Author Material

Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, Rivas GR,Holland RM,Muhleisen P, Norberg, MM, Booth J, McGregor I. (2014).Nabiximols as an Agonist Replacement Therapy During Cannabis Withdrawal.A Randomized Clinical Trial. *JAMA Psychiatry*.

Author Table 1. DSM5 symptoms mean difference from baseline by treatment and Hedge's g statistics

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Author Figure 2. Mean change in cannabis intoxication ('stoned' scale) from 5 minutes pre to 30 minutes post dose by treatment group.

Scores are averaged over the four dosing sessions per day.

Author Table 1. Daily change (from baseline) in DSM5 withdrawal symptom severity by treatment group with effect sizes (Hedge's *g*)

					Time (Day)				
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
OVERALL WITHDRAWAL SCORE									
Mean (SD) change from baseline									
Placebo	0	0.78 (1.47)	0.52 (1.51)	0.42 (1.52)	0.56 (1.57)	0.3 (1.52)	-0.23 (1.18)	-0.42 (1.03)	-0.72 (1.08)
Nabiximols	0	-0.43 (1.71)	-0.69 (1.56)	-0.89 (1.66)	-0.59 (1.56)	-0.68 (1.71)	-0.79 (1.61)	-0.89 (1.45)	-1.37 (1.71)
Pre-post correlation[a]	1	0.25	0.33	0.29	0.33	0.25	0.37	0.41	0.03
Hedge's g, 95% CI									
Hedge's g	-	0.74	0.79	0.82	0.73	0.61	0.39	0.37	0.44
-95% CI	-	0.18	0.23	0.26	0.17	0.05	-0.15	-0.17	-0.11
+95% CI	-	1.30	1.35	1.38	1.29	1.16	0.94	0.92	0.99
IRRITABILITY, ANGER OR AGGRESSION									
Mean (SD) change from baseline									
Placebo	0	1.17 (2.79)	0.91 (2.06)	0.71 (2.49)	0.81 (2.25)	0.57 (2.45)	-0.03 (2.16)	-0.42 (2)	-0.66 (1.96)
Nabiximols	0	-0.76 (2.39)	-0.31 (2.39)	-0.43 (2.59)	0.002 (2.49)	-0.25 (2.34)	-0.47 (2.18)	-0.55 (2.44)	-0.79 (2.49)
Pre-post correlation[a]	1	0.14	0.35	0.19	0.32	0.25	0.36	0.26	0.15
Hedge's g, 95% CI									
Hedge's g	-	0.74	0.54	0.44	0.34	0.34	0.22	0.08	0.07
-95% CI	-	0.18	-0.01	-0.11	-0.21	-0.20	-0.32	-0.46	-0.47
+95% CI	-	1.3	1.09	0.99	0.88	0.89	0.76	0.62	0.61

Author Table 1. Daily change (from baseline) in DSM5 withdrawal symptom severity by treatment group with effect sizes (Hedge's *g*)(continued)

					Time (Day)				
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
DECREASED APPETITE OR WEIGHT LOSS									
Mean (SD) change from baseline									
Placebo	0	1.22 (4.51)	0.65 (3.72)	0.34 (3.33)	-0.33 (3.33)	-0.45 (2.94)	-0.17 (3.48)	-0.59 (3.43)	-1.19 (3.33)
Nabiximols	0	-0.39 (4.05)	-1.24 (4)	-1.63 (4.16)	-1.78 (3.17)	-2.19 (3.59)	-1.52 (3.89)	-2.18 (3.43)	-2.99 (3.38)
Pre-post correlation[a]	1	0.13	0.13	0.13	0.31	0.24	0.09	0.18	-0.03
Hedge's g, 95% CI									
Hedge's g	-	0.37	0.46	0.52	0.45	0.53	0.37	0.49	0.54
-95% CI	-	-0.17	-0.09	-0.03	-0.1	-0.02	-0.18	-0.06	-0.01
+95% CI	-	0.92	1.01	1.07	1	1.09	0.92	1.04	1.09
SLEEP DIFFICULTY (INSOMNIA)									
Mean (SD) change from baseline									
Placebo	0	0.97 (1.76)	0.68 (2.06)	0.71 (2.4)	1.49 (2.49)	1.18 (2.4)	0.6 (2.15)	0.69 (1.96)	-0.02 (2.35)
Nabiximols	0	0.68 (2.55)	-0.19 (2.81)	-1.03 (2.96)	0.19 (2.91)	-0.05 (3.17)	0.21 (2.75)	0.42 (2.81)	-0.62 (2.81)
Pre-post correlation[a]	1	0.57	0.35	0.26	0.25	0.16	0.32	0.29	-0.02
Hedge's g, 95% CI									
Hedge's g	-	0.13	0.45	0.65	0.5	0.45	0.17	0.13	0.24
-95% CI	-	-0.41	-0.1	0.09	-0.05	-0.1	-0.37	-0.42	-0.3
+95% CI	-	0.67	1	1.2	1.05	1	0.71	0.67	0.78

