

Cannabinoid Agonist Therapy (nabiximols) for the Management of Treatment-Resistant Cannabis Dependent Patients: Methods and Baseline data



Thérapie par les agonistes des cannabinoïdes (nabiximols) pour la prise en charge des patients dépendants du cannabis résistants au traitement: méthodes et données de référence

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Disclosures

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- Medication:
 - GW Pharmaceuticals (non impliqué dans la conception, l'analyse ou la communication des résultats)
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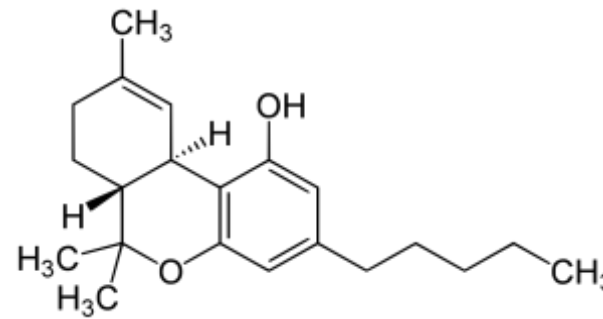
Contexte

- Dans le monde: 180 millions de personnes utilisent le cannabis
- Australia:
 - 35% adults – lifetime use, 10% past year use (AIHW 2017)
 - 10% lifetime cannabis use dependence (Swift, W, 2001 Addiction 96: 737-48)
 - Estimate ~n=200,000-300,000 current dependent users
- Problèmes de santé associés:
 - Dependence
 - Déficience cognitive
 - Aggravation de la psychose pour certains
 - Problèmes cardio-vasculaires et respiratoires

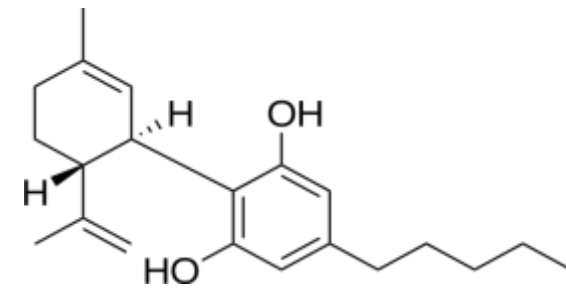
Traitement agoniste, maintenance

- Effective medication approach
 - Opioids: buprenorphine, methadone
 - Nicotine: nicotine patches, spray, gum, lozenge, inhaler
- Mechanism
 - Cross tolerance to drug used
 - Suppress use of related agonist (e.g. heroin, tobacco)
- Adherence: may be better than other approaches
 - E.g. possible advantages over antagonists, anti-craving medications?
 - If discontinue, patient experiences withdrawal

Nabiximols (Sativex)



THC



CBD

- THC, CBD oro-musocal spray 1:1 ration
 - 2.7 mg THC and 2.5 mg CBD / 100 μ l spray
 - (N.b. 50% v/v of ethanol \sim 0.5 gm ethanol/day)
- Doses:
 - Up to 12 sprays/day (titrated)
 - \sim 30 mg THC, CBD
- Approved indications (Australia):
 - Muscle spasticity from multiple sclerosis (second line treatment)
 - Treatment initiated by a neurologist/rehabilitation physician
- Approval: 18 EU countries (including France)



Nabiximols for cannabis withdrawal

Original Investigation

Nabiximols as an Agonist Replacement Therapy During Cannabis Withdrawal A Randomized Clinical Trial

JAMA Psychiatry. 2014;71(3):281-0. doi:10.1001/jamapsychiatry.2013.3947
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- Rationale:
 - Lack of effective medications for cannabis withdrawal
 - Many used, none specific: diazepam (other BZDs), anti-psychotics

Programme de traitement

- Une semaine d'hospitalisation
 - 2 hospitals – Sydney, Newcastle NSW
 - Assessed prior to admission:
 - Adults, cannabis dependent (DSM IV TR), want to stop using cannabis, no major unstable medical, psychiatric conditions, pregnant, other substance dependence (except tobacco)
 - Routine care:
 - CBT workbook (self completed), drug & alcohol nursing withdrawal support
 - NRT – tobacco dependence
 - Medication:
 - Nabiximols/placebo spray

