Cannabinoid replacement therapy for management of cannabis withdrawal: A Randomized Controlled Trial of Sativex

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Sativex regulatory context in Australia

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*Sativex is a **botanical extract of Cannabis sativa** indicated as **second line** treatment for moderate to severe **spasticity in MS.***

So…why Sativex for cannabis withdrawal?

Last 12 month drug use (1991-2010)

National Drug Strategy Household Survey

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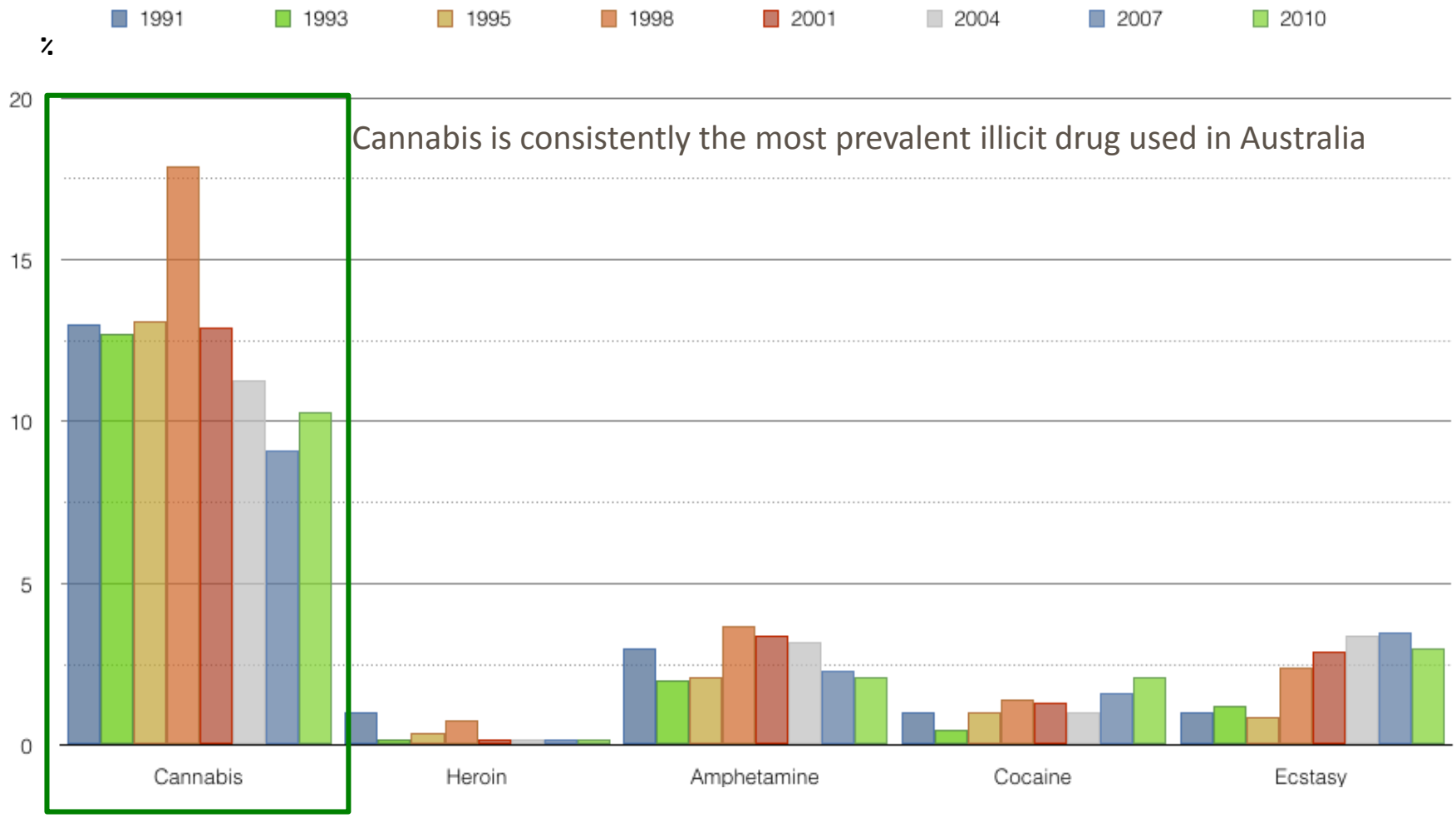

Number of treatment episodes 2008/2009

Report on the National Minimum Data Set

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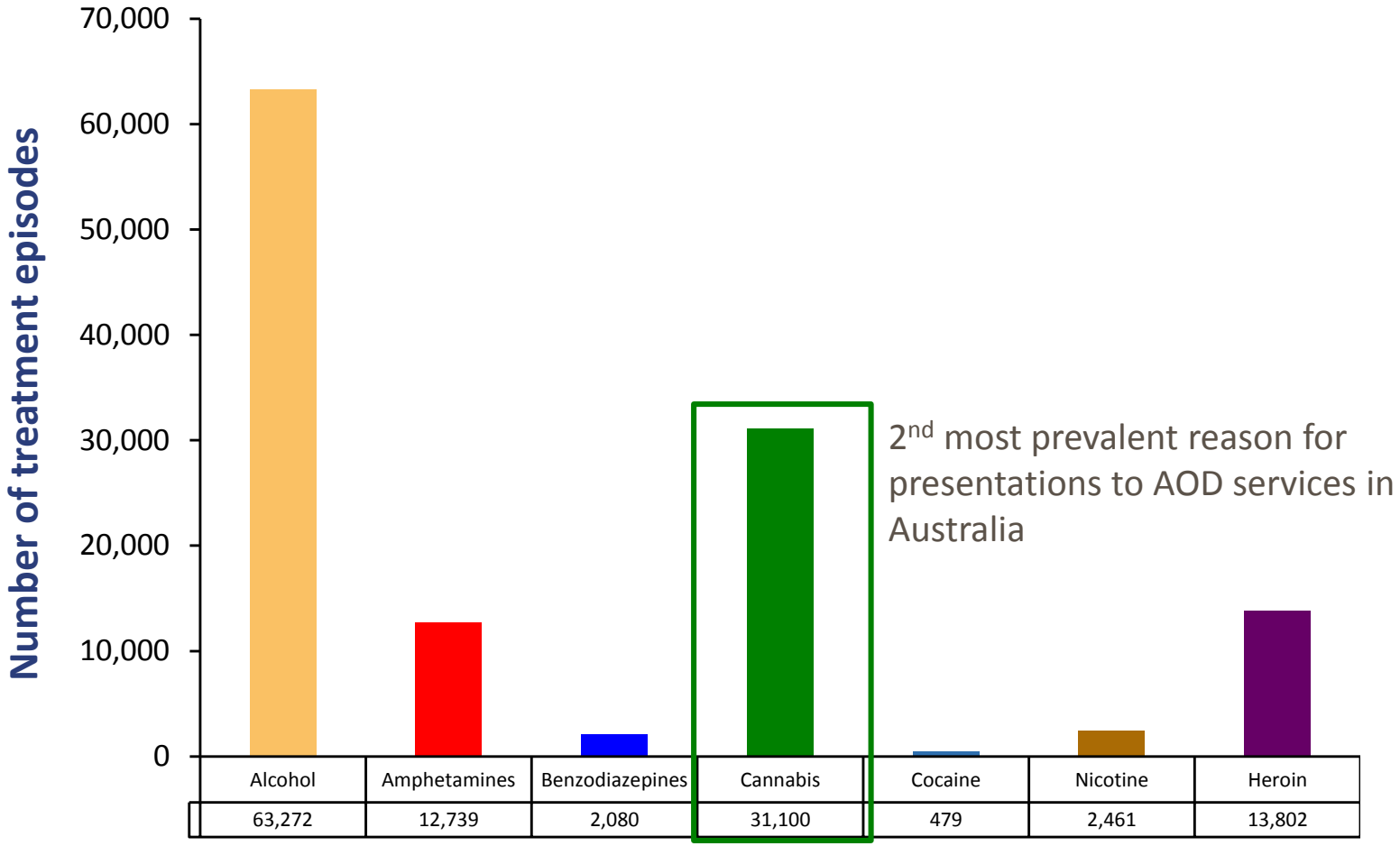
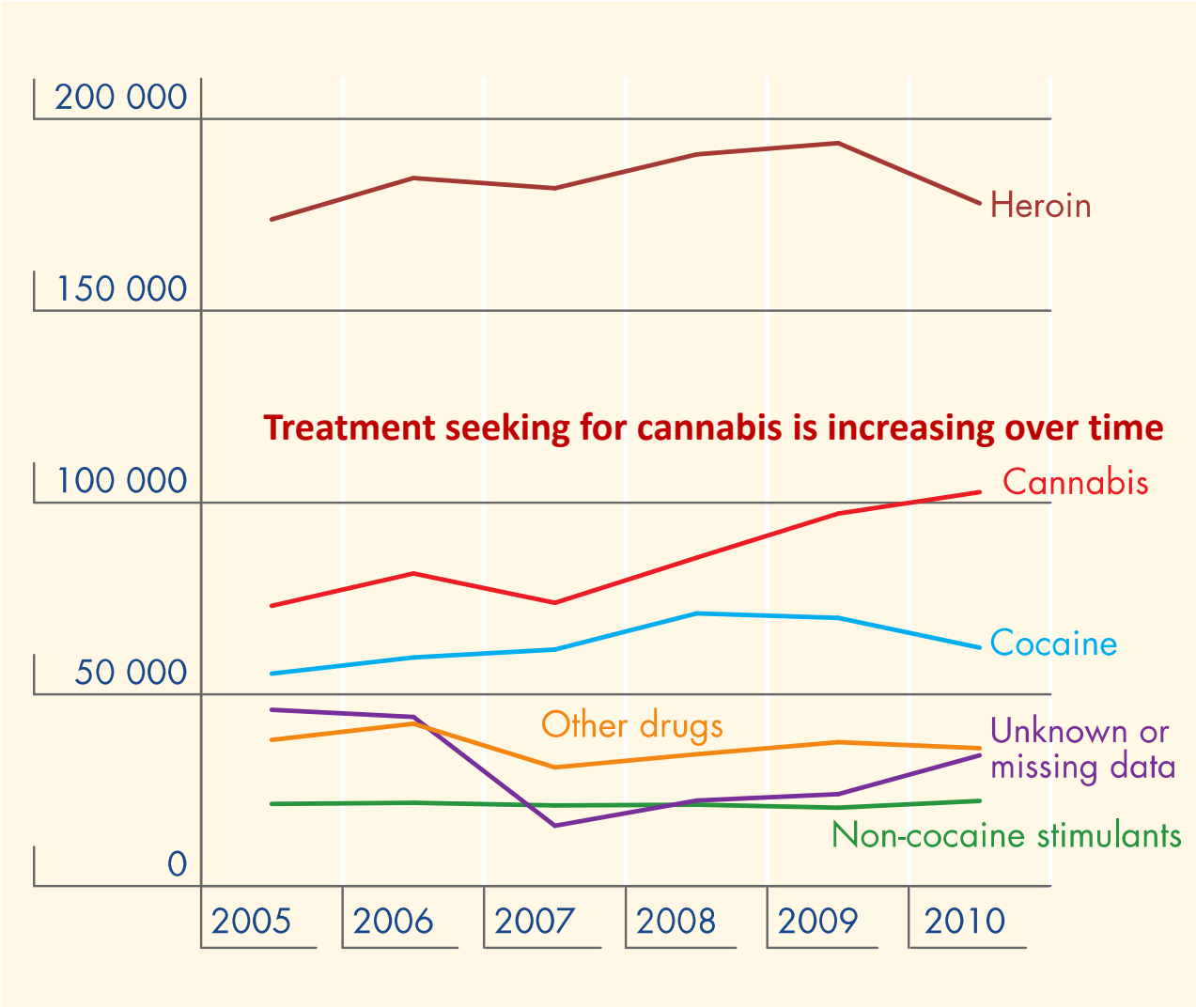


