Journal Club at the Laboratory of Clinical Psychopharmacology of Addictions (LCPA) is a monthly gathering to discuss research papers with a focus on addiction.

Mission: to promote a better understanding of the research process and an improve ability to critically appraise research in addiction and related diseases (e.g. infectious, mental health, etc.).

Discussion topics and learning objectives include (but not limited by) the concepts of addiction, terminology used in the field, socio-cultural and biological risk factors, contemporary public health issues and policies, prevention, treatment and treatment systems.

Values:

- Learning
- Respect
- Collaboration
- Multidisciplinary
- Excellence

Please be open, flexible, realistic, and understanding!

Housekeeping notes

Video-recording

The meeting will be entirely video-recording and published on the Pavlov University website and YouTube, so if you wish not be in the recorded video, please make sure that your webcam off during the meeting.

Q&A

The seminar is interactive and we strongly encourage you to actively ask questions during the presentation but keep in mind that we have dedicated time at the end of the webinar (10 minutes) to group discussion and Q&A. Please raise your hand if you have any questions or comment. You also may use chat option to post your questions or comments.

Mic and Video

Please keep your mic mute during entire meeting unless you want to make a question or comment. We recommend keeping your camera on during the meeting.

Post-meeting survey

After the meeting we would like to send you the survey. Please make sure that we have your email.

CONTACTS

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Nabiximols for the Treatment of Cannabis Dependence
A Randomized Clinical Trial

Lintzeris N, Bhardwaj A, Mills L, et al.

Presenter: Ekaterina Protsenko, 4-year medical student

1й Мед
ФГБОУ ВО ПСПбГМУ им. Павлова Минздрава России

PROBLEM

1. Apart from alcohol and tobacco **cannabis** is the most widely used psychoactive substance and accounts for the largest number of people dependent on illicit drugs globally.
2. Cannabis dependence is associated with a range of cognitive, psychiatric, and physical health problems.
3. There are is **no effective medications** for treating cannabis use disorder (abuse F12.1 and dependence F12.2).

Previous study of cannabinoid agonist treatment (capsules of dronabinol, 40 mg) failed to show efficacy.

CURRENT TREATMENT OPTIONS

- **Behavioral**
  - Substance use disorder treatment setting
    - cognitive-behavioral therapy, contingency management, motivational enhancement, therapeutic living
  - General medical settings
    - Brief interventions

- **Pharmacotherapy**
  - No currently approved medication
    - cannabinoid antagonist
    - oral THC for withdrawal, maintenance or short-term treatment?
      - cannabinoid agonist—Levin FR DAD 2011
    - N-Acetylcysteine

FEATURED ARTICLE

Research

JAMA Internal Medicine | Original Investigation

Nabiximols for the Treatment of Cannabis Dependence
A Randomized Clinical Trial

Nicholas Lintzeris, MBBS, PhD; Anjali Bhardwaj, PhD; Llewellyn Mills, PhD; Adrian Dunlop, MBBS, PhD; Jan Copeland, PhD; Iain McGregor, PhD; Raimondo Bruno, PhD; Jessica Gugusheff, PhD; Nghi Phung, MBBS, PhD; Mark Montebello, PhD; Therese Chan, BPharm; Adrienne Kirby, BSc(Hons); Michelle Hall, GradCertHlthSc; Meryem Jefferies, PhD; Jennifer Luksza, PhD; Marian Shanahan, PhD; Richard Kevin, PhD; David Allsop, PhD; for the Agonist Replacement for Cannabis Dependence (ARCD) study group

IMPORTANCE There are no effective medications for treating dependence on cannabis.

OBJECTIVE To examine the safety and efficacy of nabiximols in the treatment of patients with cannabis dependence.

DESIGN, SETTING, AND PARTICIPANTS This parallel double-blind randomized clinical trial comparing nabiximols with placebo in a 12-week, multisite outpatient study recruited participants from February 3, 2016, to June 14, 2017, at 4 outpatient specialist alcohol and drug treatment services in New South Wales, Australia. Participants had cannabis dependence (as defined by the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*) and were seeking treatment, were nonresponsive to prior treatment attempts, were 18 to 64 years of age, had no other substance use disorder, had no severe medical or psychiatric conditions, were not pregnant, were not mandated by a court to undergo treatment, and provided informed consent. Results for primary efficacy measures and all secondary outcomes were obtained using a modified intention-to-treat data set.