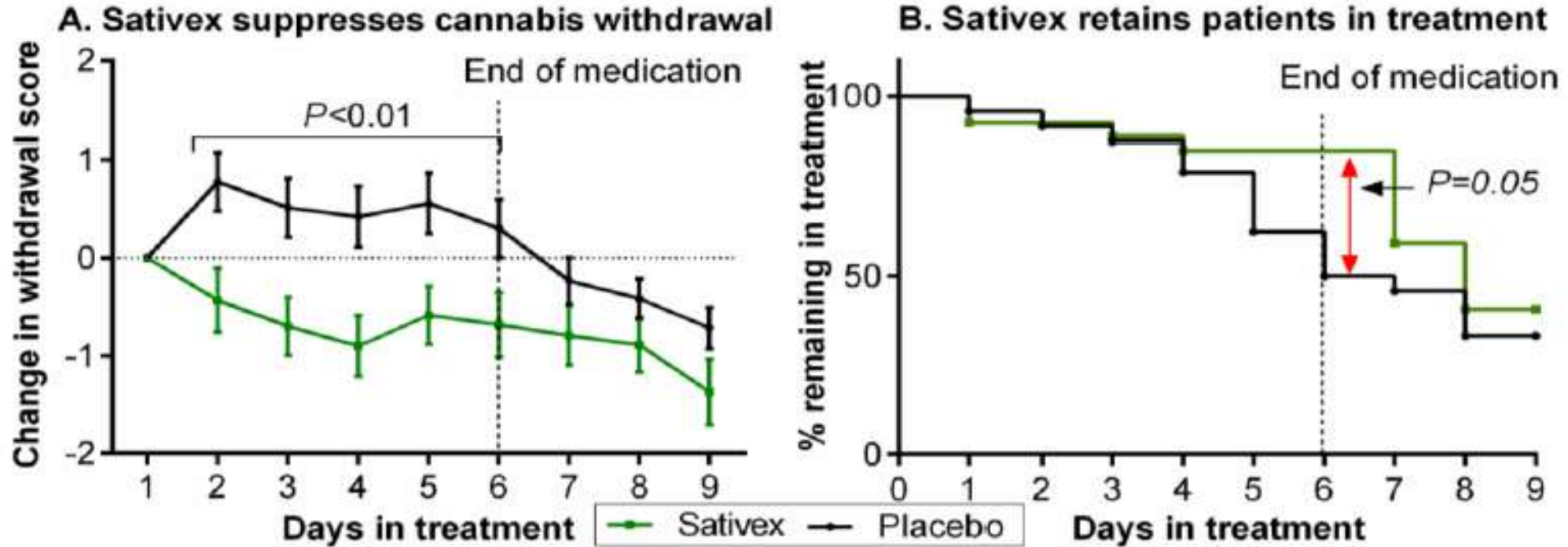
Nabiximols dosing

	dose totale (n sprays)	THC (mg)	CBD (mg)
jour 1	16	43.2	40
jour 2	32	86.4	80
jour 3	32	86.4	80
jour 4	24	64.8	60
jour 5	16	43.2	40
jour 6	8	21.6	20
jour 7	0	0	0
jour 8	0	0	0
jour 9	0	0	0

Table 1. Baseline Characteristics According to Treatment Group^a

Characteristic	Nabiximols (n = 27)	Placebo (n = 24)	Total (N = 51)	P Value ^b
Demographics, No. (%)				
Age, mean (SD), y	34.96 (9.70)	35.88 (8.05)	35.39 (8.89)	.72
Male sex	18 (67)	21 (88)	39 (76)	.08
Aboriginal or Torres Strait Islander	2 (7)	1 (4)	3 (6)	.62
Completed school	15 (56)	13 (54)	28 (55)	.99
Unemployed	15 (56)	12 (50)	27 (53)	.67
Married, including de facto	4 (15)	9 (38)	13 (25)	.35
Substance use history, mean (SD)				
Cannabis use, g ^f	23.39 (16.79)	22.52 (24.54)	22.98 (20.66)	.88
Carboxy-THC/creatinine ratio, ng/mg	2392.70 (1441.69)	3285.56 (5525.82)	2815.63 (3911.64)	.49
Years of cannabis use	20.11 (9.83)	20.79 (8.67)	20.43 (9.22)	.79
Cannabis SDS	11.96 (3.03)	12.13 (2.35)	12.04 (2.71)	.83