Author Table 1. Daily change (from baseline) in DSM5 withdrawal symptom severity by treatment group with effect sizes (Hedge's *g*)(continued)

					Time (Day)				
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
NERVOUSNESS OR ANXIETY									
Mean (SD) change from baseline									
Placebo	0	-1.52 (3.33)	-1.86 (3.09)	-1.64 (3.04)	-1.96 (3.09)	-2.18 (2.99)	-2.59 (3.38)	-2.55 (3.23)	-2.73 (3.23)
Nabiximols	0	-2.65 (3.43)	-2.95 (3.64)	-2.91 (3.53)	-2.71 (3.64)	-2.82 (3.38)	-2.60 (3.85)	-2.45 (3.59)	-3.18 (3.69)
Pre-post correlation[a]	1	0.24	0.23	0.29	0.19	0.31	0.14	0.19	-0.03
Hedge's g, 95% CI									
Hedge's g	-	0.33	0.46	0.39	0.22	0.21	0.06	0.07	0.14
-95% CI	-	-0.21	-0.09	-0.15	-0.32	-0.34	-0.48	-0.47	-0.40
+95% CI	-	0.88	1.01	0.94	0.76	0.75	0.60	0.61	0.68
PHYSICAL SYMPTOMS									
Mean (SD) change from baseline									
Placebo	0	0.59 (1.42)	0.57 (1.62)	0.58 (1.76)	0.60 (1.57)	0.56 (1.52)	0.04 (1.18)	-0.08 (0.98)	-0.33 (1.08)
Nabiximols	0	-0.18 (1.29)	-0.40 (1.25)	-0.19 (1.45)	-0.06 (1.56)	0.13 (1.61)	-0.19 (1.4)	-0.31 (1.4)	-0.57 (1.61)
Pre-post correlation[a]	1	0.32	0.21	0.15	0.21	0.28	0.31	0.31	-0.05
Hedge's g, 95% CI									
Hedge's g	-	0.56	0.51	0.47	0.43	0.28	0.18	0.21	0.20
-95% CI	-	0.01	-0.04	-0.08	-0.11	-0.27	-0.37	-0.33	-0.35
+95% CI	-	1.11	1.06	1.02	0.98	0.82	0.72	0.75	0.74

Author Table 1. Daily change (from baseline) in DSM5 withdrawal symptom severity by treatment group with effect sizes (Hedge's *g*)(continued)

					Time (Day)				
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
DEPRESSED MOOD									
Mean (SD) change from baseline									
Placebo	0	1 (2.99)	0.83 (2.89)	0.48 (2.99)	0.49 (2.94)	0.03 (2.99)	-0.19 (2.65)	-0.59 (2.45)	-0.84 (2.55)
Nabiximols	0	-0.77 (3.17)	-0.36 (3.07)	-0.67 (3.27)	-0.81 (3.17)	-0.99 (2.91)	-1.13 (3.01)	-0.97 (2.91)	-1.65 (2.86)
Pre-post correlation[a]	1	0.24	0.27	0.13	0.15	0.14	0.16	0.23	0.15
Hedge's g, 95% CI									
Hedge's g	-	0.57	0.45	0.36	0.42	0.35	0.34	0.15	0.31
-95% CI	-	0.02	-0.10	-0.18	-0.13	-0.20	-0.21	-0.39	-0.23
+95% CI	-	1.13	1.00	0.91	0.97	0.89	0.88	0.69	0.86
RESTLESSNESS									
Mean (SD) change from baseline									
Placebo	0	0.68 (4.07)	0.39 (3.04)	0.04 (3.28)	0.38 (2.94)	-0.34 (3.58)	-1.45 (3.38)	-1.71 (2.79)	-1.51 (2.89)
Nabiximols	0	-0.28 (4.78)	-0.72 (3.74)	-0.7 (3.89)	-0.78 (4.05)	-0.68 (3.89)	-0.92 (4)	-1.55 (3.48)	-1.68 (4.16)
Pre-post correlation[a]	1	-0.09	0.28	0.18	0.24	0.16	0.13	0.29	-0.11
Hedge's g, 95% CI									
Hedge's g	-	0.22	0.45	0.21	0.33	0.11	0.16	0.08	0.07
-95% CI	-	-0.33	-0.10	-0.33	-0.21	-0.43	-0.38	-0.46	-0.47
+95% CI	-	0.76	1.00	0.75	0.88	0.65	0.70	0.62	0.61