Alcohol	Amphetamines	Benzodiazepines	Cannabis	Cocaine	Nicotine	Heroin
63,272	12,739	2,080	31,100	479	2,461	13,802

Number of treatment episodes over time



Data: EMCDDA

CANNABIS WITHDRAWAL IS ASSOCIATED WITH RELAPSE

Two separate issues in treatment of drug pro

NO APPROVED PHARMACOTHERAPIES

DSM-5
2013

Which pharmacotherapies have been tried?

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Drug	Type	Action	Authors
Rimonabant	CB1	Antagonist	Huestis et al 2001, *Gen. psych*
Naltrexone	Mu 0pioid receptor	Attenuate reinforcing effects	Haney et al 2003, *Psychopharmacology*
Lofexidine	alpha2-adrenergic receptor agonist	Attenuate withdrawal	Haney et al 2008, *Psychopharmacology*
Divalproex	Antipsychotic/Mood	Attenuate specific withdrawal symptoms	Haney et al 2004, *Neuropsychopharmacology*
Lithium	Mood stabiliser	Attenuate specific withdrawal symptoms	Winstock et al 2009 Johnston et al(in prep)
Fluoxetine	Anti-depressant	Attenuate specific withdrawal symptoms	
Bupropion	Antidepressant/ nicotine antagonist	Attenuate specific withdrawal symptoms	Haney et al 2001, *Psychopharmacology*
Nefazodone	Antidepressant good for anxiety + sedative	Attenuate specific withdrawal symptoms	Haney et al 2003, *Psychopharmacology*
Mirtazapine	Antidepressant	Attenuate specific withdrawal symptoms	Frewen et al 2007
Dronabinol (THC)	CB1 Agonist	Attenuate withdrawal	Haney, M. et al 2004 Budney, AJ et al. 2007
Nabilone (THC)	CB1 Agonist	Attenuate withdrawal	Haney et al 2013
Sativex (THC and CBD)	CB1 Agonist	Attenuate withdrawal	Allsop et al 2013 JAMA Psychiatry (in press)

Cannabinoid replacement therapy

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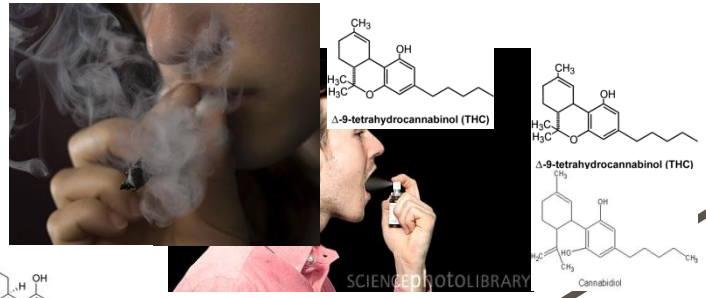
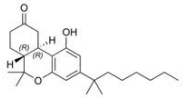
Effective pharmacological substitution

Smoked cannabis (THC)
Sativex

- Reduced withdrawal
- Reduce cannabis relapse in non-treatment seekers in a lab

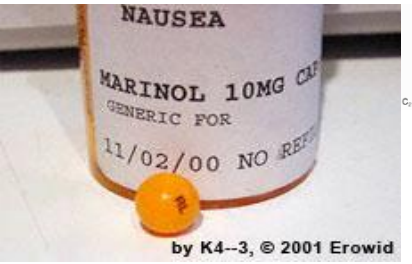


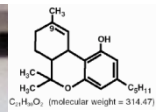
Nabilone



- Reduced withdrawal in non treatment seekers
- Did not reduce cannabis us clinical populations

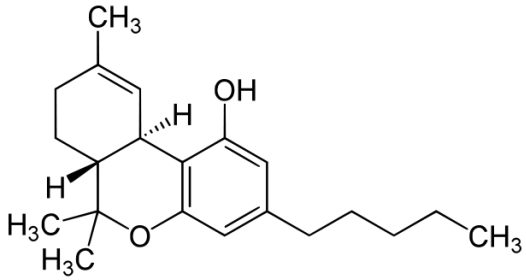
Dronabinol





Increasing Bioavailability (absorption)

THC (2.7 mg per spray)



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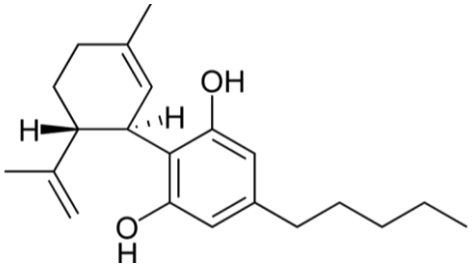
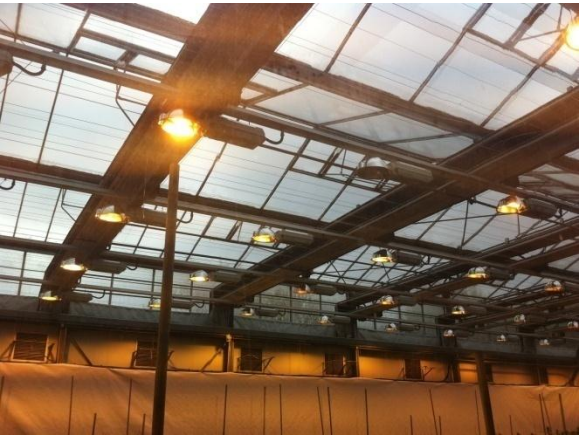
CBD (2.5 mg per spray)