Effets sur les symptômes de sevrage du cannabis et rétention dans le traitement



- Benefit over placebo in inpatient setting as a withdrawal medication
 - Reduction in withdrawal severity
 - Improvement in retention at 1 week

Other outcomes

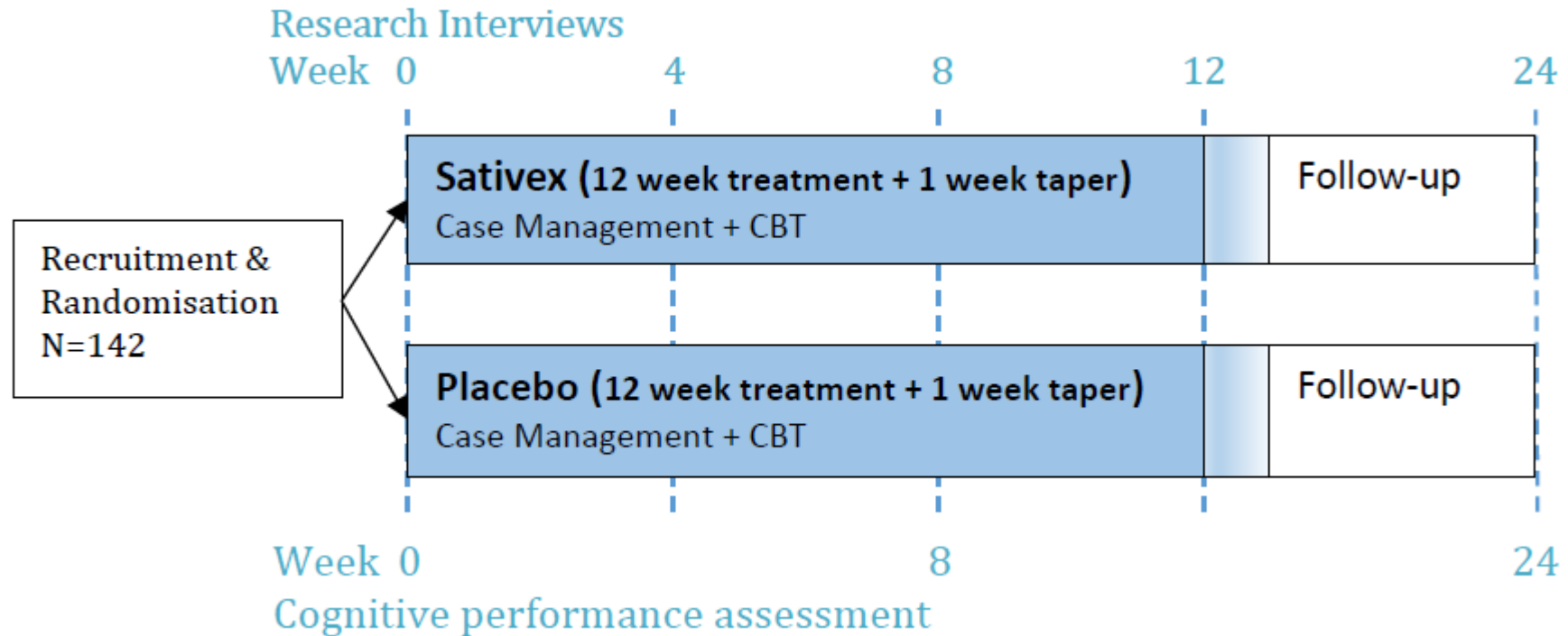
- Participants could not detect which arm (placebo or active)
 - ($\chi^2 1 = 0.79$; $P = .67$)
- Those on nabiximols did not report any more intoxication
 - ($F_{1,6} = 0.22$; $P = .97$)
- Adverse events no - between group differences
 - Number ($F_{1,50} = 0.3$; $P = .59$) or severity ($F_{1,50} = 2.69$; $P = .10$)
- No difference in cannabis use at Day 28

Outcome Variable	Mean Scores		Time	Treatment	Time × Treatment
	Baseline	Follow-up			
Weekly mean cannabis use, g					
Nabiximols	23.39 (16.79)	2.81 (5.94)	$F_{1,48} = 38.79^a$	$F_{1,48} = 0.52$	$F_{1,48} = 0.29$
Placebo	22.52 (24.54)	5.21 (10.74)			

Nabiximols comme traitement agoniste à plus long terme?

