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Cannabidiol for At Risk for psychosis Youth (CanARY): A Randomised Controlled Trial

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Short/running title: CanARY study protocol

Key words: Cannabidiol; youth; ultra-high risk; psychosis; RCT.

ABSTRACT

Background: No biological treatment has been firmly established for the at-risk stage of psychotic disorder. In this study we aim to test if subthreshold psychotic symptoms can be effectively treated with cannabidiol (CBD), a non-psychoactive compound of the plant Cannabis sativa. The question has taken on increased importance in the wake of evidence questioning both the need and efficacy of specific pharmacological interventions in the ultra-high risk (UHR) for psychosis group.

Methods: Three-arm randomised controlled trial of 405 patients (135 per arm) aged 12-25 years who meet UHR for psychosis criteria. The study includes a 6-week lead-in phase during which 10% of UHR individuals are expected to experience symptom remission. Participants will receive CBD (per oral) at doses 600 mg or 1000 mg per day (fixed schedule) for 12 weeks. Participants in the third arm of the trial will receive matching placebo capsules. Primary outcome is severity of positive psychotic symptoms as measured by the Comprehensive Assessment of At-Risk Mental States (CAARMS) at 12 weeks. We hypothesise that CBD will be significantly more effective than placebo in improving positive psychotic symptoms in UHR patients. All participants will also be followed up 6 months post baseline to evaluate if treatment effects are sustained.

Conclusion: This paper reports on the rationale and protocol of the Cannabidiol for At Risk for psychosis Youth (CanARY) study. This study will test CBD for the first time in the UHR phase of psychotic disorder.

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1 INTRODUCTION

Schizophrenia and related psychotic illnesses are amongst the most disabling and costly disorders for health care systems (Zeidler, Slawik, Fleischmann, & Greiner, 2012; Christensen et al., 2020). For most patients, an often prolonged period of prodromal subthreshold psychotic symptoms and impaired functioning precedes the first psychotic episode (Yung et al., 1996). Intervening at this stage might have greatest impact through delaying, or even preventing, the onset of fully-fledged psychotic disorder or other unfavourable mental health outcomes (Lin et al., 2015).

1.1 The ultra-high risk stage

In the 1990s, our research team developed operational criteria for prospectively identifying help-seeking young people at increased risk of developing a psychotic disorder in the near future (Yung et al., 1998). This clinical population is described as having an “at risk mental state”, or as being at “ultra-high risk” (UHR) for psychosis. Subsequently, in the US, the term “clinical high risk” was coined (Cornblatt, Lencz, & Obuchowski, 2002). The development of these criteria stimulated a wave of new prediction research and clinical trials internationally over the past two decades (Fusar-Poli et al., 2013), with a major impact on the field of early psychosis. Since our first intervention trial in UHR individuals that aimed to reduce the rate of transition to first episode psychosis in the late 1990s (McGorry et al., 2002), 25 further RCTs have been conducted in UHR cohorts, testing a range of psychological, pharmacological, nutritional and multi-component psychosocial interventions in a total of 2,351 participants (Mei et al., 2021). In this latest meta-analysis, cognitive behavioural therapy (CBT) was associated with a reduction in incidence at 12-months, with benefit maintained at 18-48-months, while all other outcomes were non-significant. Integrated psychosocial interventions have also been shown to be effective (Bechdolf et al., 2012; Nordentoft et al., 2006). Antipsychotic medication has shown some efficacy in earlier trials (McGlashan et al., 2006), but they are not recommended as first-line treatment for UHR patients because of their side effects and the associated stigma. Accordingly, the NICE (https://www.nice.org.uk/guidance/cg155) and the Australian Clinical Guidelines for Earl Psychosis (2nd Edition, 2016) state to not offer antipsychotic medication for psychotic symptoms or mental state changes that are not sufficient for a diagnosis of psychosis or schizophrenia and there is no difference in recommendations for youth and adults regarding the use of antipsychotic medication in UHR patients. Omega-3 fatty acids have shown a strong and sustained benefit in one double-blind randomised placebo-controlled trial (Amminger et al., 2010), but we could not replicate this finding in a subsequent larger-scale study (the NEURAPRO study) (McGorry et al., 2017). Furthermore, while psychosocial

treatments often seem effective in the UHR stage, genuinely reducing the early risk of transition to psychosis, they do not typically result in full remission of all types of symptoms, functional recovery or definitive cure (Beck et al., 2019). They also may not directly influence core biological processes that are potentially relevant for illness progression such as dopaminergic and serotoninergic neurotransmission, oxidative stress and inflammation. The key message from recent meta-analyses and clinical data is that further research to expand the range of safe biological agents is urgently required (Davies et al., 2018).