INTERVENTIONS Participants received 12-week treatment involving weekly clinical reviews, structured counseling, and flexible medication doses—up to 32 sprays daily (tetrahydrocannabinol, 86.4 mg, and cannabidiol, 80 mg), dispensed weekly.

Supplemental content

Impact Factor:* 20.8

*2018

1й Мед

ФГБОУ ВО ПСПбГМУ им. Павлова Минздрава России

OBJECTIVE

- To examine the safety and efficacy of nabiximols in the treatment of patients with ICD-10 cannabis dependence.

NABIXIMOLS

- Nabiximols (tradename Sativex®) is a whole plant extract from the Cannabis species *Cannabis sativa L.* Sativex® is available in a 1:1 formulation of THC:CBD as an oro-mucosal pump spray used as a treatment for the relief of symptoms in patients with moderate to severe spasticity due to multiple sclerosis (MS) that has not been adequately treated with currently used therapies.
- Available in Canada, UK, Australia and New Zealand, Switzerland, Norway, Turkey, Israel, Brazil, Colombia and Chile.

Image courtesy of GW Pharmaceuticals

STUDY DESIGN

- Multisite outpatient randomized, double-blind, parallel-design study compared a 12-week course of nabiximols with placebo
- Where: 4 outpatient alcohol and drug treatment services in New South Wales, Australia
- When: 2016-2017

PARTICIPANTS, N =128

Inclusion criteria:

- age 18-65
- cannabis dependence *(ICD-10)*
- inability to stop cannabis in previous quit attempts
- provision of informed consent
- agreement to study procedures

Exclusion criteria:

- another substance use disorder (apart nicotine and caffeine)
- severe medical or psychiatric disorder
- pregnant or lactating women or those planning pregnancy
- inability to safely store medication
- not available for follow-up
- addiction treatment mandated by a court
- treatment for cannabis dependence within past month

DEPENDENCE SYNDROME (ICD-10 CRITERIA)

Three or more of the following have been present together at some time during the previous year:

- A **strong desire** or sense of compulsion to take the substance;
- Difficulties in **controlling substance-taking** behaviour in terms of its onset, termination, or levels of use;
- **Withdrawal;**
- **Tolerance;**
- A great deal of **time is spent** in activities necessary to obtain cannabis, use cannabis, or recover from its effects;
- Persistent substance use despite clear evidence of **harmful consequences**

CANNABIS WITHDRAWAL SYNDROME

- Cessation of cannabis use that has been heavy and prolonged
- Three or more of the following signs and symptoms develop within approximately one week after the cannabis cessation:
  - Irritability, anger, or aggression
  - Nervousness or anxiety
  - Sleep difficulty (eg, insomnia, disturbing dreams)
  - Decreased appetite or weight loss
  - Restlessness
  - Depressed mood
  - At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
- Cause distress or impairment
- No other explanation for symptoms
- Symptoms generally resolve in 7-14 days but may persist for weeks.

STUDY MEDICATIONS

- Medication canisters were identically labeled and dispensed weekly.

Nabiximols oral spray
Flexible dosing: mean number of sprays per day 17.6 sprays, equivalent to a mean of 47.5 mg of THC

