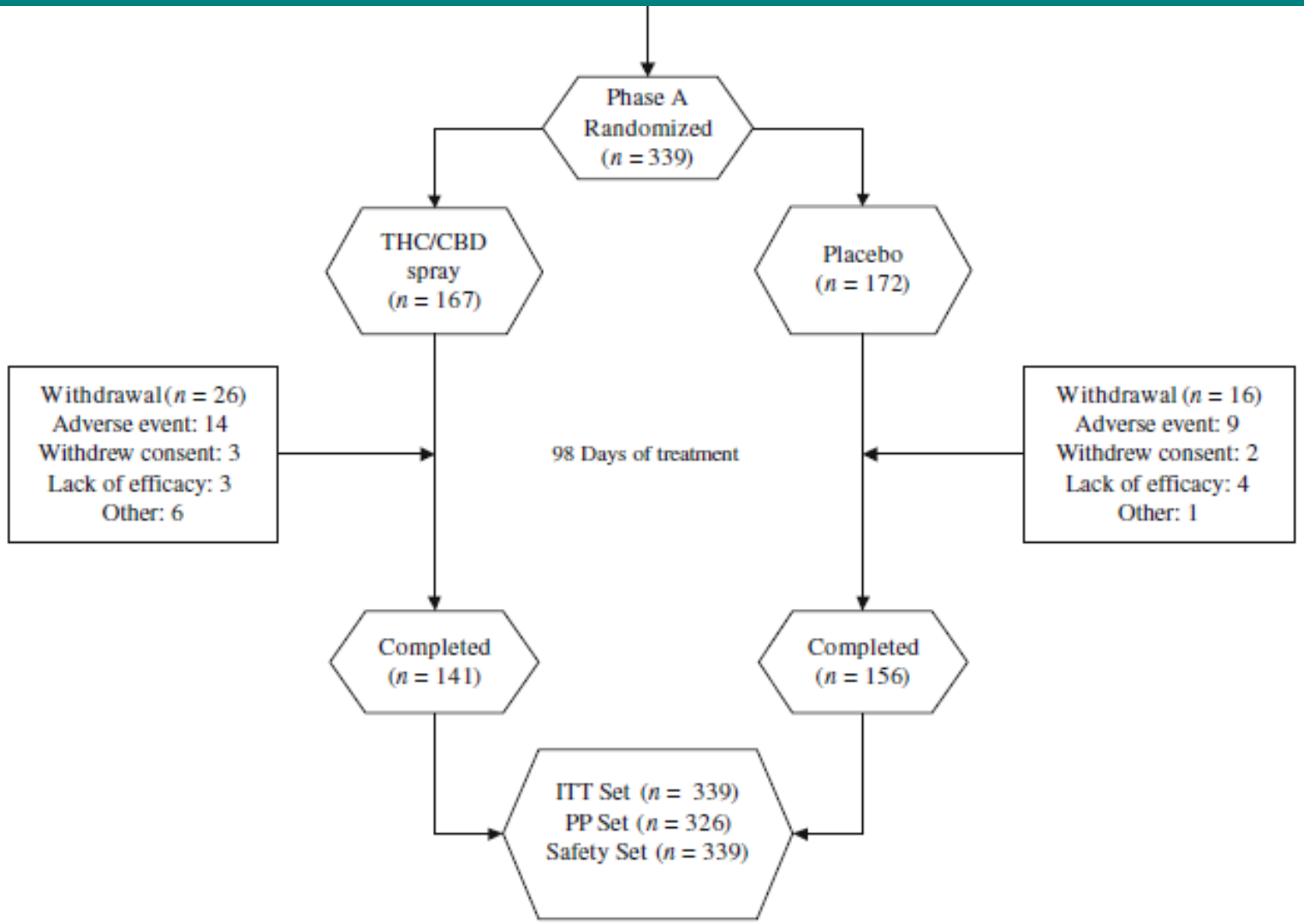
- Legislation
- Homogeneity of diagnosis
  - E.g. different pain diagnoses

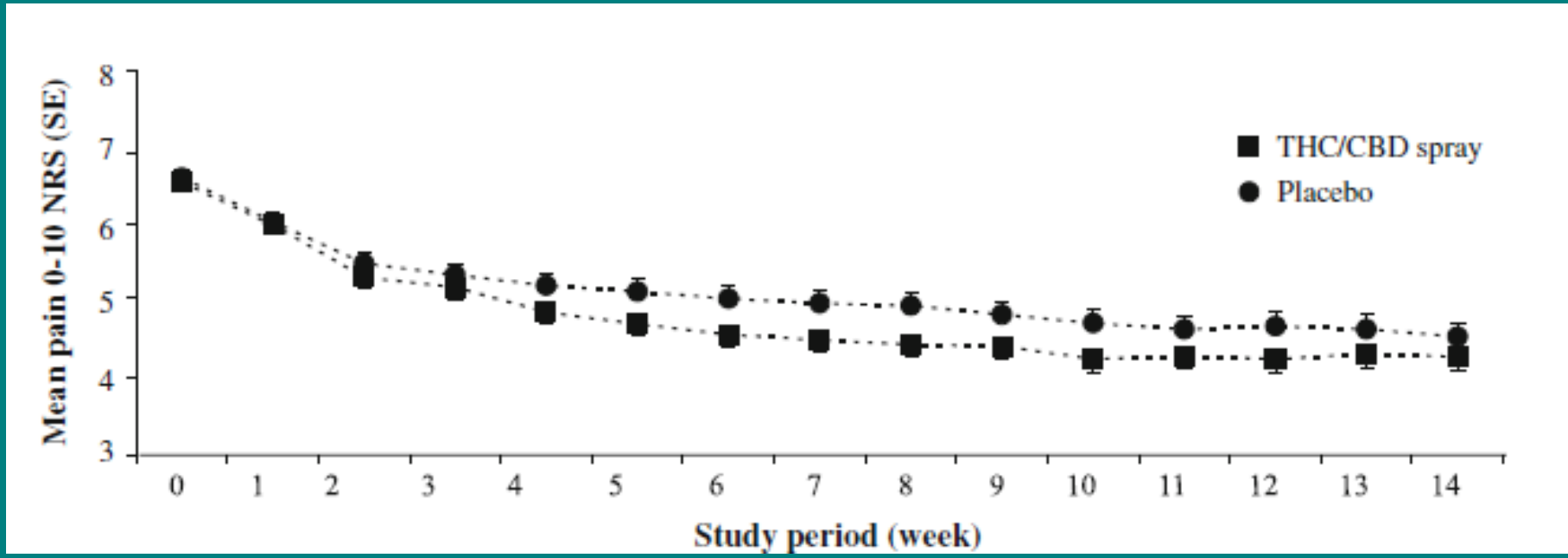
- Numbers - neuropathic pain
- Industry sponsorship-vested interest
- Systematic reviews