1.1.2 Neuroprotection, oxidative stress and inflammation

Current biological treatment options for psychotic disorders have predominantly centred on the dopamine theory of psychosis onset. However, it is unclear how useful this pathoetiological model is likely to be for UHR patients (Egerton et al., 2014; Kaur & Cadenhead, 2010). There is now a body of evidence to support a role for both inflammation and oxidative stress in the pathophysiology of psychotic disorders (Fineberg & Ellman, 2013; Flatow, Buckley, & Miller, 2013)1, including evidence of increased blood concentrations of inflammatory cytokines at least in a sub-set of patients (Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011). Inflammatory abnormalities have also been shown in medication-naïve first episode patients and in UHR patients (Mongan, Ramesar, Föcking, Cannon, & Cotter, 2019), suggesting the association could be independent of antipsychotic treatment. Furthermore, levels of some inflammatory molecules vary with the clinical status of patients, which could indicate separate groups of state and trait markers (Kirkpatrick & Miller, 2013).

Oxidative stress is also well documented in schizophrenia (Flatow et al., 2013), in first-episode psychosis (FEP) (Fraguas, Díaz-Caneja, Rodríguez-Quiroga, & Arango, 2017) and UHR patients (Lavoie et al., 2017; Perkins et al., 2014). Importantly, inflammation and oxidative stress can induce each other in a positive feedback manner (Bitanihirwe & Woo, 2011). The incorporation of these factors and processes into traditional neurotransmitter based models facilitates a more comprehensive understanding of disease, potentially relevant to the progression of illness in psychosis (Berk, Yucel, & McGorry, 2011). In turn this has facilitated the identification of new therapeutic targets and neuroprotective treatments with the potential to interrupt neurotoxic cascades (Dodd et al., 2013). Cannabidiol (CBD) has strong anti-inflammatory (Burstein, 2015; Rajan et al., 2016), antioxidant (Rajan et al., 2016) and neuroprotective properties (Campos et al., 2017), suggesting it may offer a viable treatment and preventative strategy during early stages of psychosis when functional and structural brain alterations can occur (Jalbrzikowskime et al., 2019).

1.1.3 Need for treatments with a favourable risk-benefit ratio

Pharmacological intervention in UHR stage has been questioned because only a minority of patients develop a full-threshold psychotic disorder. Treatment agents investigated in the pre-psychotic phase of psychotic disorders must have a favourable risk-benefit ratio to avoid exposing a substantial proportion of 'false positives' for psychosis transition to unwanted side effects. The favourable safety profile of CBD in humans has been consistently shown in two reviews (Bergamaschi, Queiroz, Zuardi, & Crippa, 2011; Iffland & Grotenhermen, 2017) and one meta-analysis (Chesney et al., 2020). The majority of the clinical studies included in these reviews were performed for treatment of epilepsy and psychotic disorders. The most commonly reported side effects were tiredness, diarrhoea, and changes of appetite/weight. Most adverse events were mild or moderate in severity. In comparison with other drugs used for the treatment of psychotic disorders, CBD has a more favourable side effect profile. This could improve compliance and adherence to treatment in young people. More recent observations of declining rates of psychosis transitions in UHR samples further highlight the need for benign interventions (Nelson et al., 2016).

1.3 The endocannabinoid system

Accumulating evidence suggests a role of the endocannabinoid system in the pathophysiology of schizophrenia and other psychotic disorders (Leweke & Koethe, 2008). For example, epidemiological studies indicate that the use of cannabis increases the risk for developing schizophrenia (Arseneault, Cannon, Witton, & Murray, 2004; Moore et al., 2007), and is associated with lower age of onset of the illness (Veen et al., 2004). A systematic literature review in UHR individuals found current cannabis use was frequent in approximately a quarter of patients and commonly reported in association transition to psychosis (Farris et al., 2020). In patients with schizophrenia, cannabis use has been related to higher relapse rates, poor treatment outcome, and increased severity of symptoms,(Foti, Kotov, Guey, & Bromet, 2010) as well as accelerated loss of grey matter volume (Rais et al., 2008). In addition, schizophrenia patients show increased levels of endogenous cannabinoids in cerebrospinal fluid (Giuffrida et al., 2004; Leweke, Giuffrida, Wurster, Emrich, & Piomelli, 1999). Neuroimaging studies measuring in vivo CB1 receptor availability in schizophrenia patients reported a widespread increase in levels of CB1 receptors, including the nucleus accumbens, insula, cingulate cortex, inferior frontal cortex, parietal cortex, mediotemporal lobe and pons (Ceccarini et al., 2013; Wong et al., 2010). The endocannabinoid system is also one of the most important neurotransmitter systems in the brain that mainly fulfils a homeostatic role by modulating other neurotransmitter systems and processes related to inflammation (Leweke, Mueller, Lange, & Rohleder, 2016). Specifically, the upregulation of anandamide (Leweke, 2012) and an increase in CB1