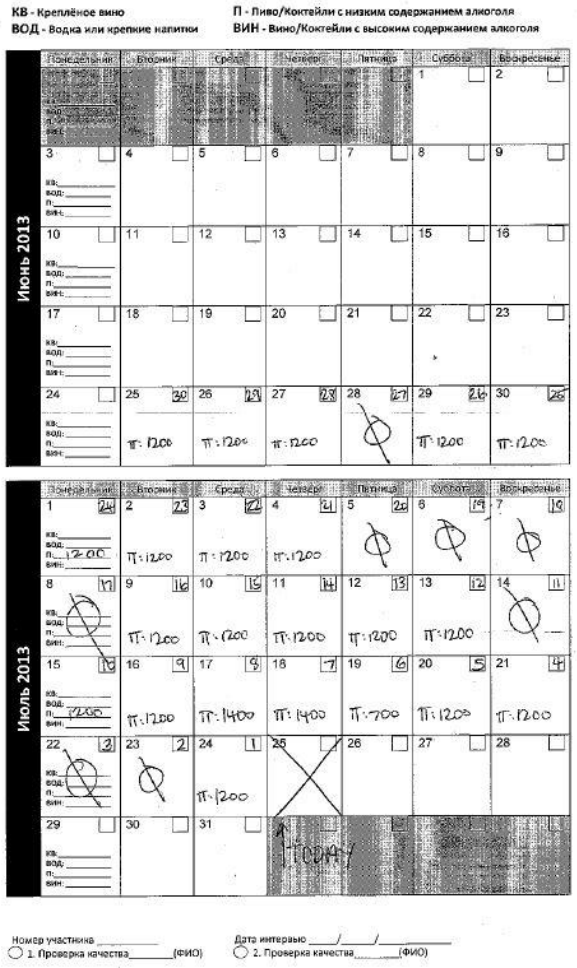
=

Placebo spray (same carrier and flavoring)

PRIMARY OUTCOME

Self-reported number of days using illicit cannabis during the 12-week period

Method: Time Line Follow Back (TLFB)