**A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis**

R. M. Langford · J. Mares · A. Novotna · M. Vachova · I. Novakova · W. Notcutt · S. Ratcliffe

- MS with Central pain
- How do you diagnose? No gold standard or test to diagnose.
- Leads to variable sample


Phase A
Randomized
(n = 339)
THC/CBD
spray
(n = 167)
Placebo
(n = 172)
Withdrawal (n = 26)
Adverse event: 14
Withdrew consent: 3
Lack of efficacy: 3
Other: 6
98 Days of treatment
Withdrawal (n = 16)
Adverse event: 9
Withdrew consent: 2
Lack of efficacy: 4
Other: 1
Completed
(n = 141)
Completed
(n = 156)
ITT Set (n = 339)
PP Set (n = 326)
Safety Set (n = 339)




- 30% reduction in pain
- THC/CBD 50%
- Placebo spray 45%
- THC/CBD 1.93/10 Placebo 1.76/10

# Neuropathic pain

- Changes in
  - sensory nerves,
  - spinal cord
  - brain
- Stimulus independent pain
- Hypersensitivity (allodynia)

# Neuropathic pain

- post-herpetic neuralgia
- peripheral neuropathy
- focal nerve lesion
- radiculopathy
- Complex Regional Pain Syndrome (CRPS) type 2

# Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial

Ronald J Ellis[*,1], Will Toperoff[1], Florin Vaida[2], Geoffrey van den Brande[3], James Gonzales[4], Ben Gouaux[5], Heather Bentley[5], and J Hampton Atkinson[5]

Pain score 11.1/20

| | | |
|---|---|---|
| Cannabis Reduction | 4.1/20 | 37% |
| Placebo Reduction | 0.96/20 | 8.6% |

Cannabis 46% achieved 30% reduction pain
Placebo 18% achieved 30% reduction in pain

N = 28 - 64% took opioids, 36% NSAIDS, 29% TCAs, 64% anticonvulsants
Neuropathic pain in HIV

RESEARCH CMAJ

# Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducruet MSc, Thao Huynh MD, Ann Gamsa PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

| **Average daily pain at baseline** | |
|---|---|
| Mean (SD) | 6.89 (1.37) |
| Range | 4.0–9.2 |

**Table 3:** Effects of smoked cannabis and secondary outcomes, by potency of tetrahydrocannabinol (THC) received

| | Potency of THC, %; outcome measure, mean (SD)* | | | |
|---|---|---|---|---|
| Outcome | 0 | 2.5 | 6.0 | 9.4 |
| **Pain intensity** | | | | |
| Average daily pain | 6.1 (1.6) | 5.9 (1.9) | 6.0 (1.8) | 5.4 (1.7)† |

Post traumatic and post surgical neuropathic pain
N= 23 cross over trial 22% reduction pain intensity 1.49/10