- Less psychoactive than THC
- Reduces anxiety
- Antipsychotic
- Anti-inflamatory
- Reduces THC induced paranoia

GW pharmaceuticals




SATIVEX CBD

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PLOS ONE

Analysis of Cannabis Seizures in NSW, Australia: Cannabis Potency and Cannabinoid Profile

Wendy Swift[1*☯], Alex Wong[2☯], Kong M. Li[2], Jonathon C. Arnold[2,3], Iain S. McGregor[4]

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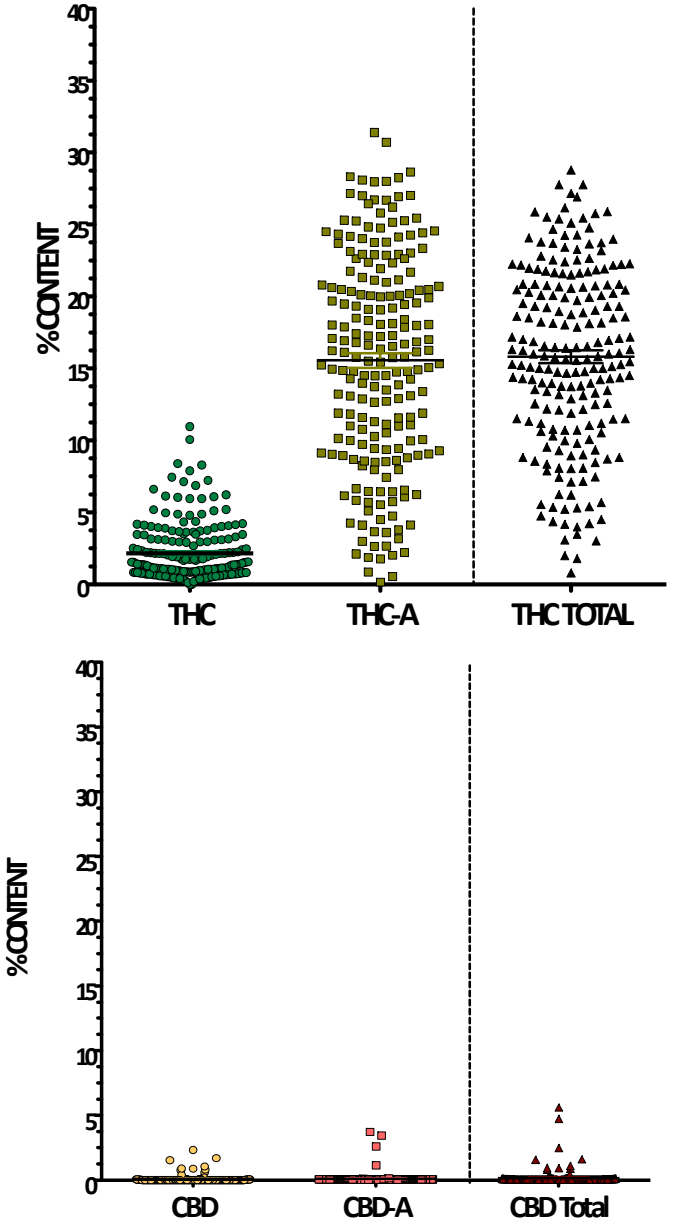
Abstract

Recent analysis of the cannabinoid content of cannabis plants suggests a shift towards use of high potency plant material with high levels of Δ^9-tetrahydrocannabinol (THC) and low levels of other phytocannabinoids, particularly cannabidiol (CBD). Use of this type of cannabis is thought by some to predispose to greater adverse outcomes on mental health and fewer therapeutic benefits. Australia has one of the highest *per capita* rates of cannabis use in the world yet there has been no previous systematic analysis of the cannabis being used. In the present study we examined the cannabinoid content of 206 cannabis samples that had been confiscated by police from recreational users holding 15 g of cannabis or less, under the New South Wales "Cannabis Cautioning" scheme. A further 26 "Known Provenance" samples were analysed that had been seized by police from larger indoor or outdoor cultivation sites rather than from street level users. An HPLC method was used to determine the content of 9 cannabinoids: THC, CBD, cannabigerol (CBG), and their plant-based carboxylic acid precursors THC-A, CBD-A and CBG-A, as well as cannabichromene (CBC), cannabinol (CBN) and tetrahydrocannabivarin (THC-V). The "Cannabis Cautioning" samples showed high mean THC content (THC+THC-A = 14.88%) and low mean CBD content (CBD+CBD-A = 0.14%). A modest level of CBG was detected (CBG+CBG-A = 1.18%) and very low levels of CBC, CBN and THC-V (<0.1%). "Known Provenance" samples showed no significant differences in THC content between those seized from indoor versus outdoor cultivation sites. The present analysis echoes trends reported in other countries towards the use of high potency cannabis with very low CBD content. The implications for public health outcomes and harm reduction strategies are discussed.



Recruitment

NEW TRIAL

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Want to give up cannabis but can't?

We are testing a new medication that may help people to manage their withdrawal symptoms when trying to stop smoking cannabis. This study is suitable for you if you are:

- Over 18 years of age
- A regular cannabis user with a desire to quit
- Have tried and failed to quit cannabis in th
- able to undertake 8 night stay in

For more information and t
brief phone interview
on **(02) 9385 04**
or email: **ca**

Expires March 2013

NSW Health Hunter New England Local Health District

THE UNIVERSITY OF SYDNEY

Gold Standard

Double blind, placebo controlled inpatient cannabis detox trial

Demographics and drug use

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Characteristic	No. (%)			
	Total (n=51)	*Sativex (n=27)*	*Placebo (n=24)*	*P*
Demographics				
Age, mean (SD), years	35.39	34.96	35.88	*0.72*
Gender (n /% male)	39 (76.5)	18 (66.7)	21 (87.5)	*0.08*
Cannabis use history				
Cannabis use, mean grams (SD)	22.98 (20.66)	23.39 (16.79)	22.52 (24.54)	*0.88*
Years of cannabis use	20.43 (9.22)	20.11 (9.83)	20.79 (8.67)	*0.79*
Cannabis SDS[c]	12.04 (2.71)	11.96 (3.03)	12.13 (2.35)	*0.83*

Dosing regime over inpatient days

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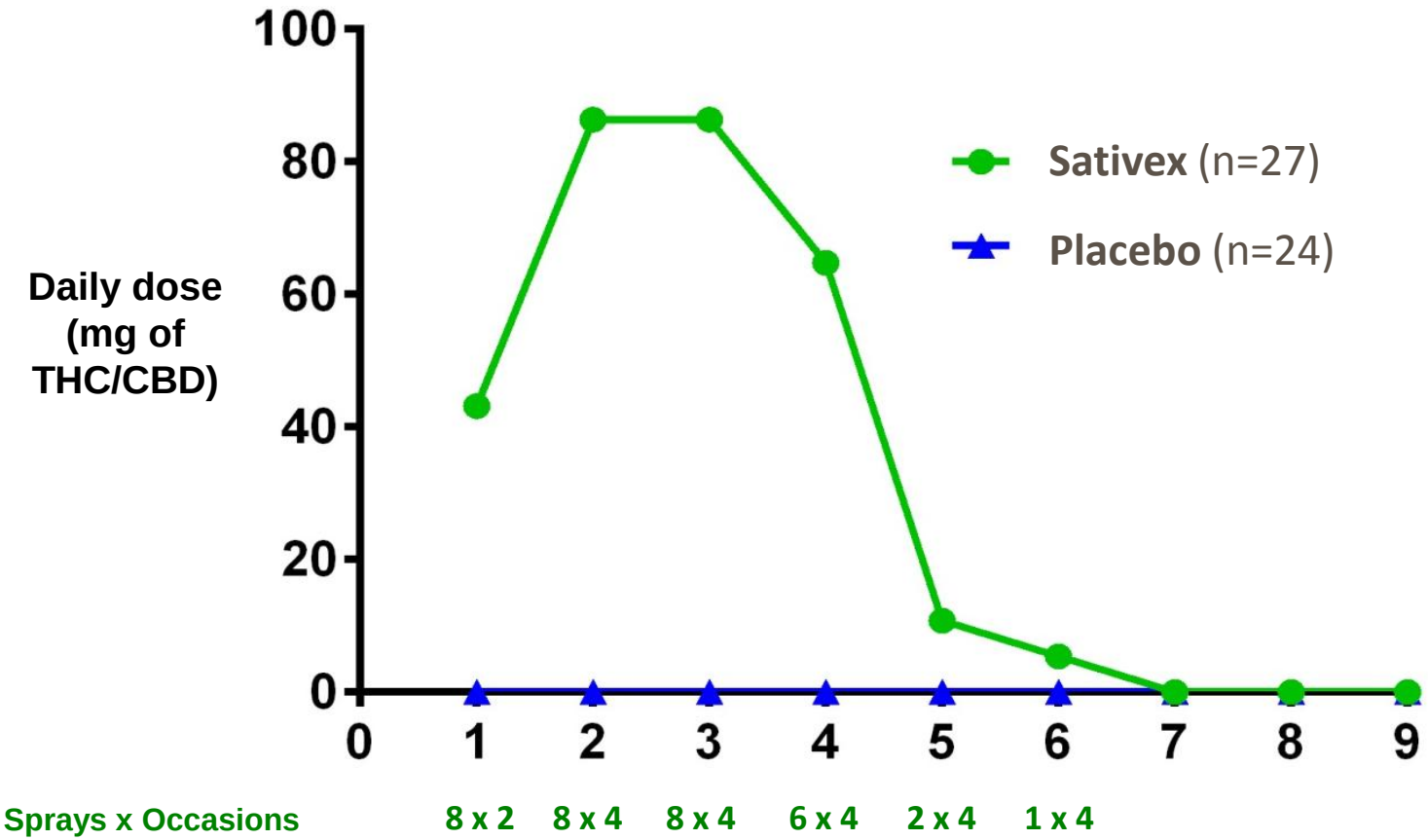