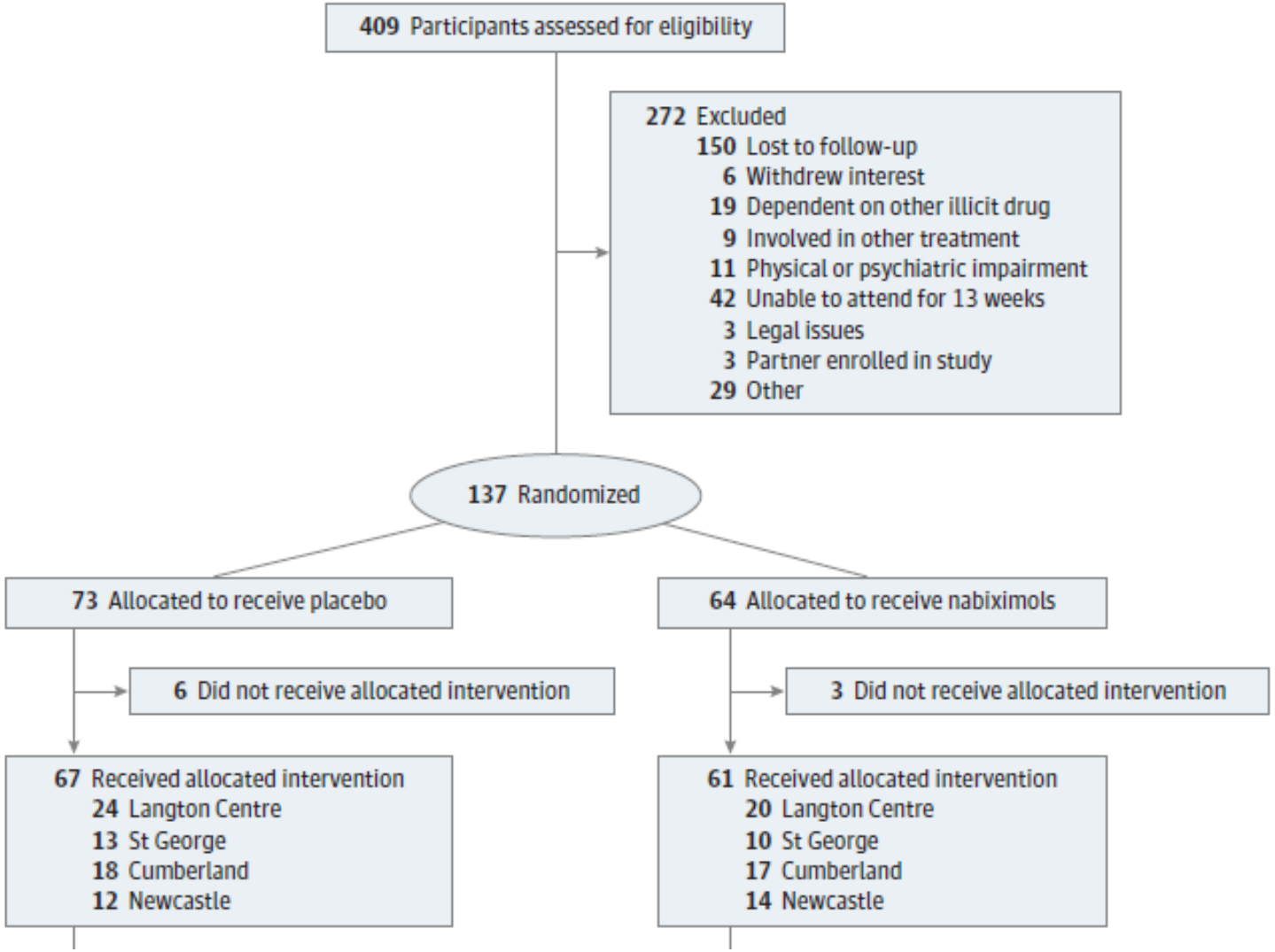


SECONDARY OUTCOMES

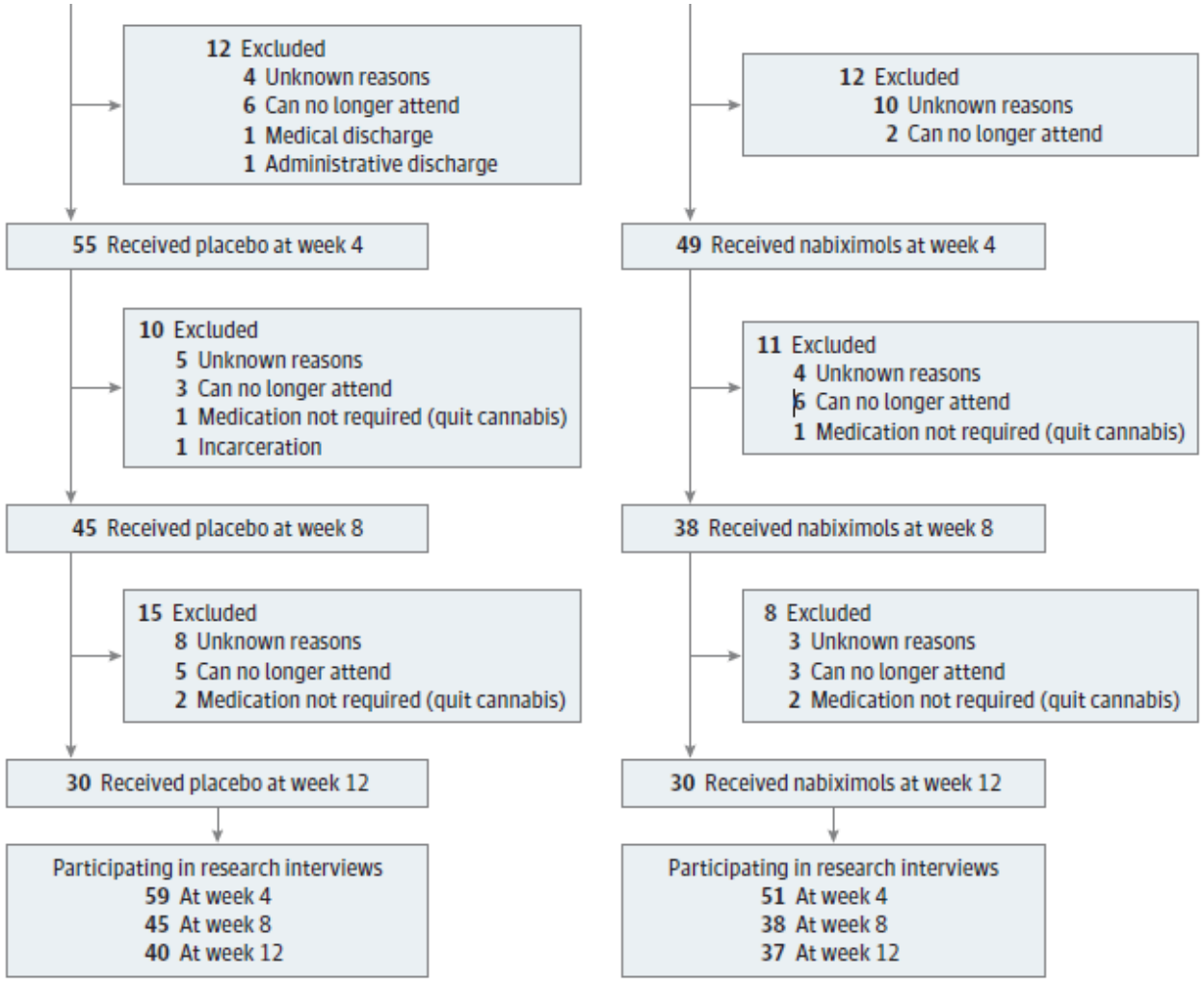
1. Periods of abstinence during the trial (TLFB)
2. Reduction of cannabis use by 50% or more from baseline (TLFB)
3. Withdrawal (Cannabis Withdrawal Scale)
4. Cravings (Marijuana Craving Questionnaire)
5. Cannabis-related problems (Cannabis Problems Questionnaire)
6. Safety Parameters (Adverse Events, aberrant medical behavior)
7. Health Status (36-item Short Form Survey, Opioid Treatment Index–Crime subscale)
8. Other substance use (AUDIT, Fagerstrom Test for Nicotine Dependence)
9. Treatment retention (do not miss 2 or more consecutive follow up visits)
10. Global satisfaction (“Would you recommend this medication to a friend seeking treatment?”)