EJP
European Journal of Pain
EFIC

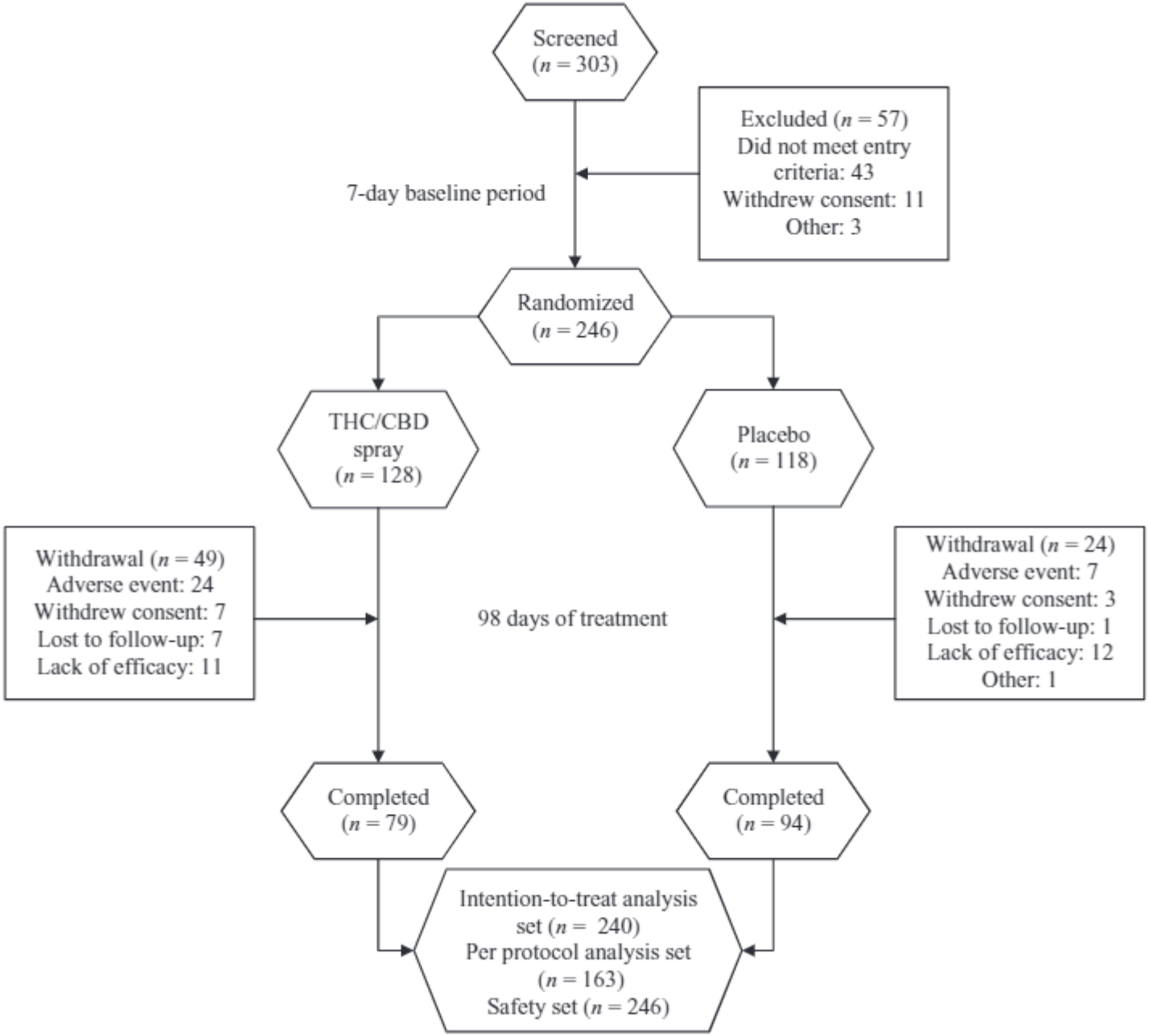
Original Article

# A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment

M. Serpell ✉, S. Ratcliffe, J. Hovorka, M. Schofield, L. Taylor, H. Lauder, E. Ehler

First published: 13 January 2014 | https://doi.org/10.1002/j.1532-2149.2013.00445.x | Cited by: 30

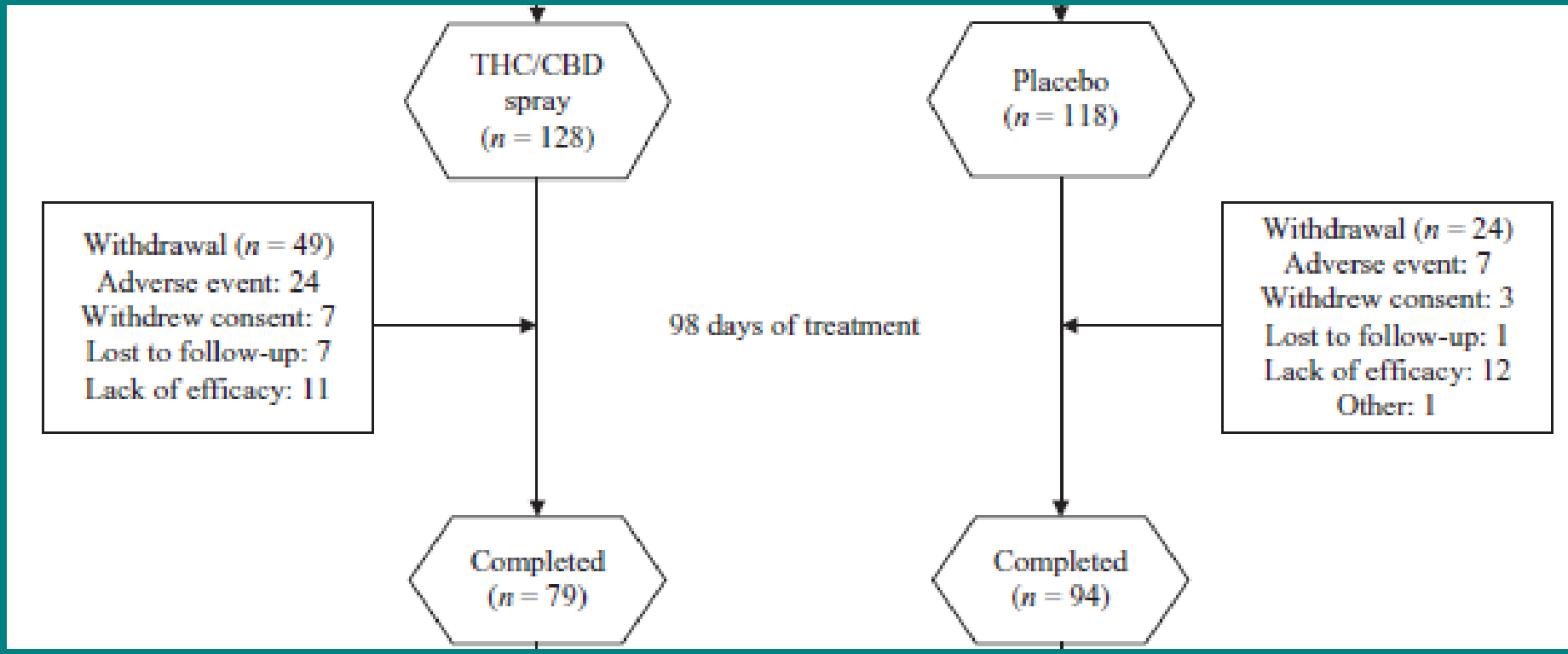
- N = 303
- Neuropathic pain with allodynia - 6 years
- THC/CBD Spray in addition to usual analgesia


Screened
(n = 303)
Excluded (n = 57)
Did not meet entry
criteria: 43
Withdrew consent: 11
Other: 3
7-day baseline period
Randomized
(n = 246)
THC/CBD
spray
(n = 128)
Placebo
(n = 118)
Withdrawal (n = 49)
Adverse event: 24
Withdrew consent: 7
Lost to follow-up: 7
Lack of efficacy: 11
98 days of treatment
Withdrawal (n = 24)
Adverse event: 7
Withdrew consent: 3
Lost to follow-up: 1
Lack of efficacy: 12
Other: 1
Completed
(n = 79)
Completed
(n = 94)
Intention-to-treat analysis
set (n = 240)
Per protocol analysis set
(n = 163)
Safety set (n = 246)

olled in

# 30% reduction pain
# 28% vs 16%

# Analysis




- 35/128  35/79 responders

# 2017 review

Cochrane Library

Cochrane Database of Systematic Reviews

## Cannabis-based medicines for chronic neuropathic pain in adults (Review)

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

# Cochrane review Neuropathic pain

- THC/CBD oromucosal spray (nine studies with 1433 participants) was superior to placebo. SMD was -0.40 (95% CI -0.75 to -0.05) (P value 0.03).