Plasma was taken at 3 time points for cannabinoid assays

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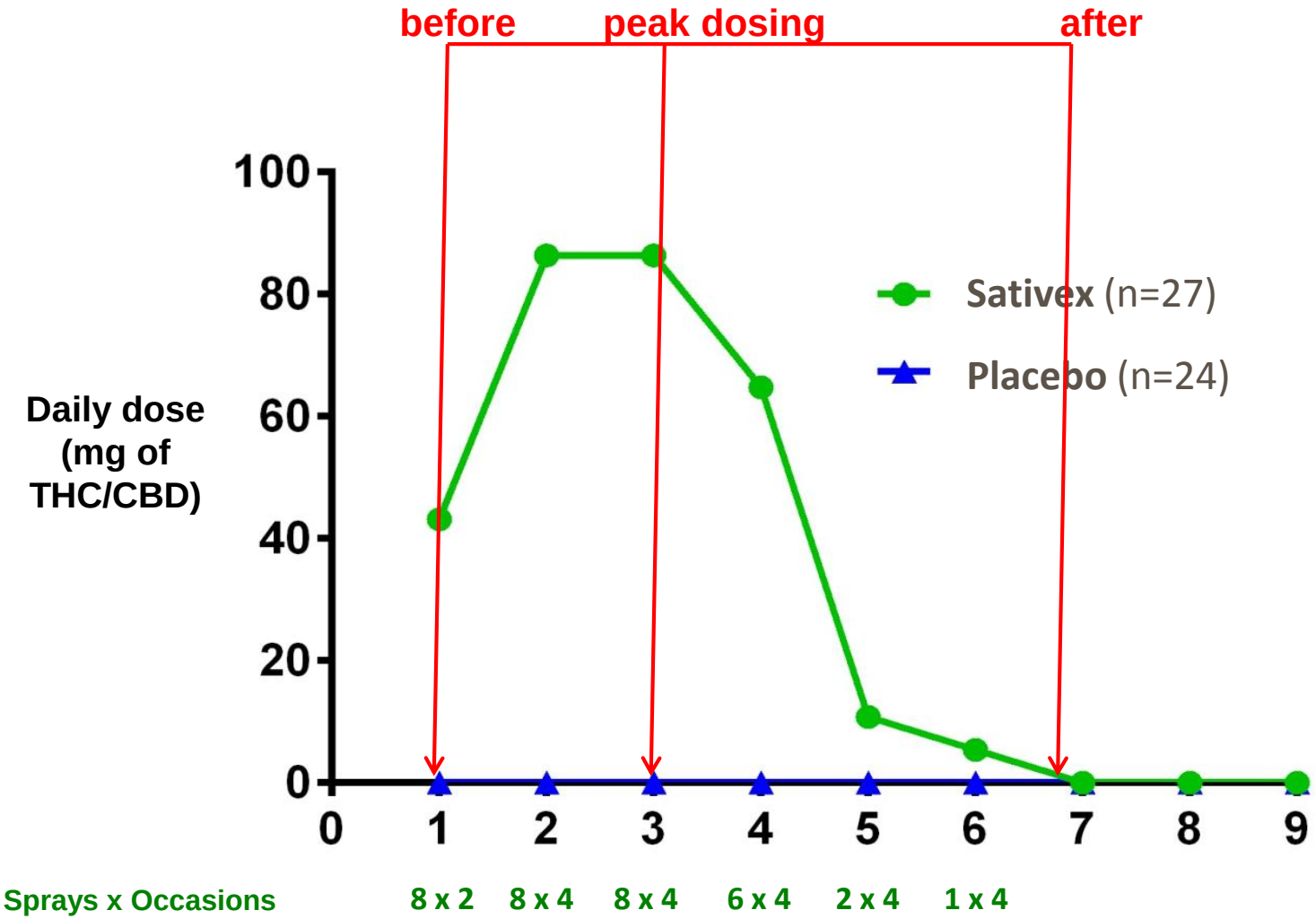

Participants showed undetectable plasma CBD at baseline: increased by Sativex

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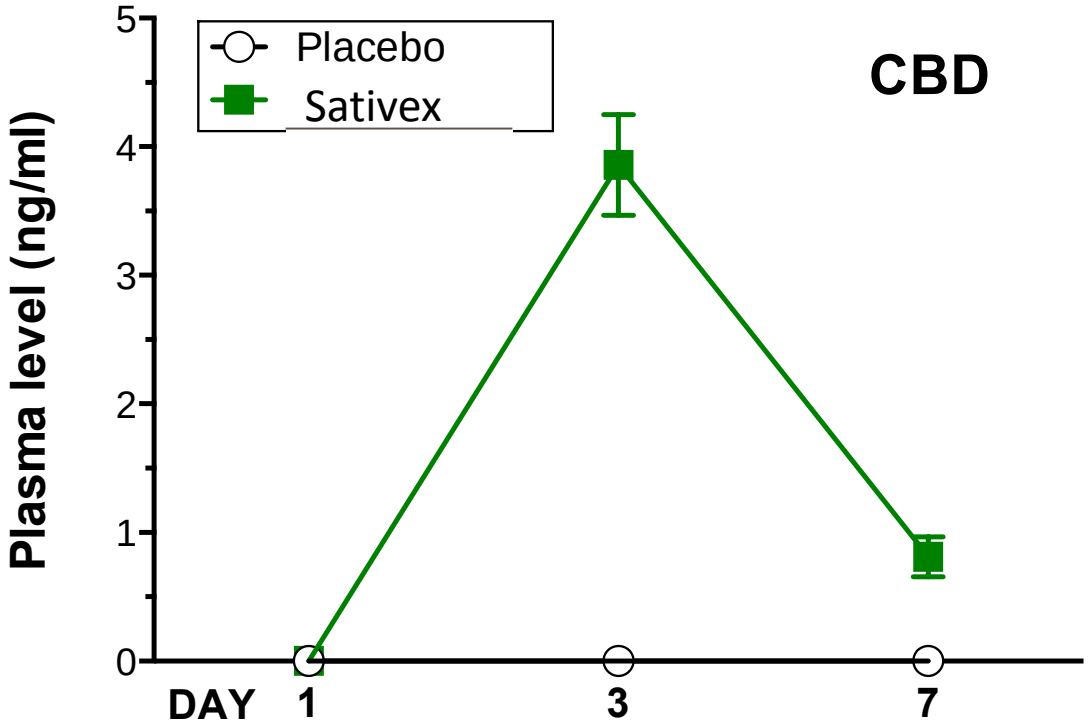