Author Table 1. Daily change (from baseline) in DSM5 withdrawal symptom severity by treatment group with effect sizes (Hedge's *g*)(continued)

					Time (Day)				
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
CANNABIS CRAVINGS									
Mean (SD) change from baseline									
Placebo	0	0.52 (2.94)	-0.10 (3.09)	-0.37 (2.69)	-0.36 (2.84)	-1.09 (2.21)	-1.32 (2.16)	-1.53 (2.16)	-1.71 (1.91)
Nabiximols	0	-1.29 (3.27)	-1.80 (3.07)	-2.12 (3.07)	-2.2 (2.56)	-2.63 (2.81)	-2.87 (2.86)	-3.16 (2.81)	-3.42 (2.91)
Pre-post correlation[a]	1	0.16	0.15	0.20	0.26	0.26	0.29	0.13	0.04
Hedge's g, 95% CI									
Hedge's g	-	0.57	0.44	0.60	0.67	0.61	0.64	0.65	0.69
-95% CI	-	0.02	-0.11	0.05	0.12	0.05	0.08	0.10	0.13
+95% CI	-	1.12	0.98	1.16	1.23	1.16	1.19	1.21	1.25

a. Pre-post correlation is the Pearson correlation coefficient between baseline (day 1) withdrawal scores and each successive day of abstinence.

Author Table 2. Adverse events count (number of people experiencing AE) sorted with most prevalent AE's at top of table.

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
Chest pain	0 (0)	1 (4)	0.9
Feeling tired eyes	0 (0)	1 (4)	0.53
Head spin	0 (0)	1 (4)	0.53
Heart skipped a beat	0 (0)	1 (4)	0.53
Heartburn	1 (4)	0 (0)	0.47
Heightened alertness	0 (0)	1 (4)	0.53
Hypertension	0 (0)	1 (4)	0.9
Increase in salivation	0 (0)	1 (4)	0.9
Intoxication	0 (0)	1 (4)	0.9

Author Table 2. Adverse events count (number of people experiencing AE) sorted with most prevalent AE's at top of table (continued).

Adverse event	Placebo (n = 24) No. (%)	Nabiximols (n = 27) No. (%)	P[a]
Irritable	0 (0)	1 (4)	0.9
Nocturia	0 (0)	1 (4)	0.9
Panic attack	0 (0)	1 (4)	0.9
Restless	0 (0)	1 (4)	0.9
Slow thinking	1 (4)	0 (0)	0.47
Suicidal ideation	1 (4)	0 (0)	0.47
Threat of suicide*	1 (4)	0 (0)	0.47

*Serious Adverse Events

a. Statistical comparisons are from: (a) Fishers Exact test for categorical variables with any cells in the contingency table with n<5, (b) Chi square test for all other categorical variables.

Author Table 3.Testing the blind and dose adequacy.