# 30% reduction pain

- 10 studies with1586 participants.
- 323 of 819 (39.4%) CBD/THC
- 251 of 767 (32.7%) placebo group
- (RD 0.09, 95% CI 0.03 to 0.15; P value 0.004; $I^2$ = 34%). NNTB was 11 (7 to 33).

# Cancer pain

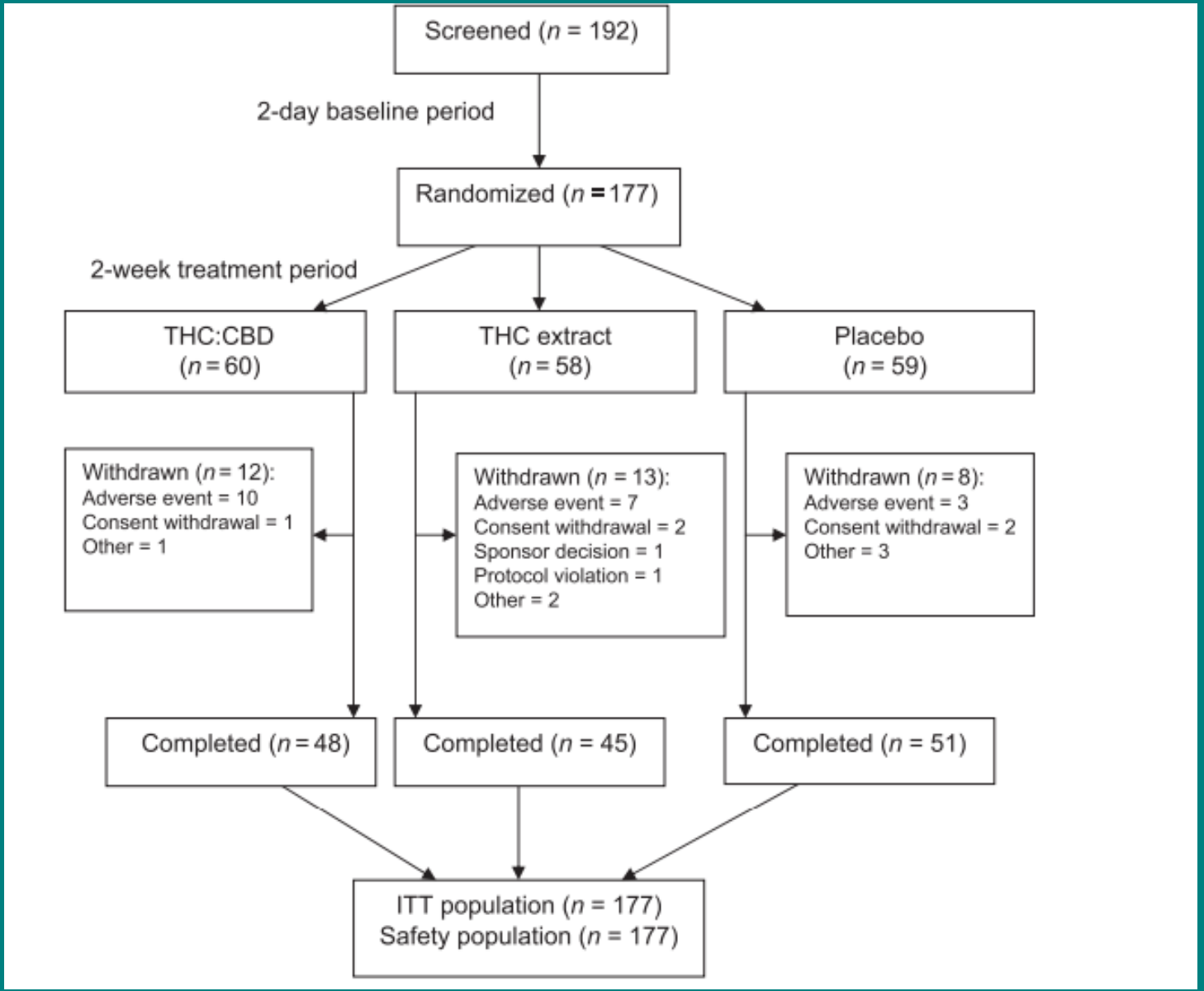
- Mass effects
  - Tissue compression bones, muscles, organs
  - Neuropathic
- Complications of treatment
  - Radiotherapy
  - Chemotherapy

Vol. 39 No. 2 February 2010 Journal of Pain and Symptom Management 167

*Original Article*

# Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain

- 2.7THC & 2.5 CBD (Sativex)
- Incurable malignancy using strong opiods
- 2 week trial
- NPRS>4/10


Screened (n = 192)
2-day baseline period
Randomized (n = 177)
2-week treatment period
THC:CBD (n = 60)
THC extract (n = 58)
Placebo (n = 59)
Withdrawn (n = 12): Adverse event = 10 Consent withdrawal = 1 Other = 1
Withdrawn (n = 13): Adverse event = 7 Consent withdrawal = 2 Sponsor decision = 1 Protocol violation = 1 Other = 2
Withdrawn (n = 8): Adverse event = 3 Consent withdrawal = 2 Other = 3
Completed (n = 48)
Completed (n = 45)
Completed (n = 51)
ITT population (n = 177)
Safety population (n = 177)