receptor availability (Ceccarini et al., 2013) may have a therapeutic and potentially even protective effect on positive psychotic symptoms. This hypothesis is supported by findings that UHR patients with higher anandamide levels in CSF were found to have a lower risk of transitioning to FEP (Koethe et al., 2009). Furthermore, an increase in serum anandamide levels was significantly associated with clinical improvement in patients with schizophrenia or schizophreniform psychosis who received 800 mg of CBD per day for 4 weeks in a controlled clinical trial (Leweke et al., 2012). Based on these findings, it has been suggested that anandamide may be able to counteract neurotransmitter abnormalities such as dopaminergic or glutamatergic abnormalities in UHR and in psychosis patients. These results also support the hypothesis that CBD exerts its antipsychotic properties by a moderate fatty acid amide hydrolase inhibition (Leweke, 2012).

1.3.1 Cannabidiol

Cannabis contains multiple compounds that may have different psychoactive properties (Fernández-Ruiz et al., 2013). In particular, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant and both can modulate psychotic and anxiety symptoms (Fusar-Poli et al., 2009). CBD has therapeutic properties for numerous disorders exerted through molecular mechanisms that are yet to be completely identified (Hurd, 2017). CBD acts in some experimental models as an anti-inflammatory, anticonvulsant, anti-oxidant, anti-emetic, anxiolytic and antipsychotic agent, and is therefore a potential medicine for the treatment of neuroinflammation, epilepsy, oxidative injury, vomiting and nausea, anxiety and schizophrenia, respectively (Fernández-Ruiz et al., 2013). CBD appears to have the ability to counteract the psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC or ketamine administration (Hallak et al., 2011). These effects are possibly mediated by opposite effects of CBD and THC on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia and other psychotic disorders, such as the striatum, hippocampus and prefrontal cortex (Bhattacharyya et al., 2010; Fusar-Poli et al., 2009).

1.3.1.1 Treatment of psychotic symptoms

Four studies have been published in which patients with schizophrenia were treated with CBD. In a case report, successful treatment with 1200mg/day CBD was described in a 19-year old female with schizophrenia (Zuardi, Morais, Guimarães, & Mechoulam, 1995). Therapy of three treatment resistant schizophrenia patients with escalating doses up to 1280 mg/day of CBD was described, of whom only one patient showed symptom improvement (Zuardi et al., 2006). The authors speculate that a low initial CBD dose and the treatment resistance in these patients might explain this negative finding. Leweke et al (Leweke et al.,

2012) performed an RCT of CBD (N=20) vs. amisulpride (N=19) in schizophrenia. After 4 weeks of treatment (maximum of 800 mg/day orally), both CBD and amisulpride resulted in significant clinical improvement as measured with both the Positive and Negative Symptom Scale and Brief Psychiatric Rating Scale. It is important to note that CBD treatment displayed a markedly superior side-effect profile in this study (Leweke et al., 2012). In the second clinical trial of CBD treatment for schizophrenia , McGuire et al (McGuire et al., 2018) found people with schizophrenia (N=88) receiving CBD (1000 mg/day orally) for 6 weeks, alongside their existing antipsychotic medication, had significantly lower levels of positive psychotic symptoms, were more likely to have been rated as clinically improved, and had better cognitive performance when compared with the placebo group. These findings suggest that CBD has beneficial effects in patients with schizophrenia who have not responded to conventional D2 blocking antipsychotic medication. The results also support the view that CBD's effects do not appear to depend solely on dopamine receptor antagonism (Pacher, Bátkai, & Kunos, 2006). The studies of CBD as antipsychotic treatment in psychotic patients are promising in that participants exhibited significant clinical improvement from CBD treatment (Iseger & Bossong, 2015; Leweke et al., 2012; McGuire et al., 2018). This agent may represent a new class of treatment for schizophrenia and other psychoses with specific advantages for early intervention and non-responder groups.