RESULTS: STUDY FLOW

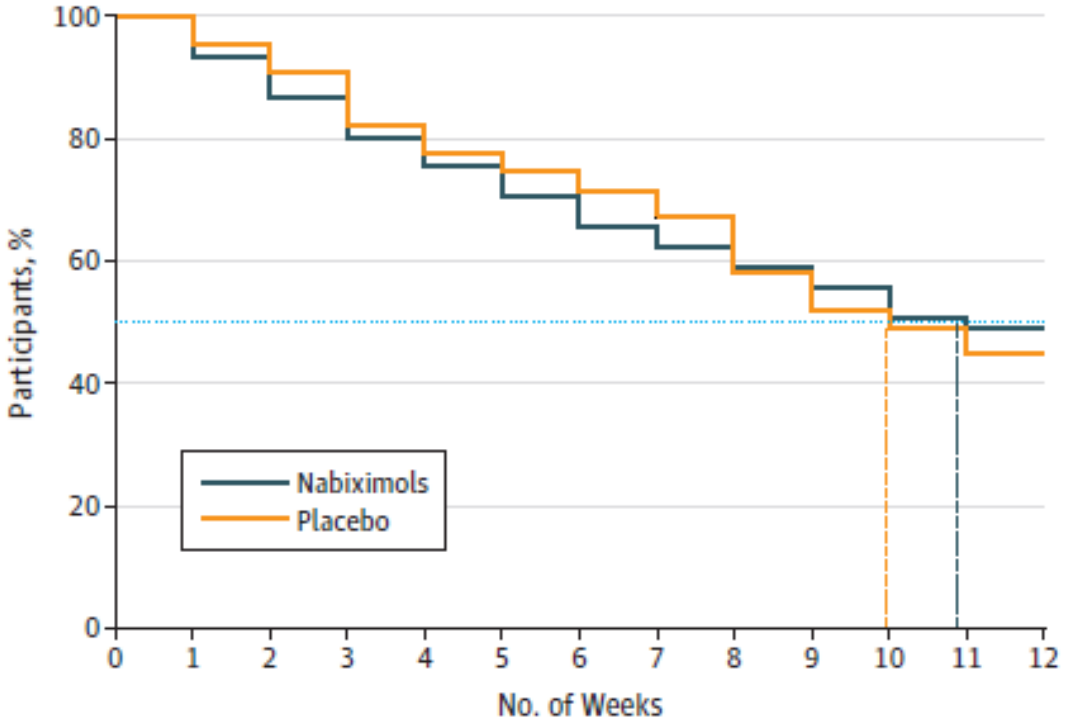
STUDY FLOW


409 Participants assessed for eligibility
272 Excluded
150 Lost to follow-up
6 Withdrew interest
19 Dependent on other illicit drug
9 Involved in other treatment
11 Physical or psychiatric impairment
42 Unable to attend for 13 weeks
3 Legal issues
3 Partner enrolled in study
29 Other
137 Randomized
73 Allocated to receive placebo
64 Allocated to receive nabiximols
6 Did not receive allocated intervention
3 Did not receive allocated intervention
67 Received allocated intervention
24 Langton Centre
13 St George
18 Cumberland
12 Newcastle
61 Received allocated intervention
20 Langton Centre
10 St George
17 Cumberland
14 Newcastle

STUDY FLOW (CONTINUATION)



TREATMENT RETENTION



Retention rates were comparable (and low):
49.2% in Nabiximols and 44.8% in Placebo

CONCLUSION

- Was the assignment of patients to treatments randomized?
- Were patients, health workers, and study personnel "blind" to treatment?
- Do the retention rate concern you?