# Response Rate

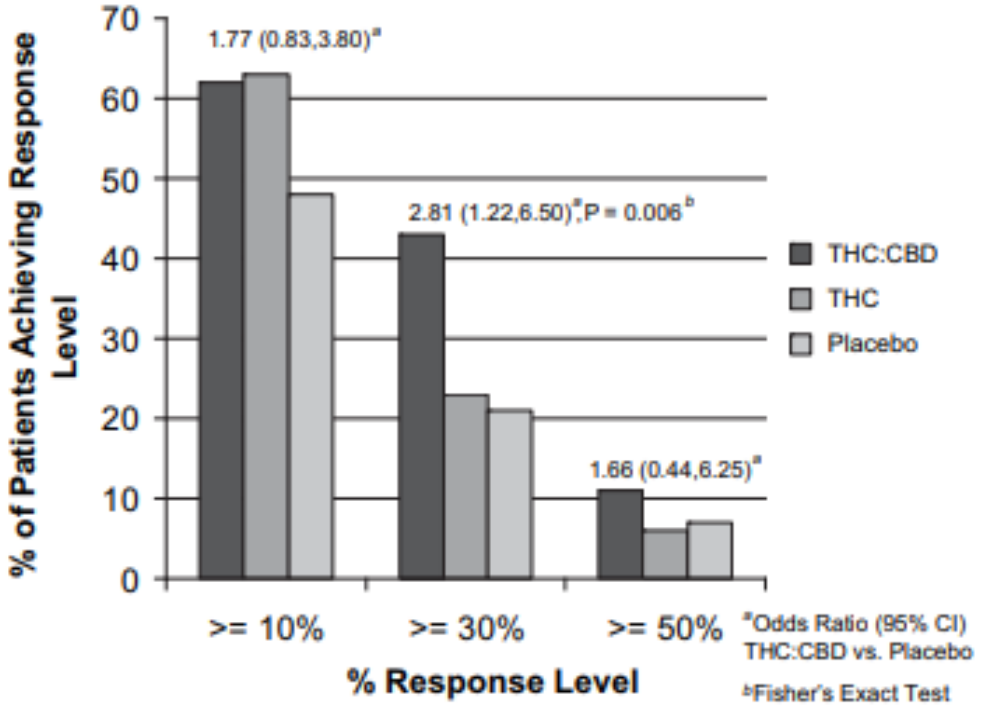



Fig. 3. Pain 0–10 Numerical Rating Scale scores: responder analysis (ITT analysis). [a]Odds ratio (95% CI) THC:CBD vs. placebo; [b]Fisher's exact test.

# NPRS (Pain score)

*Table 3*

**Primary and Secondary Endpoints Showing Baseline Score, Change from Baseline, Treatment Difference, and Statistical Significance of the Difference in Change From Baseline for THC:CBD, THC, and Placebo**

| | | | | Comparison with Placebo | |
|---|---|---|---|---|---|
| Endpoint | Treatment Group | Baseline | Change From Baseline | Treatment Difference | Statistical Significance, *P*-value |
| Mean pain severity NRS score (coprimary) | THC:CBD | 5.68 | −1.37 | −0.67[a] | 0.014 |
| | THC | 5.77 | −1.01 | −0.32[a] | 0.245 |
| | Placebo | 6.05 | −0.67 | — | — |

# Side Effects (60%)

- Somnolence
- Nausea
- Dizziness

*Table 4*

**Most Common Treatment-Related Adverse Events (Reported by Three or More Patients)**

| Description of Event | THC:CBD *n* (%) | THC extract *n* (%) | Placebo *n* (%) |
|---|---|---|---|
| Somnolence | 8 (13) | 8 (14) | 6 (10) |
| Dizziness | 7 (12) | 7 (12) | 3 (5) |
| Confusion | 4 (7) | 1 (2) | 1 (2) |
| Nausea | 6 (10) | 4 (7) | 4 (7) |
| Vomiting | 3 (5) | 4 (7) | 2 (3) |
| Raised gamma GT | 2 (3) | 5 (9) | 1 (2) |
| Hypercalcemia | 0 | 0 | 3 (5) |
| Hypotension | 3 (5) | 0 | 0 |

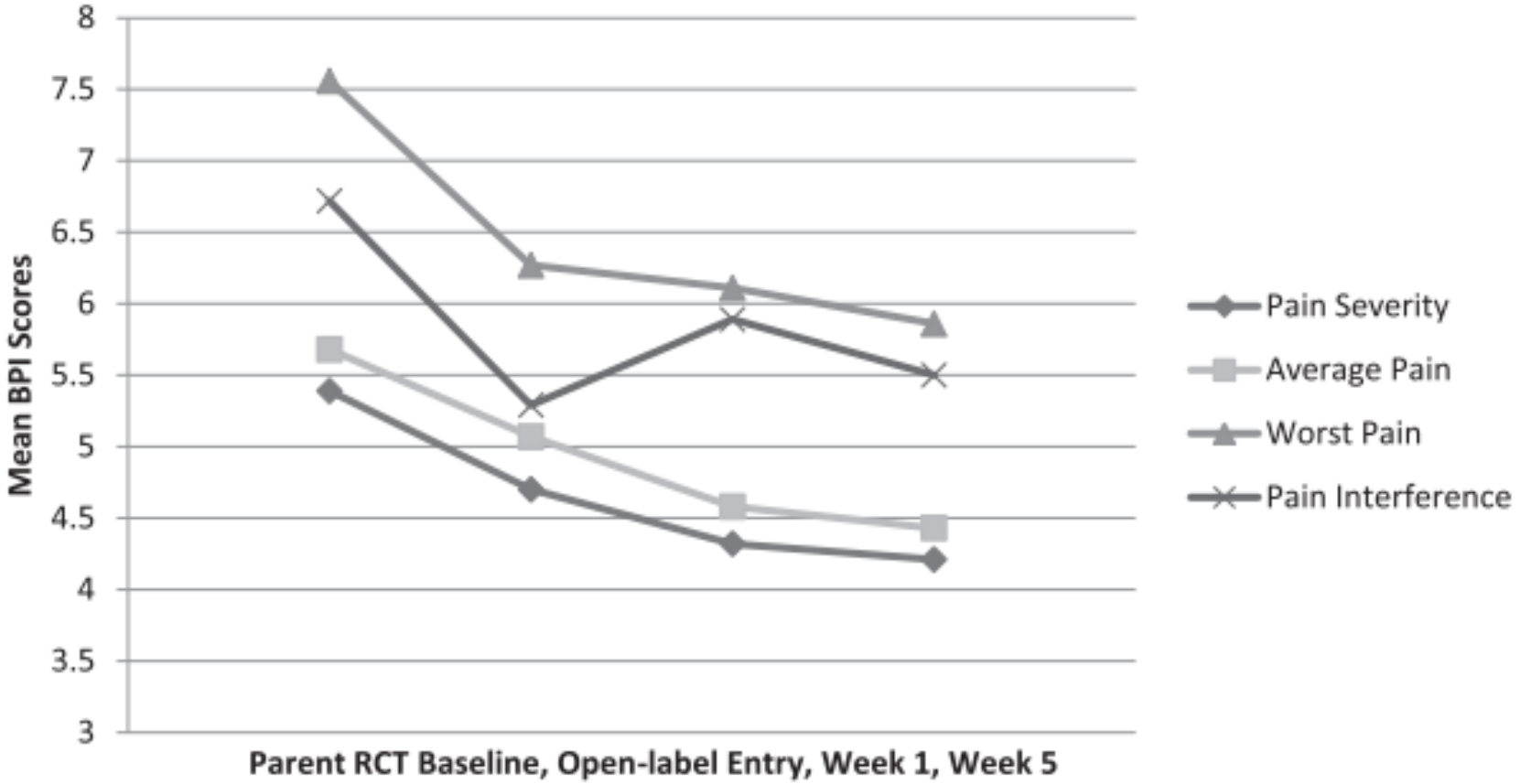
Gamma GT = gamma glutamyl transferase.