Sativex maintains plasma THC during abstinence

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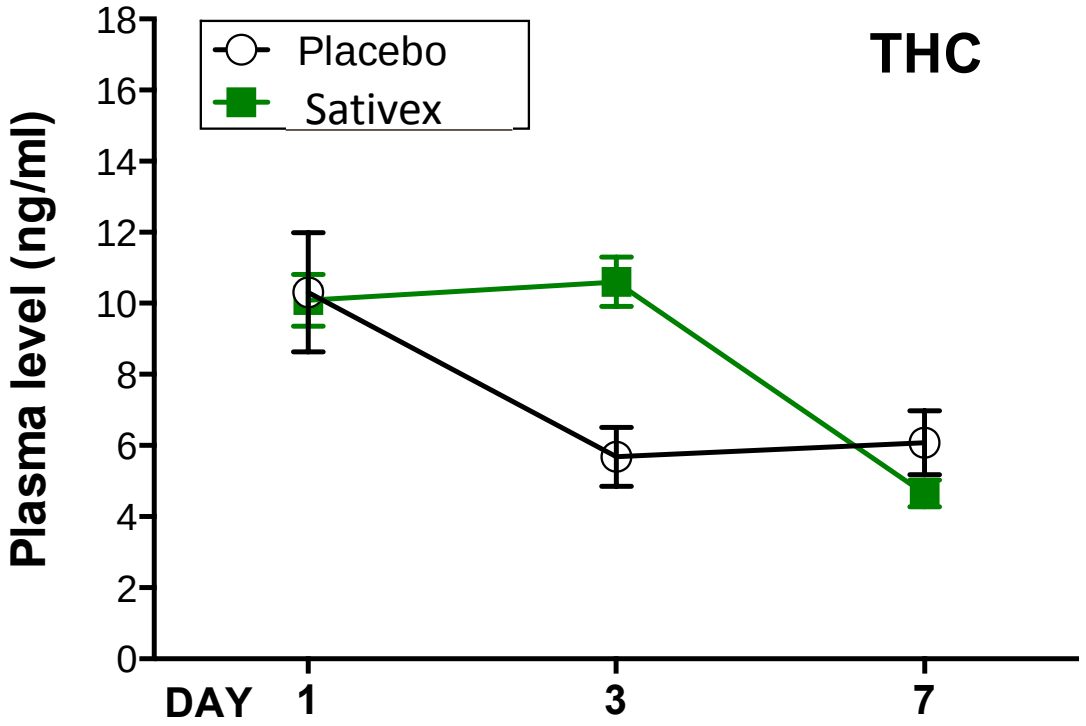

Cannabis withdrawal outcome measures

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The Cannabis Withdrawal Scale

Instructions: This version of the CWS asks about symptoms experienced over the last 24 hours, and can be administered by an interviewer OR by self report.

The following statements describe how you have felt over the last 24 hours. Please **circle the number** that most closely represents your personal experiences for each statement. For each statement, please rate its negative impact on normal daily activities on the same scale (0 = Not at all to 10 = Extremely), writing the number in the right hand column.

		Not at all						Moderately				Extremely	Negative Impact on daily activity (0 – 10)
1	The only thing I could think about was smoking some cannabis	0	1	2	3	4	5	6	7	8	9	10	
2	I had a headache	0	1	2	3	4	5	6	7	8	9	10	
3	I had no appetite	0	1	2	3	4	5	6	7	8	9	10	
4	I felt nauseous (like vomiting)	0	1	2	3	4	5	6	7	8	9	10	
5	I felt nervous	0	1	2	3	4	5	6	7	8	9	10	
6	I had some angry outbursts	0	1	2	3	4	5	6	7	8	9	10	
7	I had mood swings	0	1	2	3	4	5	6	7	8	9	10	
8	I felt depressed	0	1	2	3	4	5	6	7	8	9	10	
9	I was easily irritated	0	1	2	3	4	5	6	7	8	9	10	
10	I had been imagining being stoned	0	1	2	3	4	5	6	7	8	9	10	
11	I felt restless	0	1	2	3	4	5	6	7	8	9	10	
12	I woke up early	0	1	2	3	4	5	6	7	8	9	10	
13	I had a stomach ache	0	1	2	3	4	5	6	7	8	9	10	
14	I had nightmares and/or strange dreams	0	1	2	3	4	5	6	7	8	9	10	
15	Life seemed like an uphill struggle	0	1	2	3	4	5	6	7	8	9	10	
16	I woke up sweating at night	0	1	2	3	4	5	6	7	8	9	10	
17	I had trouble getting to sleep at night	0	1	2	3	4	5	6	7	8	9	10	
18	I felt physically tense	0	1	2	3	4	5	6	7	8	9	10	
19	I had hot flashes	0	1	2	3	4	5	6	7	8	9	10	

Score by summing each items value to a maximum withdrawal score of 190 (you can derive two scores from the scale: one for withdrawal intensity and one for the negative impact of withdrawal – each separate score has a theoretical maximum of 190).

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

The Cannabis Withdrawal Scale development: Patterns and predictors of cannabis withdrawal and distress☆

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[b] Shanlin Fu, Centre for Forensic Science, School of Chemistry and Forensic Science, University of Technology, Sydney 2007, Australia
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PLOS ONE

Quantifying the Clinical Significance of Cannabis Withdrawal

David J. Allsop[1]*, Jan Copeland[1], Melissa M. Norberg[1], Shanlin Fu[2], Anna Molnar[2], John Lewis[2], Alan J. Budney[3]

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Overall withdrawal scores reduced by Sativex

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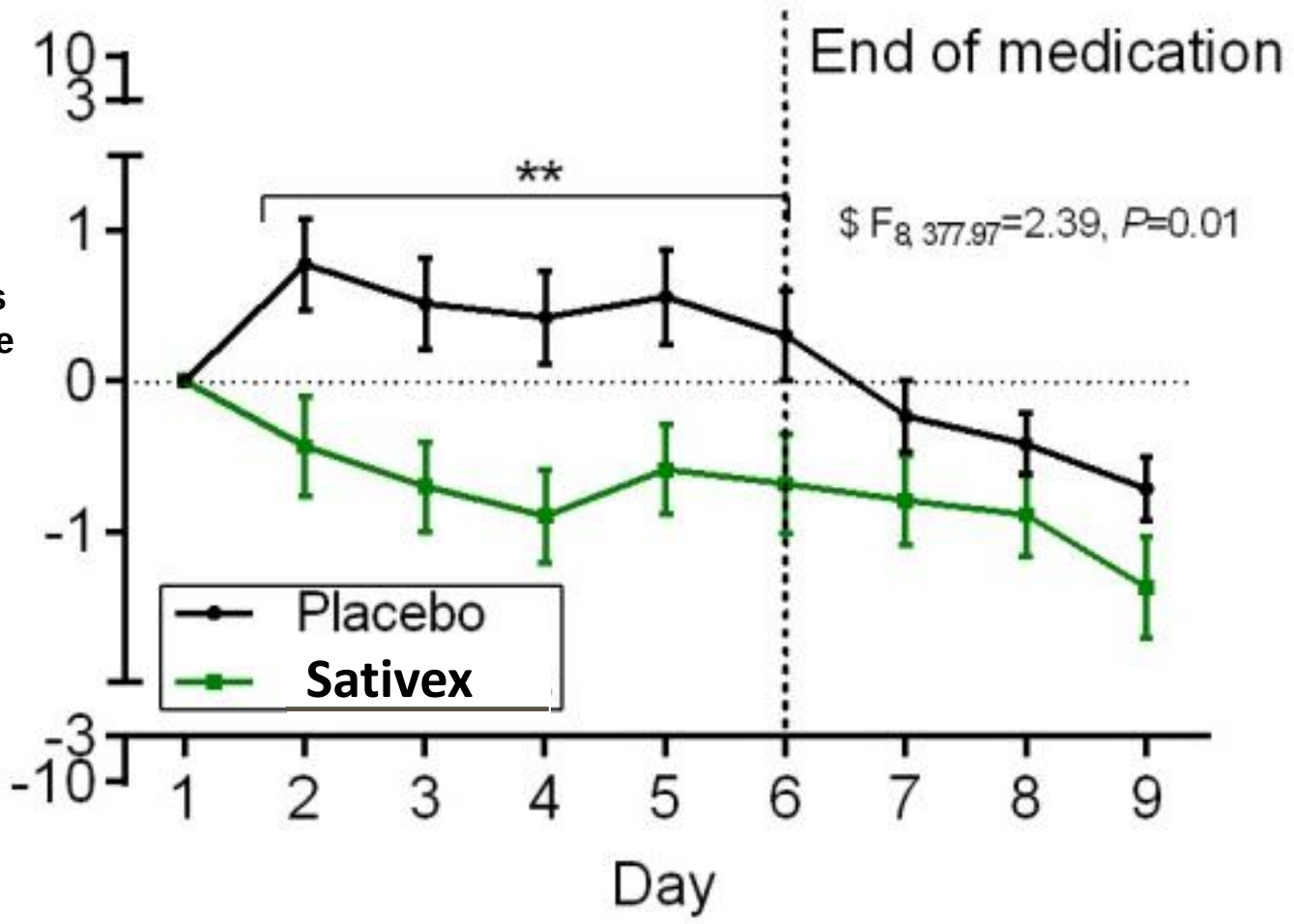

