Overview of an RCT of cannabinoid replacement therapy (Sativex) for the management of treatment-resistant cannabis dependent patients in an outpatient setting

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Acknowledgements

• Chief investigators
  – A/Prof N Lintzeris (Uni Sydney, SESLHD)
  – Dr D Allsop (Uni Sydney)
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  – Prof I McGregor (Uni Syd, Psychopharmacology)
  – A/Prof A Dunlop (HNELHD, Newcastle Uni)
  – Dr M Shanahan (UNSW)
  – A/Prof R Bruno (Tas Uni)

• Associate Investigators
  – Drs Mark Montebello, Craig Sadler, Nghi Phung

• Funding
  – NHMRC Project Grant
  – Participating LHDs
  – GW Pharmaceuticals providing trial medications
Medications for cannabis use disorders

- Range of ‘symptomatic’ medications trialled with no consistent benefits
  - Antidepressants (nefazodone, bupropion, ....)
  - Mood stabilisers/anticonvulsants (gabapentin, lithium)
  - Anxiolytics (buspirone)
  - Alpha adrenergic agonists antihypertensive (lofexidine)
  - Norepinephrine reuptake inhibitor (atomoxetine)
  - N-acetylcysteine (NAC)

- Promise seen with agonist cannabinoid medications (e.g. dronabinol, nabilone) - as in treatment of other withdrawal syndromes (e.g. opioids, nicotine)
Why Sativex?

• Generic name: nabiximols
• Licensed for treatment
  – spasticity in MS (Australia 2014 + >15 other countries)
  – neuropathic pain in Canada, Israel
• 1:1 ratio of THC and CBD
  – Oro-mucosal spray
  – Each spray: 2.7mg THC, 2.5mg CBD
  – Plant extracted cannabinoids with rapid onset of action (unlike oral synthetic THC medications such as dronabinol, nabilone)
• RCT of Sativex for cannabis withdrawal
• N=51, inpatient trial (Sydney, Newcastle)
• Placebo-controlled double-blind RCT
• UNSW, SESLHD, HNELHD

Mean Change from Baseline for Overall Withdrawal Scores and for Symptoms that were Significantly Suppressed by Sativex

Overall Withdrawal Score

End of medication

Mean Change in Withdrawal Score

Effect size: Hedges $g$

Placebo Nabiximols

$F_{8325.5} = 2.83, P \leq .01$

Irritability

End of medication

Mean Change in Irritability Score

Effect size: Hedges $g$

Effect size: Hedges $g$

Placebo Arm

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Retention in Withdrawal Treatment

Retention rates for Placebo and Nabiximols over time. The graph shows the percentage of patients remaining in treatment at each day elapsed. The hazard ratio (HR) for Placebo compared to Nabiximols is 4.09 with a p-value of 0.05, indicating a statistically significant difference. For Nabiximols, the HR is 1.5 with a p-value of 0.35, indicating no significant difference.

No. at risk:
- Placebo: 24, 23, 22, 21, 19, 15, 12, 11, 8, 7
- Nabiximols: 27, 25, 25, 24, 23, 23, 23, 16, 11, 10
Intoxication & Testing the Blind

Intoxication scores

\[ P = 0.89 \]

Intoxication scores (0-10)

Testing the blind

- Allocated to sativex
- Allocated to placebo

What did they think they were prescribed?
Conclusions Sativex RCT1

- Sativex was effective in reducing withdrawal severity
- Sativex increased retention in withdrawal treatment
- Sativex was safe and feasible in this clinical population
  - Not intoxicating and blind maintained in both groups
- However after withdrawal 69% relapsed within the 1 month f/up
  - Current treatment (withdrawal, counselling) results in about 20-30% abstinence at 3 months
- Is there a role for longer term cannabinoid substitution treatment – as per NRT or OST?
  - The longer term use of a safer agonist to reduce unsanctioned drug use and improve health & social outcomes
SATIVEX RCT2.0: OUTPATIENT TRIAL

• NHMRC Project Grant successful to commence 2015

• Trial overview
Study Objective

• To examine the efficacy, safety and cost-effectiveness of Sativex for outpatient treatment of cannabis dependence
Specific hypotheses

• Sativex treatment will result in significantly **improved cannabis treatment outcomes** (reduced illicit cannabis use and greater treatment retention) compared to placebo

• Sativex will have an **acceptable adverse event and abuse liability profile** in a cannabis-dependent population

• Sativex treatment will be **cost effective** compared to placebo in achieving improved QALYs

• Sativex treatment will result in significant improvements in a range of physical and mental health, cognitive performance, and psychosocial functioning measures compared to placebo
Trial Sites

• Trial sites are the NSW Specialist Cannabis Clinics in SESLHD, HNELHD, WSLHD

• Sites
  – Surry Hills (SESLHD - Langton Centre)
  – Kogarah (SESLHD - StGH)
  – Parramatta (WSLHD)
  – Newcastle (HNELHD)
Participants