RESULTS: BASELINE CHARACTERISTICS

DEMOGRAPHICS AND CANNABIS USE

Characteristic	Participants, No. (%)		
	Placebo (n = 67)	Nabiximols (n = 61)	Total (N = 128)
Age, mean (SD), y	33.8 (10.3)	36.2 (11.5)	35.0 (10.9)
Female sex	14 (20.9)	16 (26.2)	30 (23.4)
Born in Australia	56 (83.6)	51 (83.6)	107 (83.6)
Aboriginal or Torres Strait Islander	6 (9.0)	4 (6.6)	10 (7.8)
Tertiary education	22 (32.8)	27 (44.3)	49 (38.3)
Employment as main source of income	36 (53.7)	35 (57.4)	71 (55.5)
In a relationship	27 (40.3)	18 (29.5)	45 (35.2)
Have ≥1 child	23 (34.3)	21 (34.4)	44 (34.4)
Current legal problems	6 (9.0)	2 (3.3)	8 (6.2)
Baseline cannabis use			
No. of days cannabis used in last 28, mean (SD)	25.6 (4.5)	25.9 (4.6)	25.7 (4.5)
Amount of cannabis used, mean (SD), g/d	2.6 (2.5)	2.0 (1.4)	2.3 (2.1)
Age at first cannabis use, mean (SD), y (range, 5-40 y)	15.0 (4.3)	16.0 (3.4)	15.5 (3.9)
Duration since first regular cannabis use, mean (SD), y	15.2 (9.8)	16.2 (9.9)	15.7 (9.8)
ICD-10 score, mean (SD) (maximum = 8)	7.2 (1.1)	6.9 (1.2)	7.1 (1.2)

Amount of THC used ≈ 46 mg/d

OTHER CHARACTERISTICS

Other variables			
Fagerström nicotine dependence score, mean (SD) (maximum = 10)[a]	2.1 (2.4)	3.4 (2.8)	2.7 (2.7) *
AUDIT score, mean (SD) (maximum = 50)	4.4 (5.1)	4.7 (4.3)	4.5 (4.7)
BPRS-18 score, mean (SD) (maximum = 128	23.6 (11.5)	24.1 (12.0)	23.8 (11.7)
Sheehan disability scale score, mean (SD) (maximum = 30)	14.1 (8.2)	12.9 (7.4)	13.5 (7.8)
SF-36 score, mean (SD) (maximum = 100)			
Physical functioning	87.2 (18.4)	86.2 (20.7)	86.71 (19.4)
Role limitations owing to physical health	36.6 (42.3)	34.4 (41.4)	35.57 (41.7)
Role limitations owing to emotional problems	48.3 (44.7)	48.1 (45.8)	48.18 (45.0)
Energy or fatigue	43.4 (18.3)	40.8 (19.3)	42.19 (18.8)
Emotional well-being	56.1 (20.2)	54.7 (18.1)	55.06 (19.2)
Social functioning	54.9 (30.6)	59.1 (26.7)	56.60 (28.8)
Pain	69.8 (26.2)	70.5 (25.6)	70.12 (25.8)
General health	49.3 (19.7)	53.9 (21.6)	51.48 (20.6)
OTI crime			
Committed any drug-related crime in last month	24 (35.8)	21 (34.4)	45 (35.2)
Committed any nondrug-related crime in the last month[b]	3 (4.6)	1 (1.6)	4 (3.2)

