Supplementary Online Content


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**eFigure 3.** Time to relapse following discharge from the hospital

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Urine and blood cannabinoid toxicology analysis.

Cannabinoid plasma analysis

Cannabinoids were extracted from 0.5 mL plasma samples using Styre Screen® SSTHC063 solid phase extraction columns (60 mg/3 mL) from United Chemical Technologies (PA, USA) as per manufacturer instructions. Briefly, 2 mL cold acetonitrile was added to each sample to precipitate plasma proteins. The supernatant was aspirated following centrifugation, reduced to 200 uL using a vacuum concentrator and diluted to 2 mL with distilled water. The diluted sample was loaded directly onto the column, washed with 1 mL Water/Acetonitrile/Ammonia (84:15:1), dried under vacuum and eluted with 3 mL Hexane/Ethyl Acetate/Glacial Acetic Acid (49:49:2). Extracts were dried under nitrogen at 60°C and reconstituted in 50μL initial mobile phase (40% methanol and 60% 10 mM ammonium acetate) for analysis. Chromatographic separation was performed on a Pinnacle DB Biphenyl column (100 mm x 2.1 mm, 1.9 μm) from Restek Inc (PA, USA) via gradient elution at 0.3 mL/min using a Shimadzu Nexera™ ultra high performance liquid chromatograph (Shimadzu Corp, Kyoto, Japan). Analyte and internal standard ion transitions were acquired via multiple reaction monitoring using a Shimadzu 8030 triple quadrupole mass spectrometer operated in positive atmospheric pressure chemical ionisation mode. Cannabinoid standards obtained from Cerilliant® (TX, USA) were diluted to yield stock solutions for calibrator and quality control (QC) sample preparation. Drug-free human plasma (Australian Red Cross Blood Service, NSW, Australia) was fortified with stock solution to form calibrators and QC samples covering concentration ranges 1-40 ng/mL for CBD, 0.5-20 ng/mL for THC, 5-200 ng/mL for THC COOH and 2.5-100 ng/mL for 11OH THC. The limits of quantification were 1.5, 0.5, 5 and 4 ng/mL, respectively.

Cannabinoid urine analysis

Urinalysis was performed under commercial in confidence procedures by the Toxicology unit, a business unit of the Northern Sydney Central Coast Area Health Network and a subunit of the Pacific Laboratory Medicine Services (PaLMS). The Toxicology Unit works to the Australian Standard AS/NZS4308 and is accredited by the National Association of Testing Authorities, Australia under category 10.61.16 Drugs for toxicological purposes to AS/NZS 4308 (2001) to perform both clinical and medico-legal drugs of abuse testing. The Toxicology Unit operates in accordance with IS/IEC 17025.
eTable 1. Mapping of Cannabis Withdrawal Scale items to proposed *DSM-5* cannabis withdrawal symptom groupings.

<table>
<thead>
<tr>
<th>DSM-5 symptom category</th>
<th>Items on the Cannabis Withdrawal Scale&lt;sup&gt;a&lt;/sup&gt;</th>
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| Irritability, anger or aggression    | - I had some angry outbursts  
- I had mood swings  
- I was easily irritated                                           |
| Nervousness or anxiety               | - I felt nervous                                                                                           |
| Sleep difficulty (insomnia)          | - I woke up early  
- Nightmares and/or strange dreams  
- Trouble getting to sleep                                           |
| Decreased appetite or weight loss    | - I had no appetite                                                                                       |
| Restlessness                         | - I felt restless                                                                                         |
| Depressed mood                       | - I felt depressed  
- Life felt like an uphill struggle                                                                               |
| Physical symptoms.                  | - I had a headache  
- I felt nauseous (like vomiting)  
- I had a stomach ache  
- I felt physically tense  
- I had hot flashes  
- I woke up sweating at night   |
| Cannabis cravings                    | - I have been imagining being stoned  
- All I could think about was smoking some cannabis                                                  |

<sup>a</sup> Mean CWS scores are reported in this study (instead of sum total as in previous studies) as the analysis for DSM5 symptom groupings takes mean values across items where multiple items contribute to a DSM5 symptom grouping. The mean value is mathematically equivalent to the sum total for the purposes of the analyses.
eFigure 1. Mean creatinine-normalized urine THC-COOH levels measured at baseline (premedication), the evening of day 3 of inpatient stay (peak dose), and at 28-day follow-up.
eFigure 2.

Mean plasma cannabinoid levels (THC and CBD) and cannabinoid metabolite levels (THC-COOH and 11-OH-THC) on day 1 (premedication; n = 19 for placebo, n = 23 for nabiximols), day 3 (peak dose; n = 19 for placebo, n = 23 for nabiximols), and day 7 (1st day with no medication; n = 10 for placebo, n = 20 for nabiximols) split between treatment groups.
eFigure 3.

Time to relapse following discharge from the hospital.