- Aims
 - measure efficacy, safety and cost-effectiveness of longer-term nabiximols treatment for outpatient cannabis dependent patients who have not responded to previous conventional treatment approaches
- Setting
 - Four specialist drug and alcohol outpatient clinics in New South Wales, Australia
- Participants
 - 142 treatment seeking cannabis dependent adults, with no significant medical, psychiatric or other substance use disorders
- Clinical Trial Registration: [ACTRN12616000103460](https://www.anzctr.org.au/Trial/Registration/Trial.asp?id=12616000103460)

Design



- A phase III multi-site outpatient, randomised, double-blinded, placebo controlled parallel design
- Une étude parallèle multicentrique de phase III, randomisée, en double aveugle et contrôlée par placebo

Traitement

- Medication Nabiximols - flexible dose regimen
 - maximum daily dose of 32 sprays; 8 sprays (total 21.6mg tetrahydrocannabinol (THC) and 20mg cannabidiol (CBD)) four times a day,
 - or matching placebo
 - dispensed weekly.
- Psychosocial care
 - Six-sessions of individual cognitive behavioural therapy (CBT) and weekly clinical reviews.

Outcomes/Résultats

- Primary endpoints
 - use of non-prescribed cannabis (self-reported cannabis use days, urine toxicology)
 - safety measures (adverse events and abuse liability)
 - cost effectiveness (incremental cost effectiveness in achieving additional Quality Adjusted Life Years)
- Secondary outcomes
 - improvement in physical and mental health parameters,
 - substance use other than cannabis,
 - cognitive functioning
 - patient satisfaction measures

		Total N=132 (%)	Langton N=45	St George N=24	Westmead N=35	Newcastle N=28	Significance
Gender	Male, N (%)	98 (74.2)	39 (86.7)	18 (75)	25 (71.4)	16 (57.1)	P=0.081
Age	Mean (SD), years	35.4 (±10.8)	35.4 (±1.5)	36.3 (±2.1)	30.7 (±1.6)	40.4 (±2.2)	P=0.004
Country of Birth	Australia, N (%)	111 (84.1)	39 (86.7)	18 (75)	27 (77.1)	27 (96.4)	P=0.104
Education Level	Year 10, N (%)	40 (30.3)	9 (20)	4 (10)	9 (25.7)	18 (64.3)	P=0.007
	Year 12, N (%)	34 (25.8)	14 (31.1)	5 (20.8)	11 (31.4)	4 (14.3)	
	Tertiary, N (%)	52 (39.4)	19 (42.2)	14 (58.3)	14 (40)	5 (17.9)	
Income Status	Employed, N (%)	73 (55.3)	28 (33)	19 (79.2)	17 (48.6)	9 (32.2)	P=0.132
	Unemployed, N (%)	59 (44.7)	14 (31.1)	4 (16.7)	14 (40)	15 (53.6)	
Relationship Status	Married (incl. de-facto), N (%)	49 (37.1)	14 (20)	11 (45.8)	7 (20)	14 (50)	P=0.338
	Single (incl. separated), N (%)	81 (61.4)	28 (62.2)	13 (54.2)	27 (77.2)	13 (46.4)	
Living Situation	Renting, N (%)	73 (55.3)	26 (57.8)	12 (50)	19 (54.3)	16 (57.1)	P=0.682
	Mortgage, N (%)	27 (20.5)	9 (20)	5 (20.8)	5 (14.3)	8 (28.6)	
	Other (incl. homeless), N (%)	32 (24.2)	10 (22.2)	7 (29.2)	11 (31.4)	4 (14.3)	

		Total N=132	Langton N=45	St George N=24	Westmead N=35	Newcastle N=28	Significance
Substance Use History	Cannabis use: Grams/day, mean (SD)	2.33 (±2.05)	2.32 (±2.23)	2.58 (±2.61)	2.47 (±1.82)	1.96 (±1.38)	P=0.692
	Cannabis Withdrawal Scale, mean (SD) (/10) scale	3.36 (±2.12)	3.03 (±2.14)	2.73 (±2.10)	4.00 (±2.12)	3.60 (±1.97)	P=0.082
	AUDIT Score, mean (SD) (/40)	4.51 (±4.86)	0.51 (±0.46)	0.42 (±0.48)	0.31 (±0.42)	0.56 (±0.60)	P=0.159
	Tobacco user, N (%)	107 (89.2)	37 (84.1)	20 (83.3)	33 (94.3)	17 (68)	P=0.061
Cannabis Use	Marijuana Craving Questionnaire, mean (SD) (1-7)	3.93 (±1.41)	3.54 (±1.42)	3.76 (±1.43)	4.73 (±1.14)	3.69 (±1.36)	P<0.001
	Cannabis Problem Questionnaire, mean (SD) (/11)	4.24 (±1.82)	4.21 (±1.99)	3.90 (±1.67)	4.12 (±1.77)	4.73 (±1.70)	P=0.387
	Self-Coping & Efficacy for Quitting Questionnaire, mean (SD) (1-7)	3.19 (±1.13)	2.99 (±1.02)	2.80 (±0.88)	3.50 (±1.09)	3.45 (±1.41)	P=0.039