*106 participants - smokers

AUDIT, Alcohol Use Disorders Identification Test

BPRS, Brief Psychiatric Rating Scale

ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

OTI, Opioid Treatment Index

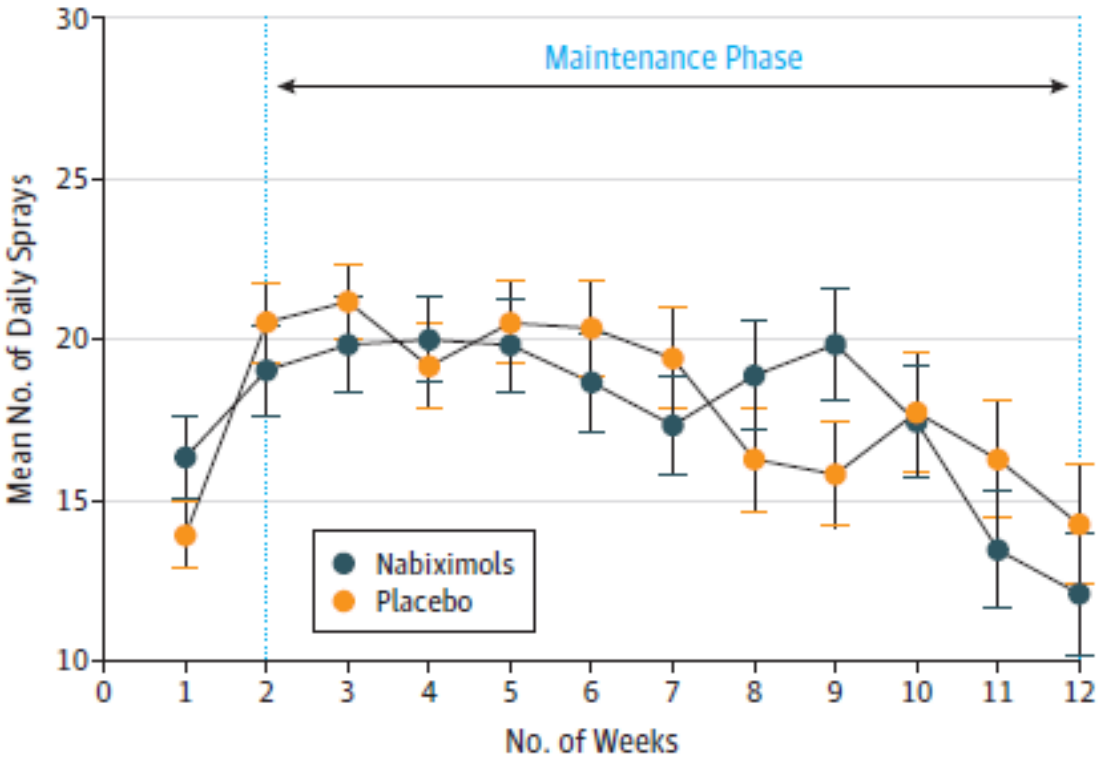
SF-36, 36-item Short Form Survey

CONCLUSION

- Were the groups similar at the start of the trial?

RESULTS: THE STRENGTH OF EXPOSURE

FIGURE 2B



Mean of sprays per day in both groups

CONCLUSION

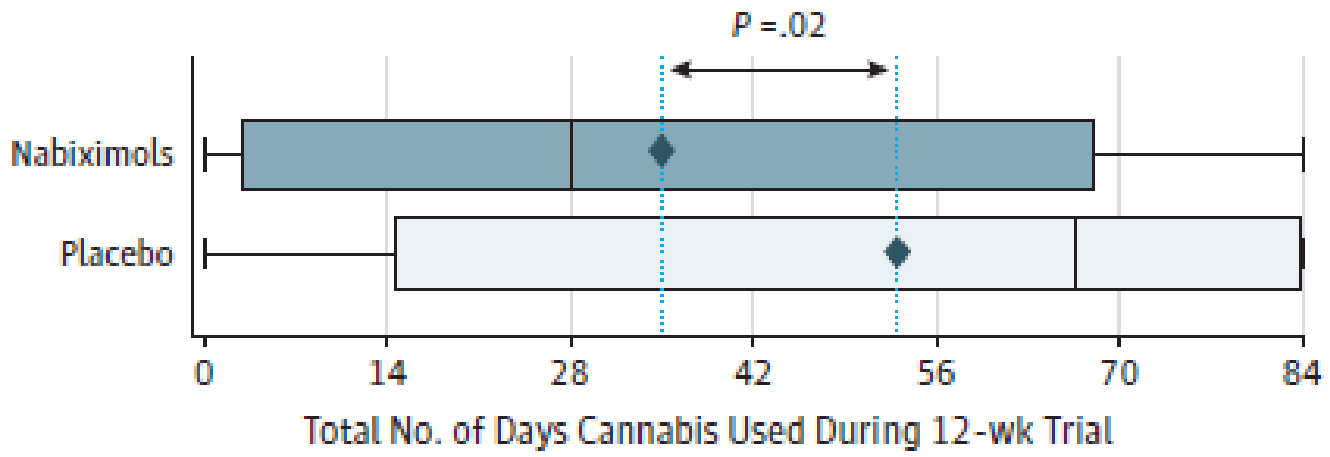
- Did the exposure of the intervention similar between two groups?
- Aside from the experimental intervention, were the groups treated equally?
- Were all patients who entered the trial properly accounted for and attributed at its conclusion?