*Original Article*

# An Open-Label Extension Study to Investigate the Long-Term Safety and Tolerability of THC/CBD Oromucosal Spray and Oromucosal THC Spray in Patients With Terminal Cancer-Related Pain Refractory to Strong Opioid Analgesics

- Followed 43 patients from previous trial
- 22 centres 21 UK, 1 Belgium
- 37 THC/CBD 2 THC
- Monthly visits
- Median 25 days with maximum 579 days

# Results

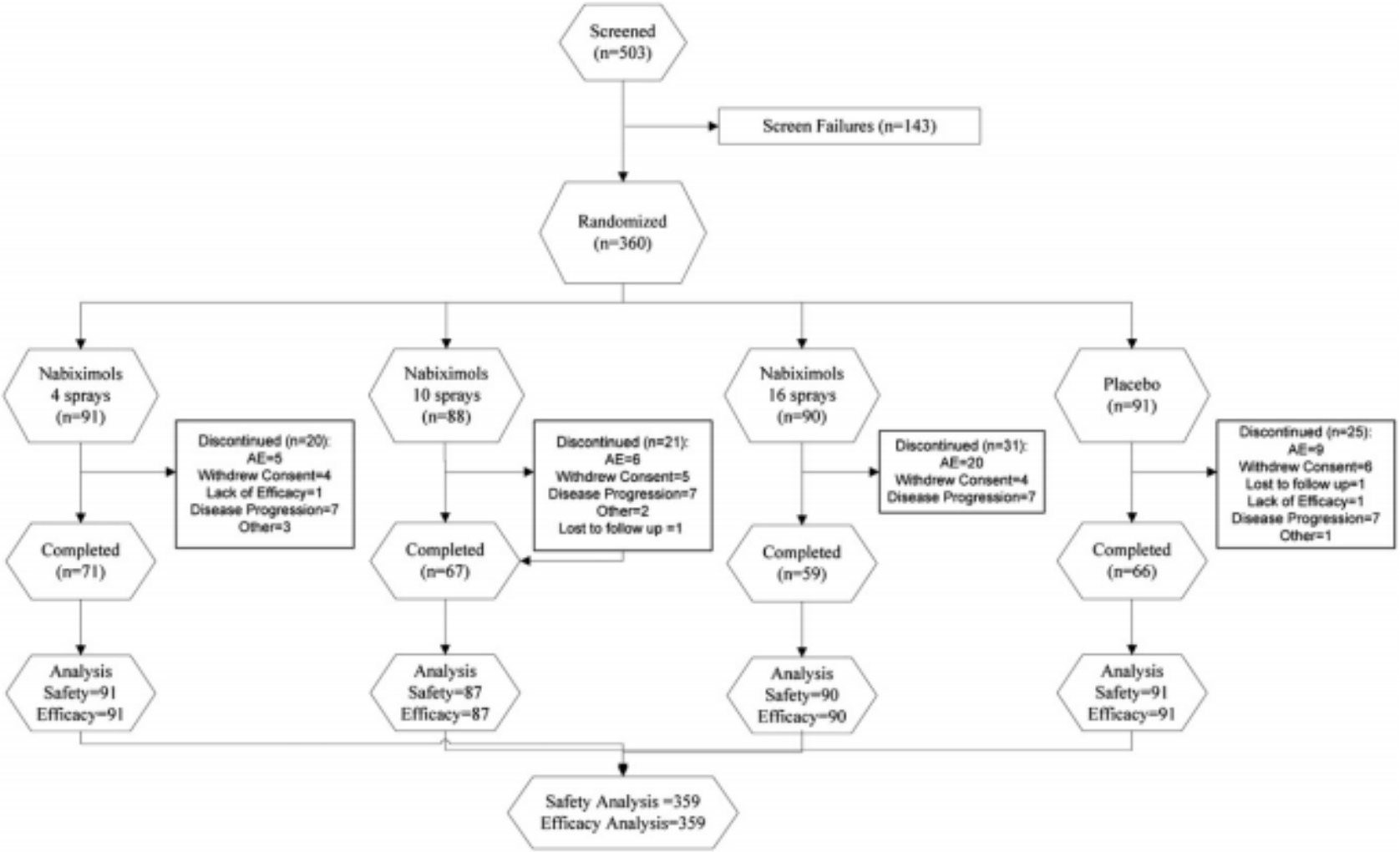

8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
Mean BPI Scores
Parent RCT Baseline, Open-label Entry, Week 1, Week 5
Pain Severity
Average Pain
Worst Pain
Pain Interference

# Side effects

- Dizziness, nausea, vomiting, dry mouth, Somnolence, confusion
- 59% withdrew

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY
ELSEVIER
The Journal of Pain, Vol 13, No 5 (May), 2012
Available online at www.jpain.org and www.scienc

# Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial


Screened
(n=503)
Screen Failures (n=143)
Randomized
(n=360)
Nabiximols
4 sprays
(n=91)
Discontinued (n=20):
AE=5
Withdrew Consent=4
Lack of Efficacy=1
Disease Progression=7
Other=3
Completed
(n=71)
Analysis
Safety=91
Efficacy=91
Nabiximols
10 sprays
(n=88)
Discontinued (n=21):
AE=6
Withdrew Consent=5
Disease Progression=7
Other=2
Lost to follow up =1
Completed
(n=67)
Analysis
Safety=87
Efficacy=87
Nabiximols
16 sprays
(n=90)
Discontinued (n=31):
AE=20
Withdrew Consent=4
Disease Progression=7
Completed
(n=59)
Analysis
Safety=90
Efficacy=90
Placebo
(n=91)
Discontinued (n=25):
AE=9
Withdrew Consent=6
Lost to follow up=1
Lack of Efficacy=1
Disease Progression=7
Other=1
Completed
(n=66)
Analysis
Safety=91
Efficacy=91
Safety Analysis =359
Efficacy Analysis=359

Portenoy et al

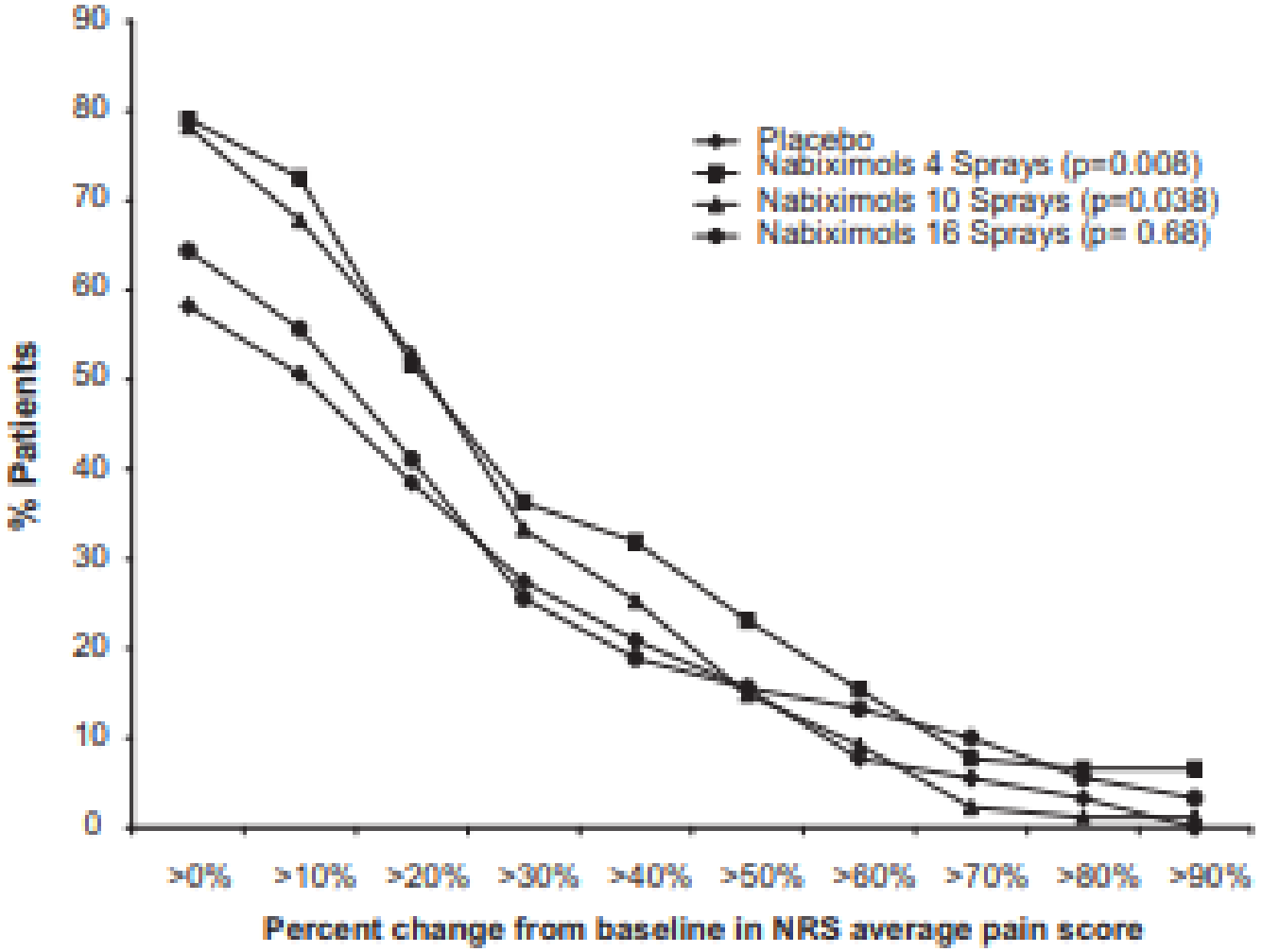



**Figure 3.** Continuous responder analysis.

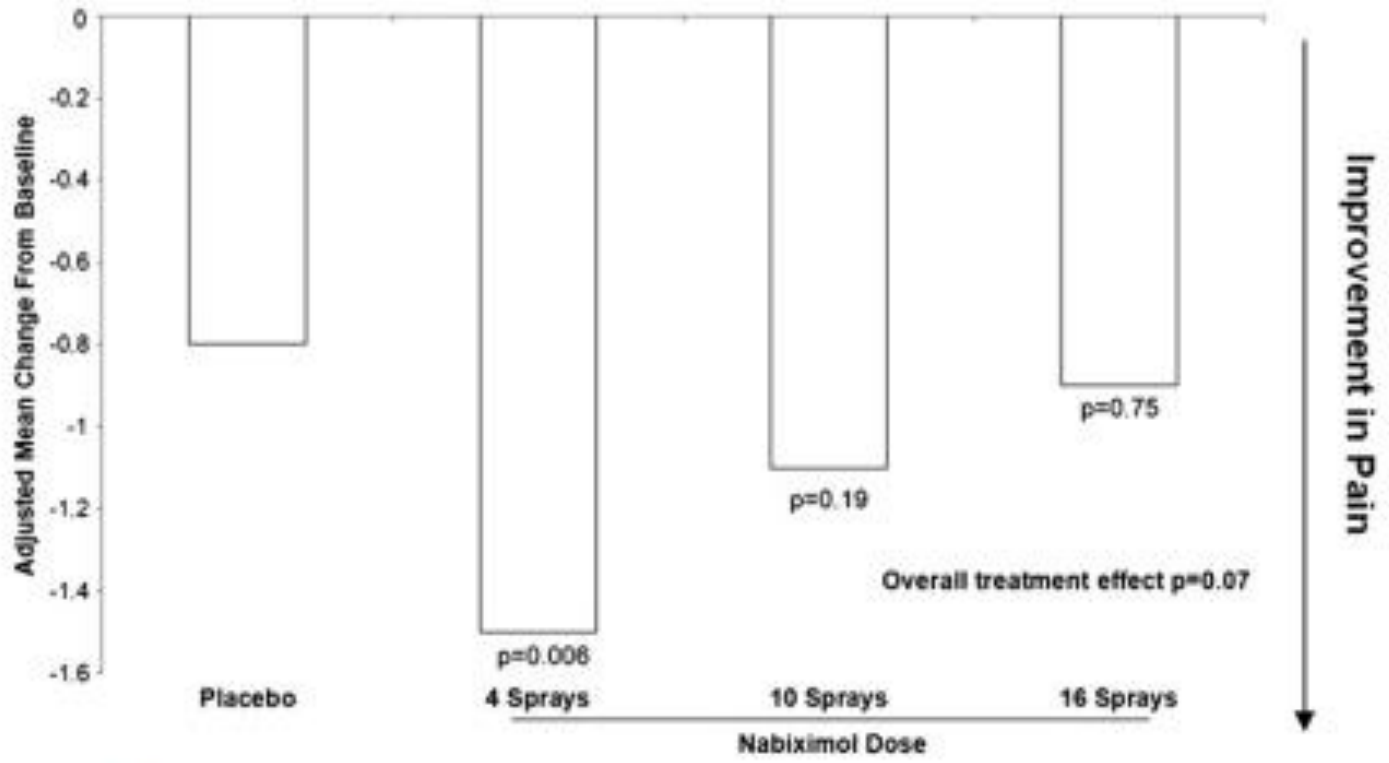



**Figure 4.** Analysis of change from baseline in NRS average pain score.

CME

# Opioids versus antidepressants in postherpetic neuralgia

## A randomized, placebo-controlled trial

S.N. Raja, MD; J.A. Haythornthwaite, PhD; M. Pappagallo, MD; M.R. Clark, MD; T.G. Travison, PhD; S. Sabeen, MD; R.M. Royall, PhD; and M.B. Max, MD

***Table 2** Unadjusted (observed) primary and secondary outcome measures*

| | Placebo | | Opioid | | TCA | |
|---|---|---|---|---|---|---|
| Parameter | Baseline | Maintenance | Baseline | Maintenance | Baseline | Maintenance |
| Pain intensity, 0 to 10 | 6.2 (2.0) | 6.0 (2.0) | 6.5 (1.9) | 4.4 (2.4) | 6.3 (2.4) | 5.1 (2.3) |
| Pain relief, 0 to 100% | — | 11.2 (19.8) | — | 38.2 (32.2) | — | 31.9 (30.4) |