Sativex decreases individual components of withdrawal

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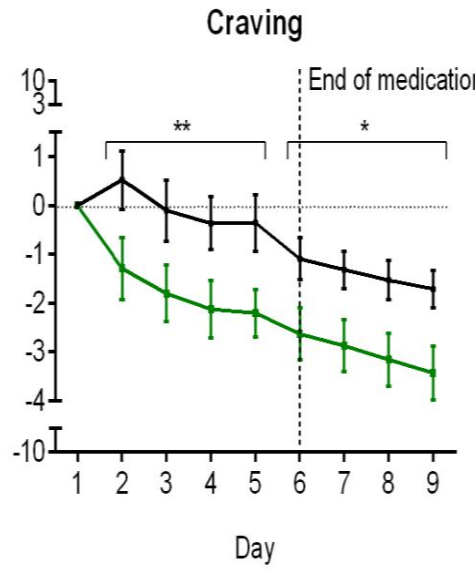

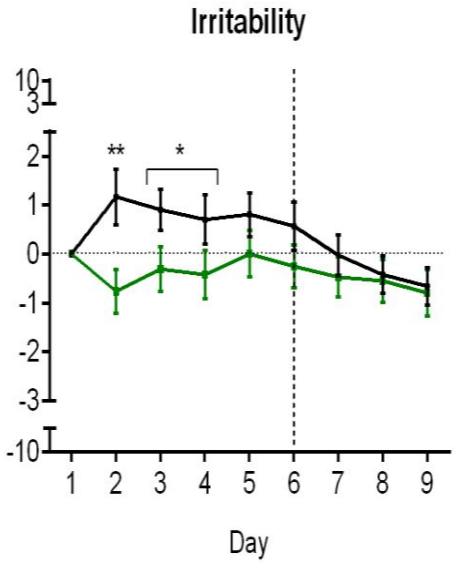

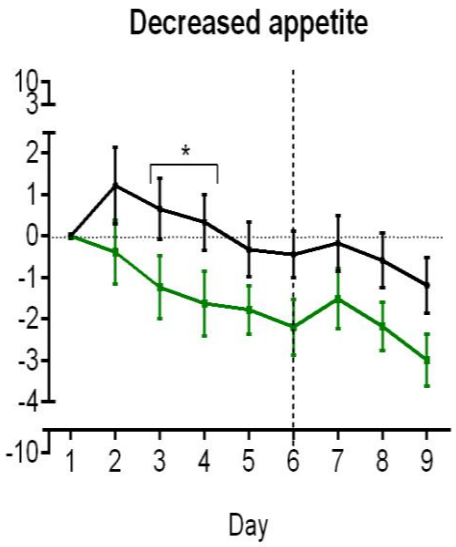

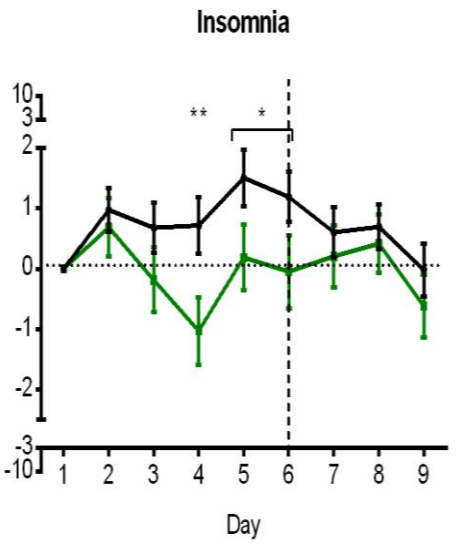

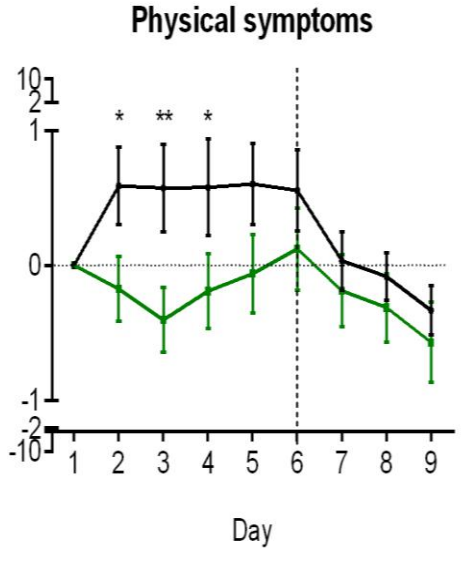

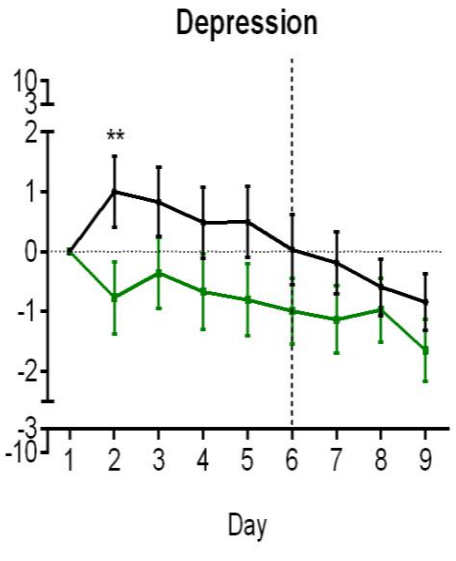

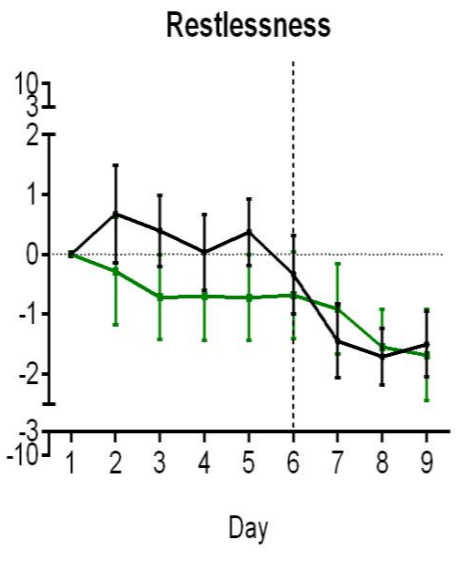

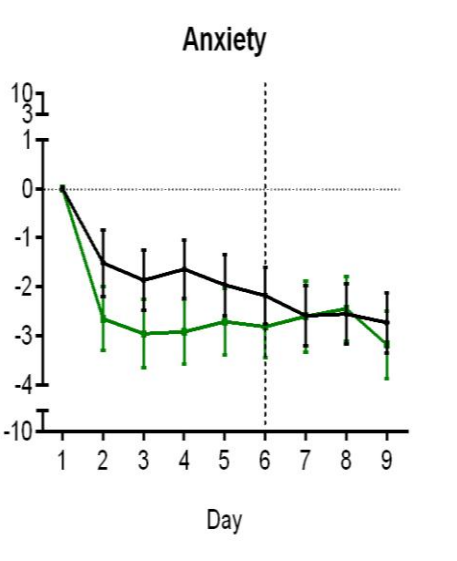

Sativex group remains in treatment longer

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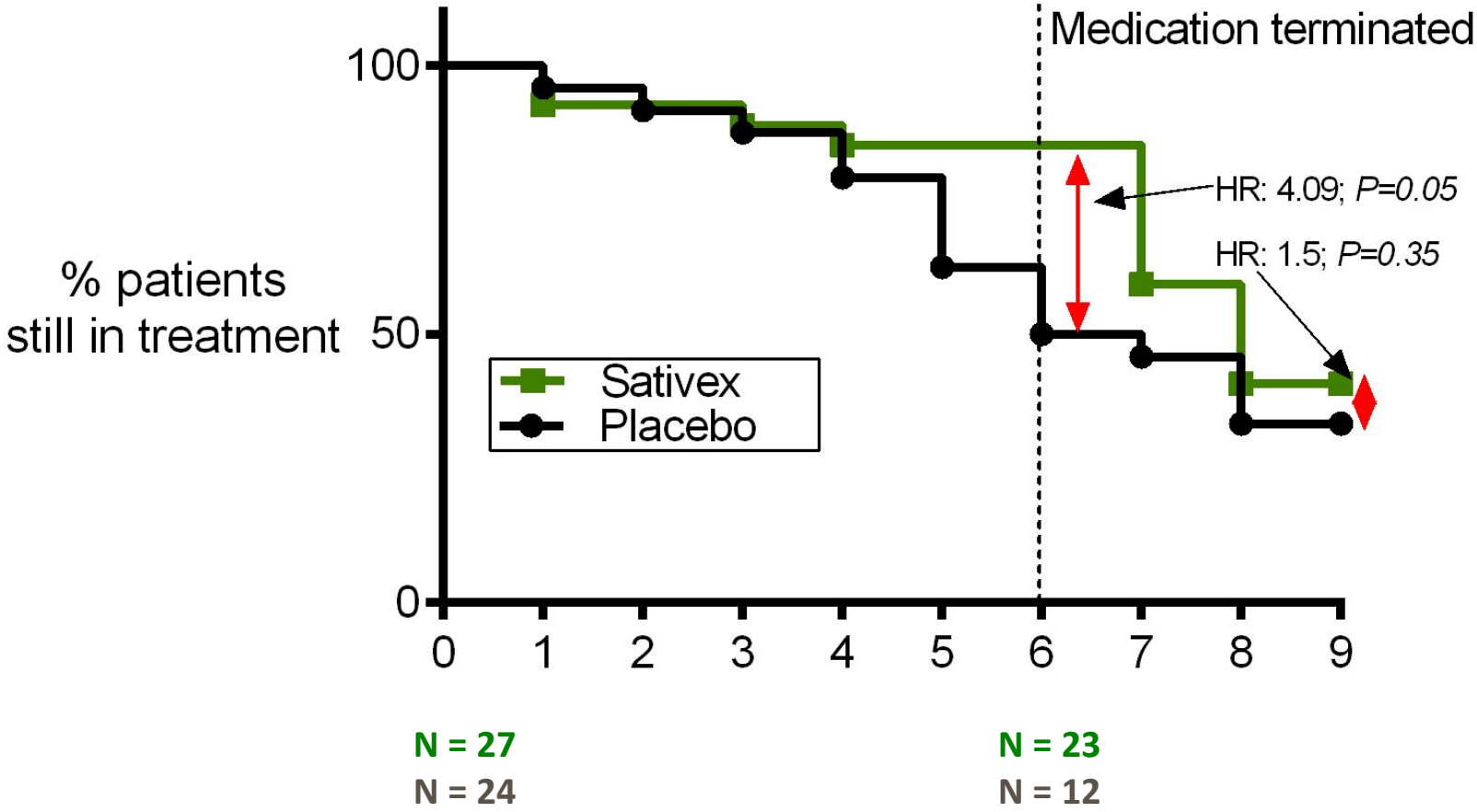