There was no significant between-group difference in the mean number of sprays per day during weeks 2 to 12

No significant between-group differences in number of CBT sessions attended.

RESULTS: EFFICACY

FREQUENCY OF CANNABIS USE DURING THE 12-WEEK TRIAL



Dotted vertical lines and diamonds indicate the mean number of days used for each group. The *P* value indicates the significance level of the treatment group coefficient from the regression of 84-day cannabis use on (1) treatment, (2) site, (3) treatment × site, and (4) baseline cannabis use, rounded to 2 decimal places. The solid vertical lines represent the median number of days used.

Significant difference of 18.6 days after adjusting for baseline cannabis use

CONCLUSION

- Were patients analyzed in the groups to which they were randomized?
- Do the nabiximols effective in treating patient with ICD-10 CD?
- Do you concern that primary outcome was assessed by **self-report measure?**

(Although the urine drug screening results in the placebo arm indicate adequate validity of self-report in this study)

SECONDARY OUTCOMES: RESULTS

- There was general improvement in health outcomes (36-item Short Form Survey and Opioid Treatment Index–Crime subscale), with significant main effects of time, but ***no between-group differences***
- No significant changes over time in other substance use
- High levels of global satisfaction: 75% of those who received placebo and 82% of those who received nabiximols said “yes” to the question “would you recommend the medication to a friend seeking treatment”.

SECONDARY OUTCOMES: RESULTS

- Illicit cannabis was still used on 41.7% of possible days.
- Abstinence from illicit cannabis was achieved by only a minority of patients (22.1%)
- A significantly ***(p=.03)*** lower proportion of the placebo group reduced their cannabis use by 50% or more from baseline to week 12 than the nabiximols group
- 22.1% of participants had 1 or more 4-week periods of abstinence during the trial ***(nonsignificant difference)***
- Cannabis-related problems, withdrawal and cravings improved in both groups over time, but with ***no significant*** between group ***differences***

CONCLUSION

- Are some other good outcomes related to nabiximols use shown in this trial?

*A significantly **(p=.03)** lower proportion of the placebo group reduced their cannabis use by 50% or more from baseline to week 12 than the nabiximols group*

RESULTS: SAFETY

ADVERSE EVENTS

- A total of 32 participants **(25.0%)** reported an AE (placebo, 17 of 67 [25.4%]; and nabiximols, 15 of 61 [24.6%]),with 14 participants (10.9%) reporting 2 or more AEs.
- **One** serious AE was reported by a participant in the placebo group who was hospitalized for suicidal ideation
- A total of 21 of all 70 participants reported any aberrant medication behaviors with ***no significant group differences.***

CONCLUSION

- Is nabiximols safe?

WILL THE RESULTS HELP ME IN CARING FOR MY PATIENTS?

1. *Can the results be applied to my patient care?*
   -Nabiximols is not available in Russia.

2. *Are the likely treatment benefits worth the potential harms and costs?*
   -1 spray (10ml) costs $125.80 (10 028 rubles)

SUMMARY

- Cannabinoid dependence is a global problem
- There is no treatment that fits everyone

Presenter: astarothscamy@gmail.com

Mentor: mvetrova111@gmail.com

JOURNAL CLUB NOTES BY PRESENTER

There is no specific symptoms for cannabis dependence and it might be unclear where passes the border between illicit use of cannabis and use disorders (although there are ICD-10 criteria and questionnaires about cravings and withdrawal that could help).

The study has two biases - selection bias and attrition bias. Although samples were comparable at the start, but were they comparable on the 12-week visit? To my mind, participants who ended the study were highly motivated persons, in both groups.

Also it is very important to read protocol of investigation (if it is available) in order to notice that authors are “playing” with outcomes, changing primary outcomes after start of the study (make data more convenient).

My take-home point is that Nabiximols shows efficacy in this study, but only on really selective sample with

determine characteristics (motivated, without psychiatric diseases).