N = 76 randomised
N = 44 completers
19 dropped out in opioid group

Rheumatology 2006;45:50–52
Advance Access publication 9 November 2005
doi:10.1093/rheumatology/

Concise Report

# Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis

D. R. Blake, P. Robson[1], M. Ho[2], R. W. Jubb[3] and C. S. McCabe

N= 58
No dropouts in CBM group
CBM 2.2/7 = 31%

TABLE 2. Efficacy endpoints: difference between change from baseline between CBM and placebo after 5 weeks of tr

| | Baseline (mean/median)[a] | | Endpoint (mean/median)[a] | | |
|---|---|---|---|---|---|
| Efficacy endpoint | CBM | Placebo | CBM | Placebo | Difference (mean/median[a]) |
| Morning pain on movement[a] | 7.0 | 6.7 | 4.8 | 5.3 | –0.95 |
| Morning pain at rest[a] | 5.3 | 5.3 | 3.1 | 4.1 | –1.04 |

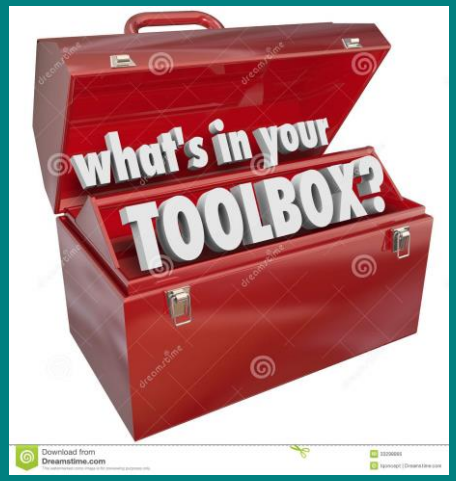
# Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison

*Paul Emery, Henning Zeidler, Tore K Kvien, Mario Guslandi, Raphael Naudin, Helen Stead, Kenneth M Verburg, Peter C Isakson, Richard C Hubbard, G Steven Geis*

| | Celecoxib | | Diclofenac | |
|---|---|---|---|---|
| | Baseline | Week 24 | Baseline | Week 24 |
| Pain VAS (mm) | 47·4 (21·5) | 40·8 (25·5) | 51·7 (21·6) | 43·1 (25·2) |

N = 655
RA for over six months
Celecoxib 6.6/27.4 = 14%
Diclofenac 8.6/51.7 = 17%

# Take home points




Cannabis is another tool in the toolbox of analgesics
It  is as effective as other analgesics in RCTs for chronic pain  including cancer pain

Cost is a significant barrier

MCID minimally clinically important difference
VAS 1.5-2/10 or 30% reduction

People are different and respond to different medications/ varying side effects due to genetic makeup/socio-cultural differences.