Sativex did not significantly increase intoxication self-report

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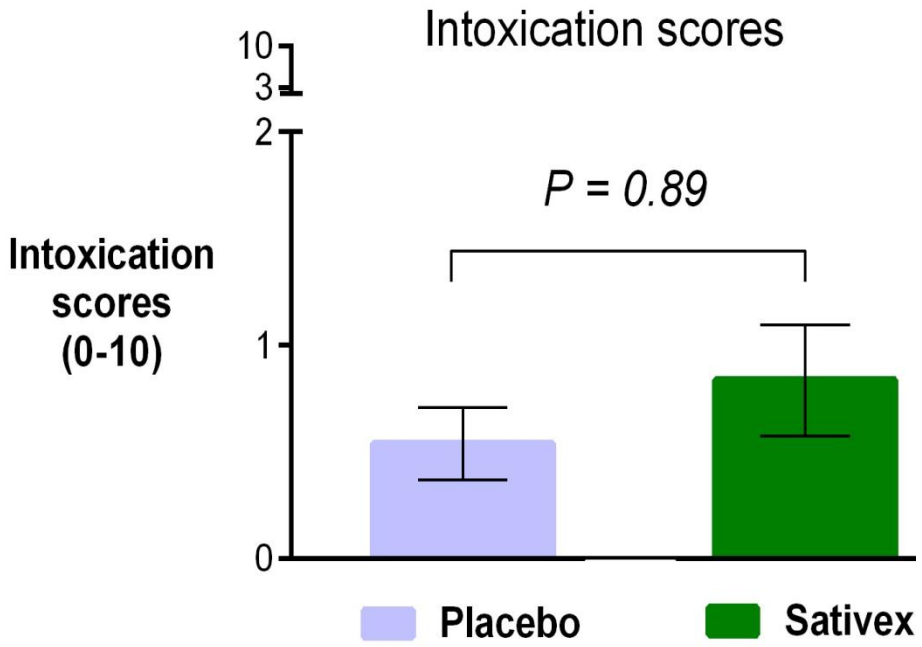

Patients could not guess their own treatment condition

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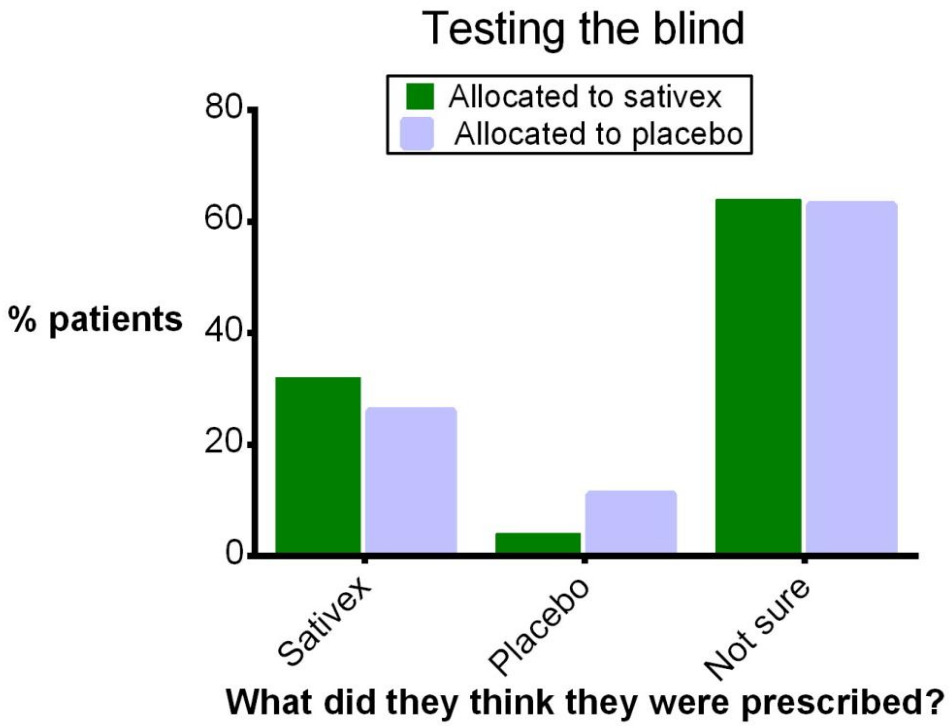
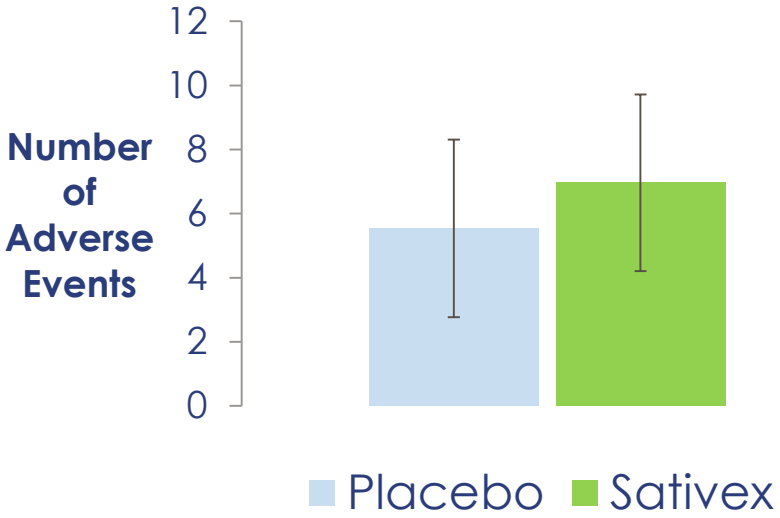
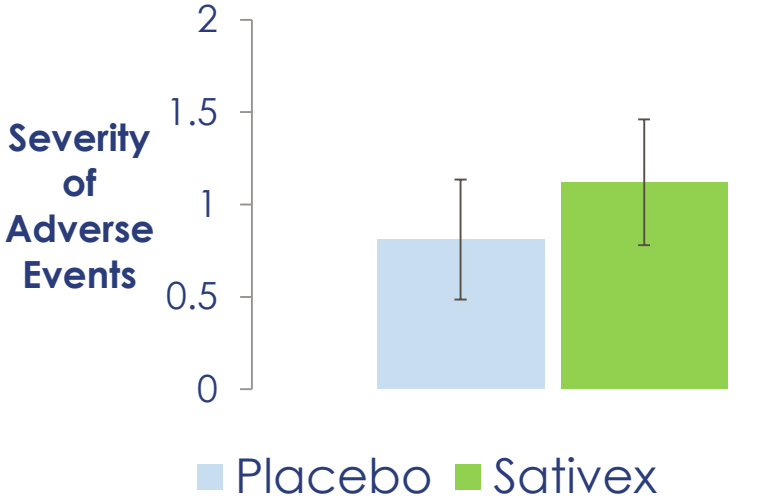