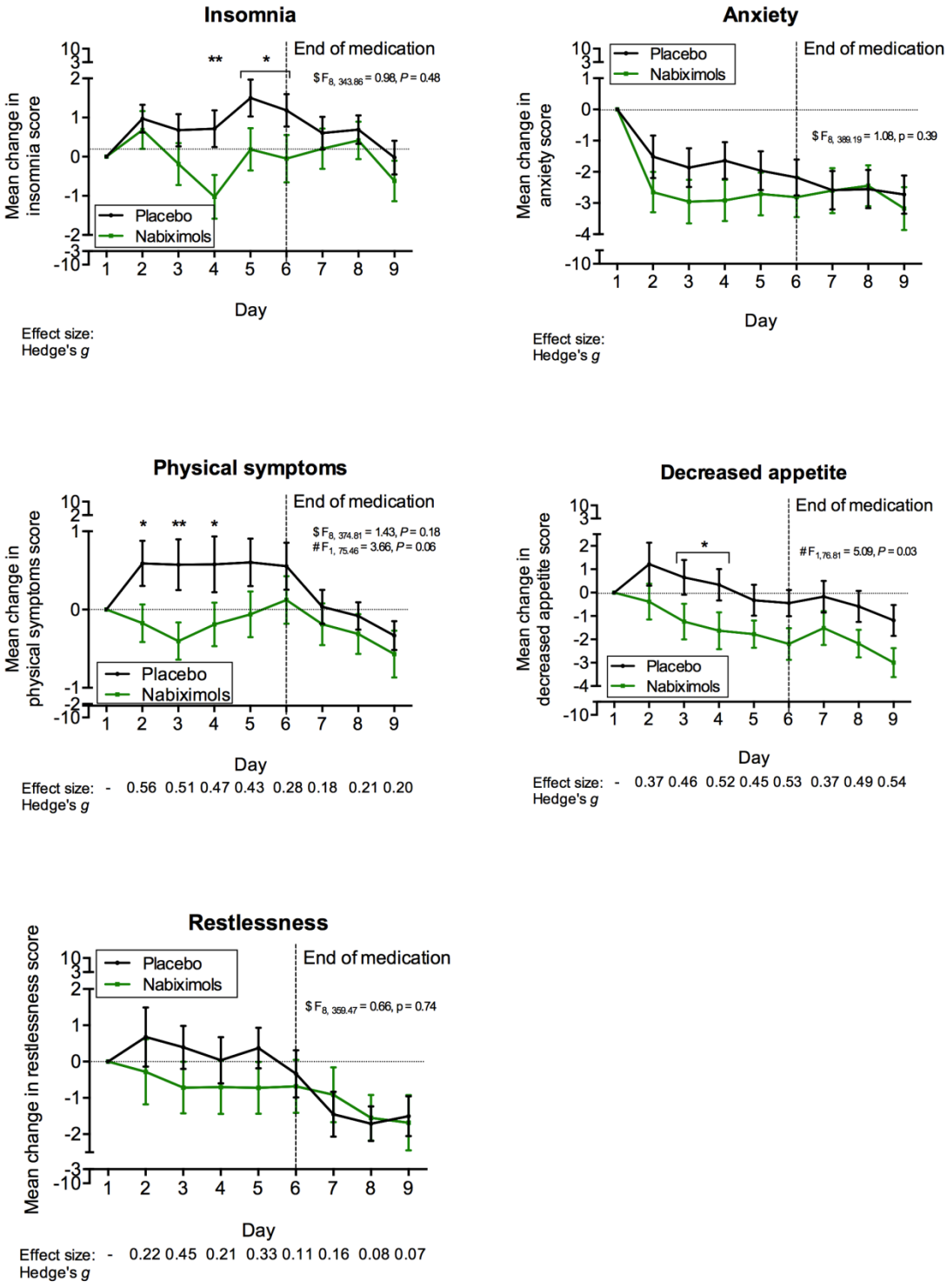
	What did they think they were prescribed? N (%)[e]				
Testing the blind	Nabiximols		Placebo		Not sure
Nabiximolsgroup[a]	8 (32)		1 (4)		16 (64)
Placebo group[b]	5 (26)		2 (11)		12 (63)
	Dose was too low		**Dose was too high**		
Dose adequacy	Yes	No	Yes	No	
Nabiximolsgroup[c]	4 (17)	20 (83)	0	24 (100)	--
Placebo group[d]	0	17 (100)	0	17 (100)	--

a. Only 25 of the 27 Nabiximols participants had the blind formally tested.
b. Only 19 of the 24 placebo participants had the blind formally tested.
c. 24 of 27 Nabiximols participants gave dose adequacy data.
d. 17 of 24 placebo particpants gave dose adequacy data.
e. χ^2_2=0.79, *P*=0.67

Author Table 4. Number of patients in each group receiving concomitant medications during hospital stay

Concomitant medication/drug use	Placebo (n=24) No. (%)	Nabiximols (n=27) No. (%)	Indication	*P*[a]
Temazepam	19 (79)	16 (59)	Insomnia	0.13
Nicotine Replacement Therapy (NRT)[b]	17 (71)	19 (70)	Nicotine withdrawal	0.97
Ibuprofen	5 (21)	7 (26)	Aches and pains/analgesia/headache/lower back pain	0.67
Paracetamol	6 (25)	5 (19)	Analgesia/fever/aches and pains/headache	0.57
Caffeine use (mean [SD] mg per day)	34.43 [81.89]	44.65 [83.11]	Usage during inpatient stay	0.17[c]
Medications prescribed as ongoing from study entry				
Antidepressants	4 (17)	3 (11)	Depression	0.69[d]
Antibiotics	1 (4)	0	Infection	0.47[d]
Anticonvulsants	1 (4)	0	Epilepsy	0.47[d]
Antipsychotics	0	1 (4)	Schizophrenia	0.53[d]