• **Eligibility**: cannabis dependent adults with ‘failed’ prior treatment attempts

• **N=142 subjects**: 30-40 per site
Inclusion criteria

• Aged 18 to 65 years
• Meet ICD-10 cannabis dependence criteria
• Have previously attempted but not responded to treatment for cannabis use (relapsed to regular cannabis use within 1 month of treatment cessation)
• Willing and able to provide informed consent to study procedures (including not driving or operating machinery)
Exclusion criteria

• Presence of another substance use disorder (alcohol, other illicit or prescription drug dependence, diagnosed by trial MO, including UDS)
• Severe **medical** (e.g. pain, hepatic, cardiovascular disease) or **psychiatric** disorder (e.g. recent drug-induced psychosis, schizophrenia, severe affective disorder), assessed by trial MO
• pregnant or lactating women (urine β-hCG)
• concerns regarding safe storage of medication (e.g. homeless, child protection concerns)
• not available for follow-up (e.g. likely travel or imprisonment)
Recruitment

• Media advertisements and flyers/posters
• **Screening**: Phone or in person by research staff. If person screens positive, then refer to a trial site for assessment & +/- enrolment
• **Assessment**: clinical assessment (trial MO), UDS (& other investigations prn), baseline research interview, written informed consent
• **Randomisation** stratified by site (1:1)
Trial design

Recruitment & Randomisation
N=142

Research Interviews

Week 0 4 8 12 24

Sativex (12 week treatment + 1 week taper)
Case Management + CBT
Follow-up

Placebo (12 week treatment + 1 week taper)
Case Management + CBT
Follow-up

Cognitive performance assessment

Follow-up
Treatment conditions

• Standardised interventions
  – Case management: weekly semi-structured review by research nursing staff
  – Medical reviews at Wks 1, 2, 4, 8, 12
  – Counselling: standardised (manualised) 6-session CBT/MI intervention delivered by trial funded staff

• Monitoring
  – UDS weekly (to identify extra cannabis use)
  – 4 weekly UDS for other drug use
Trial medications

- Dose of Sativex individually titrated to max 8 sprays per dose (21.6mg THC, 20mg CBD), up to 4 times a day (max 32 sprays per day)
- Sativex is dispensed in 10 ml containers, each delivering 90 metered sprays
- Medication dispensed once a week (3 bottles)
- S8 storage and Drug Register
- Participants asked to keep a daily dosing diary
- Weighed on return
Research interviews

- Confidential research interviews with participants at Wks 0 (baseline), 4, 8, 12 (maintenance phase) and 24 (f/u)

- Instruments include:
  - substance use (TLFB of cannabis and other substance use past 4 weeks)
  - health & psychosocial measures (SF-36, DASS-21, PHQ-15, OTI-crime)
  - adverse events
  - medication use, health service utilisation, consumer satisfaction measures

- Participants reimbursed $40 voucher per interview
Assessing cognition

• Aim is to examine if Sativex use is associated with cognitive impairment relative to placebo and relative to baseline

• Cognitive assessments at baseline (Wk 0), ‘maintenance’ dose levels (Wk 8) and after cessation medications (Wk 24)
  – A targeted series of tests sensitive to acute THC effects
  – Reaction Time Index (RTI), Rapid Visual Information Processing (RVP), Stop Signal Task (SST), Wechsler Test of Adult Reading, Ray Auditory Verbal Learning Test

• At Wk 8 assessment, cognitive testing performed 30 minutes prior to (trough) and 30 minutes after (peak effects) supervised dose. Blood samples taken for cannabinoid levels (THC, CBD)
Co-ordinating the project

• Investigators meeting
  – Chaired by CIA
  – Chief and Associate Investigators
  – Once every 1-2 months and is key decision making group for trial

• Clinical-research meetings
  – Chaired by Trail co-ordinator
  – Key clinicians and RAs from each site
  – Meet 2-4 weekly teleconferences to address operational issues

• Local site meetings
Regulatory issues

- **HREC issues**
  - NEAF: SESLHD (multisite HREC)
  - Local SSAs

- **Medication issues**
  - Clinical Trial Notification to TGA with registration for each site
  - Each participant will need an application for S8 medication to drug dependent person (PSU)
  - Import licenses

- **Contracts between institutions**
  - University of Sydney (sponsor) with each LHD
  - University of Sydney with GW Pharmaceuticals
# Project timelines

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<th>ACTIVITY</th>
<th>2015</th>
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<td><strong>ESTABLISHMENT: 9 MONTHS</strong> (Finalise study protocols &amp; ethics, staff recruitment and training)</td>
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<td><strong>RECRUITMENT, TREATMENT &amp; DATA COLLECTION</strong> Staggered recruitment over 4 sites (target of 36 participants per site to be recruited in 12 months), treatment (3/12) &amp; research follow-up (6-months) after last participant recruited.</td>
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<td><strong>DATA ANALYSIS AND DISSEMINATION: 6 MONTHS</strong></td>
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