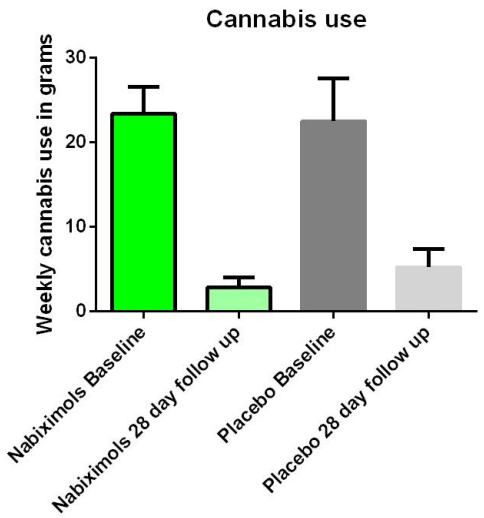
Sativex patients did not experience more Adverse Events

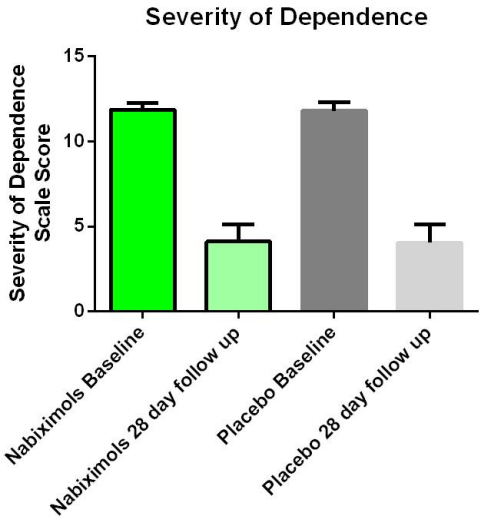
Adverse event	Placebo (n = 24) No. (%)	Nabiximols (n = 27) No. (%)	P[a]
Anxiety	11 (46)	7 (26)	0.14
Depression	9 (38)	9 (33)	0.76
Sweating	9 (38)	9 (33)	0.76
Headache	7 (29)	8 (30)	0.97
Impaired concentration	7 (29)	8 (30)	0.97
Hot flushes	5 (21)	8 (30)	0.47
Chills	4 (17)	8 (30)	0.28
Dry mouth	5 (21)	6 (22)	0.9
Sedation	5 (21)	5 (19)	0.9
Burning or numbness in mouth	3 (13)	6 (22)	0.47
Constipation	3 (13)	6 (22)	0.47
Stomach pain	5 (21)	4 (15)	0.71
Blurred vision	4 (17)	4 (15)	0.58
Dizziness	2 (8)	5 (19)	0.26
Palpitations	3 (13)	3 (11)	0.9
Impaired coordination	1 (4)	4 (15)	0.35
Impaired reaction time	2 (8)	3 (11)	0.9
Memory problems	2 (8)	3 (11)	0.9
Nausea	2 (8)	3 (11)	0.9
Feeling tired	0 (0)	4 (15)	0.07
Paranoia	0 (0)	4 (15)	0.11
Diarrhoea	3 (13)	0 (0)	0.09
Hallucinations	1 (4)	2 (7)	0.55
Impaired balance	1 (4)	2 (7)	0.9
Vomiting	1 (4)	2 (7)	0.9
Impaired motor skills	0 (0)	2 (7)	0.49
Insomnia	2 (8)	0 (0)	0.22
Lightheaded	2 (8)	0 (0)	0.22
Mouth ulcers	1 (4)	1 (4)	0.9
Stinging eyes	1 (4)	2 (7)	0.49
Unpleasant taste	0 (0)	2 (7)	0.49
Agitation	1 (4)	0 (0)	0.47

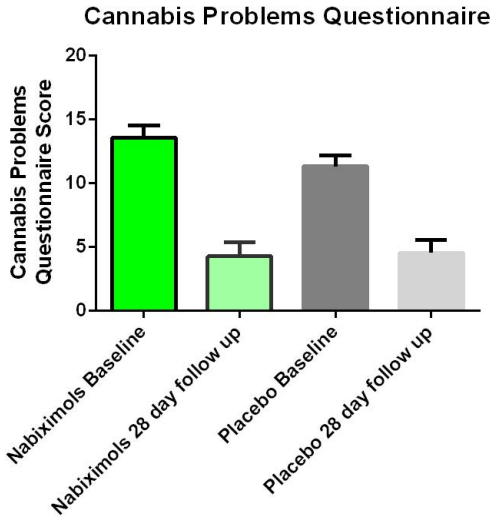


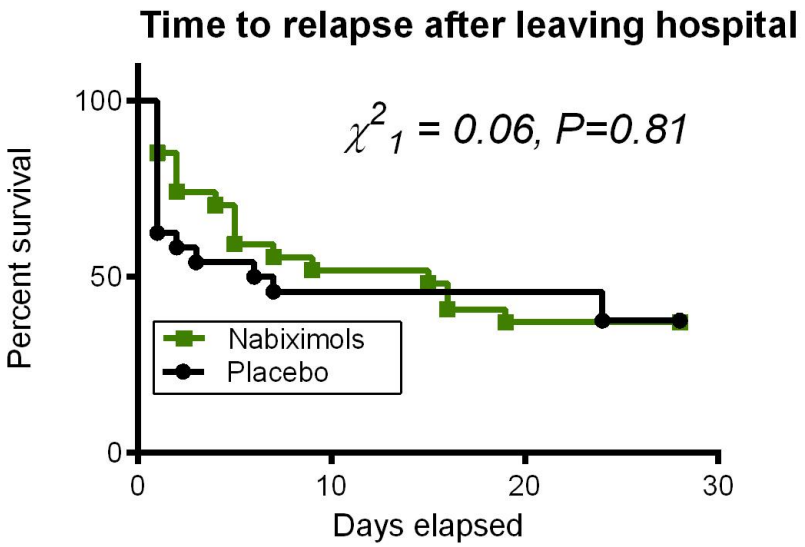


Sativex did not lead to better outcomes at 28-day follow up



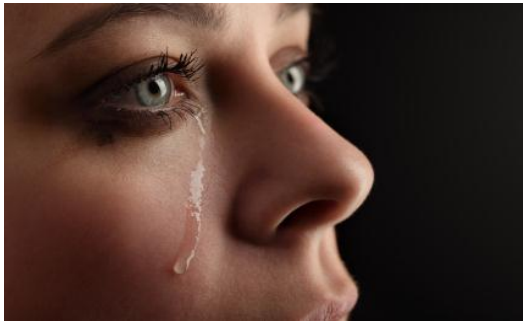






Take home messages

ncpic
national cannabis prevention and information centre




- However, a short course of sativex over the acute withdrawal period **does not lead to better cannabis use outcomes** after withdrawal management

Where to from here?

- Trying to get a longer term maintenance trial up and running for a test of relapse prevention
  - Grant wasn't funded this time around.

- Thinking about possible extensions into treatment for:
  - Comorbid pain and cannabis use
  - Comorbid PTSD and cannabis use

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Thank you!

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What do I think about legalisation?

The Australian Register of Therapeutic Goods

NABIXIMOLS (botanical extract of *Cannabis sativa* which includes the following cannabinoids: tetrahydrocannabinol, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acid, tetrahydrocannabivarol, and cannabidivarol, where tetrahydrocannabinol and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content) in a buccal spray for human therapeutic use.

- **Before October 2009** – Schedule 9 (prohibited substance – may only be used for research purposes)
    - Other drugs in schedule 9:
        - Cannabis, GHB, DMT, Heroin, LSD, MDMA, Psilosybin

- **October 2009** – Committee agreed to reschedule Sativex from an S9 to an S8 medication (Controlled Drug with high potential for abuse, misuse and physical or psychological dependence) to allow access to Sativex under the TGAs Special Access Scheme (SAS). Drs must have an S8 permit before prescribing treatment.
    - When placed in S8, comittee recommended specific restrictions to only buccal sprays

- **May 2010** – Sativex was rescheduled to S8 Appendix K (must have a “sedating” warning) and Appendix D paragraph 3, which restricts access through the SAS to only:

'persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment‘.

- **November 26 2012** – Sativex was **registered** onto the Australian Register of Therapeutic Goods, meaning it can be lawfully prescribed.

Sativex is indicated as treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other antispasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

- **September 1st 2013** – Sativex was moved from Appendix D paragraph 3 (which limits prescribing practices for non registered products) to Appendix D paragraph 1 (for registered products) – limiting the prescriber population to neurologists and rehabilitation physicians. This step essentially formalises the registration of the drug in Australia, making it now possible for it to be prescribed in the country.

- For sativex to be approved for indications other than MS, an application for extension would need to be submitted to the TGA, with accompanying evidence of safety and efficacy.