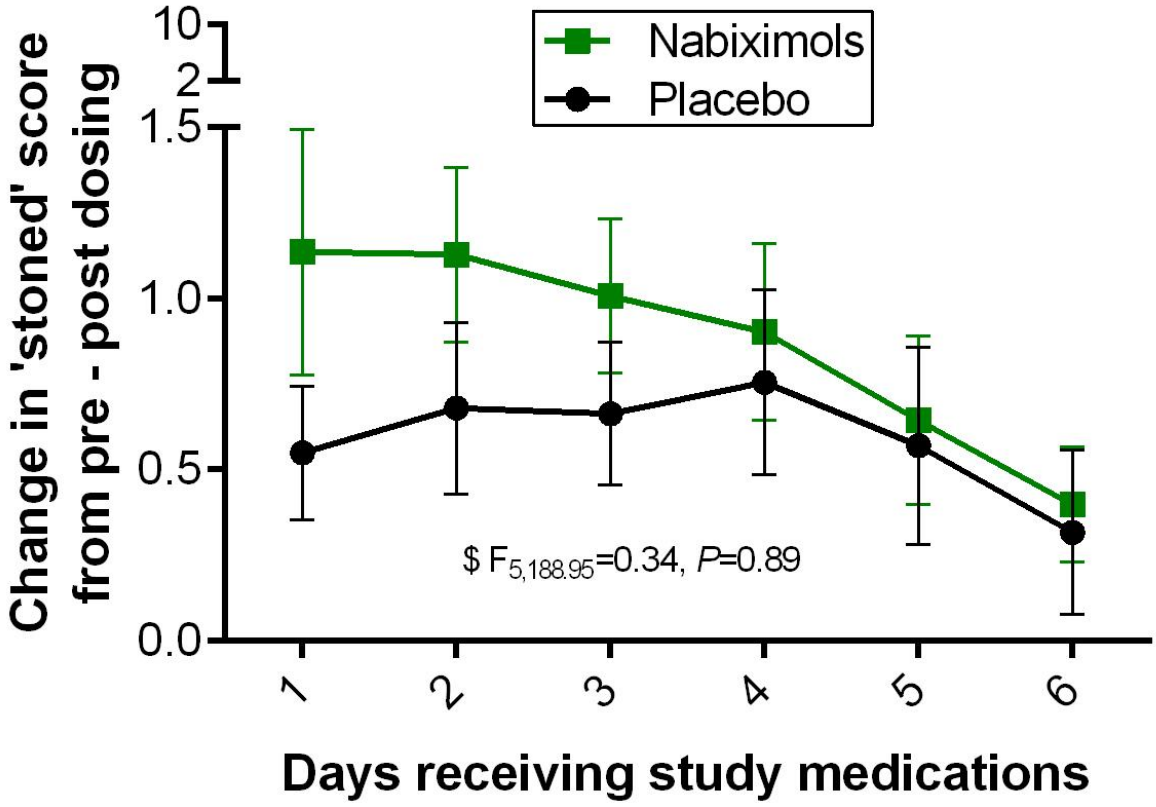
a. Chi square test
b. Includes patients from the Sydney site who smoked cigarettes during their inpatient stay (Placebo: 10 on NRT only, 4 on cigarettes only, 3 using NRT and cigarettes combined; Nabiximols: 8 on NRT only, 6 on cigarettes only, 5 using NRT and cigarettes combined).
c. Two way Anova.
d. Fishers Exact Test.



Author Figure 1.

DSM5 withdrawal symptom plots by treatment group for those symptoms whose overall omnibus test was not significantly affected by drug treatment.

* P <= 0.05, ** P <= 0.01 based on the unadjusted MMRM post hoc pairwise comparisons between groups on each day, adjusted for multiple comparisons using Bonferroni. $ Time x Treatment interaction: Omnibus type III test of fixed effects from unadjusted MMRM.# Treatment main effect: Omnibus type III test of fixed effects from unadjusted MMRM.



Author Figure 2.

Mean change in cannabis intoxication ('stoned' scale) from 5 minutes pre to 30 minutes post dose by treatment group.

Scores are averaged over the four dosing sessions per day.
$ Time x Treatment interaction: Omnibus type III test of fixed effects from unadjusted MMRM