		Total N=132	Langton N=45	St George N=24	Westmead N=35	Newcastle N=28	Significance
Mental and Physical Health	Depression, Anxiety & Stress (DASS), mean (SD)	1.32 (±0.67)	1.35 (±0.65)	1.24 (±0.62)	1.12 (±0.69)	1.63 (±0.64)	P=0.021
	Depression, mean (SD)	1.20 (±0.82)	1.20 (±0.79)	1.14 (±0.84)			P=0.045
	Anxiety, mean (SD)	1.14 (±0.69)	1.14 (±0.71)	0.94 (±0.64)	0.97 (±0.83)	1.55 (±0.78)	P=0.054
	Stress, mean (SD)	1.72 (±0.81)	1.80 (±0.79)	1.69 (±0.74)	1.04 (±0.59)	1.42 (±0.73)	P=0.054
	(0-3)				1.43 (±0.90)	1.96 (±0.68)	
	Brief Psychiatric Rating Scale (day8), mean (SD)	1.32 (±0.65) [N=122]	1.19 (±0.35) [N=42]	1.19 (±0.55) [N=22]	1.69 (±0.94) [N=31]	1.19 (±0.52) [N=27]	p=0.003
	(1-7))						
Sheehan Disability Score, mean (SD) (0-10)	4.51 (±2.61)	5.20 (±2.43)	4.68 (±2.60)	3.51 (±2.55)	4.64 (±2.75)	P=0.055	
Insomnia Severity Index, mean (SD) (0-4)	1.92 (±1.07)	1.76 (±1.18)	1.67 (±0.89)	2.05 (±1.07)	2.24 (±0.99)	P=0.148	
Brief Pain Inventory, experienced pain: N (%)	70 (53)	20 (44.4)	8 (33.3)	22 (62.9)	20 (71.4)	P=0.017	

		Total N=132	Langton N=45	St George N=24	Westmead N=35	Newcastle N=28	Significance
Mental and Physical Health	<i>SF-36, mean (SD) (0-100%)</i>						
	Physical Functioning	86.09 (20.41)					
	Role Limitations – Physical	65.15 (41.42)					
	Role Limitations – Emotional	51.77 (45.18)					
	Energy/ Fatigue	42.16 (18.66)					
	Emotional Well-being	55.24 (19.24)					
	Social Functioning	58.99 (29.36)					
	Pain	70.03 (25.97)					
	General Health	51.02 (20.67)					
Social/ Other	OTI Crime: Property, N (%)	4 (3.1)	2 (4.4)	1 (4.2)	0	1 (3.6)	P=0.367
	OTI Crime: Supplied/sold drug, N (%)	14 (10.7)	10 (22.2)	2 (8.4)	0	2 (7.1)	P=0.004
		34 (26)	13 (28.9)	11 (45.8)	2 (5.7)	9 (32.1)	P=0.005
	OTI Crime: Criminal offence, N (%)						

Trial status

- Inscription commencée en 2016, terminée mi-2017
- Suivi - terminé - Décembre 2017
- Document du protocole soumis pour publication

Summary

- Traitement agoniste pour le cannabis
 - Peut avoir un rôle dans le traitement de la dépendance au cannabis
- Importance
 - Acceptation croissante de la consommation de cannabis pour le traitement médical de diverses affections
 - La décriminalisation du cannabis dans certains pays
- Peut voir l'émergence de plus de dépendance au cannabis - besoin d'être en mesure de traiter cela
- Rôle si l'émergence continue de cannabinoïdes synthétiques (par exemple, « Spice ») ou un meilleur retrait et traitement à long terme par un agoniste?



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