Further scientific evidence for a role of CBD in the treatment of emerging psychotic symptoms in UHR patients comes from a functional MRI study conducted at the Maudsley Hospital in London (Bhattacharyya et al., 2018). In this study 16 UHR participants received a single oral dose of 600 mg of CBD, while 17 participants received a placebo. Results were that CBD normalised alterations in parahippocampal, striatal, and midbrain function associated with the UHR state (Hager & Keshavan, 2015). As these regions are critical to the pathophysiology of psychosis, the influence of CBD at these sites could underlie its therapeutic effects on psychotic symptoms (Bhattacharyya et al., 2018).

1.3.1.2 Treatment of anxiety and mood symptoms

The early stages of mental disorders are characterised by a range of non-specific symptoms, which typically precede and accompany more specific phenomena (Yung & McGorry, 1996) (McGorry, 2014). Prodromal symptoms of the range of outcome syndromes overlap substantially and intensify and recede over time. This is well illustrated by the UHR for psychosis criteria, as these criteria not only predict subsequent psychosis, but also other syndromal and functional outcomes (Amminger, Schäfer, Schlögelhofer, Klier, & McGorry, 2015; Lin et al., 2015). Our long term follow up study revealed that 70% of UHR patients who did not develop psychosis had non-psychotic disorders over a 2-14 year follow up

period, primarily mood disorders (49%) and anxiety disorders (35%) (Lin et al., 2015). Similar figures have been reported in other samples (Addington et al., 2011) (Beck et al., 2019). Anxiety and depression effect many aspects of life, including social life, productivity and health. CBD has antidepressant-like and anxiolytic-like properties based on animal models (Blessing, Steenkamp, Manzanares, & Marmar, 2015; Sales, Crestani, Guimaraes, & Joca, 2018) and small studies in humans (Blessing et al., 2015), making it an even more promising treatment for the UHR phase.

1.3.1.3 Side effects

Basic research and animal studies (reviewed by (Bergamaschi et al., 2011)) suggest that CBD is non-toxic in non-transformed cells and does not affect food intake, physiological parameters (heart rate, blood pressure and body temperature), gastrointestinal transit, psychomotor or psychological functions and does not induce catalepsy. Also, chronic use and high doses up to 1500 mg/day of CBD are reportedly well tolerated in humans. Consistent with this review, McGuire et al. in their RCT of CBD (1000 mg/day; N=43) or placebo (N=45), found only one-third of the patients in both the CBD and the placebo group reported treatment-emergent adverse events. The majority of these were mild and resolved spontaneously, with no significant differences in frequency between the CBD and placebo groups (McGuire et al., 2018). This is also in line with observations of patients with schizophrenia (Leweke et al., 2012; Zuardi et al., 2006), and patients with other disorders (Zuardi et al., 2012), all of which indicate that CBD has a favourable tolerability profile. A recent literature review (Iffland & Grotenhermen, 2017) confirmed and extended the previous safety report (Bergamaschi et al., 2011). This review included also data from clinical trials in children suggestive of an adequate safety profile in this age group.

2 STUDY RATIONALE

Spearheaded from 1992 by the work of EPPIC and its international collaborators, and since 2001, Orygen in Melbourne (McGorry, Goldstone, Parker, Rickwood, & Hickie, 2014; McGorry, Killackey, & Yung, 2008), a paradigm shift has occurred from largely palliative psychiatry to pre-emptive psychiatry (Insel, 2010). This work built an approach which gave rise to clinical staging and has informed the design of the current study (McGorry, 2010). The clinical trial presented here focuses on Stage 1b: UHR, which involves a need for care before the threshold for use of conventional D2 receptor blocking antipsychotic medication is reached. As outlined above, it is based on the manifest need to further extend the evidence base for biological treatments in UHR patients, since no biological treatment has been established for this stage of psychosis. CBD is a promising candidate for testing due to its favourable safety and tolerability profile and strong preliminary evidence for its efficacy

in psychosis (see 1.3.1.1). Moreover, CBD acts on targets (e.g., oxidative stress (Rajan et al., 2016), inflammation (Burstein, 2015; Rajan et al., 2016), neuroprotection (Campos et al., 2017)) that are unrelated to D2 receptor blockade (Renard, Norris, Rushlow, & Laviolette, 2017). These neuroprotective properties of CBD are specifically relevant to the *timing* and the *duration* of intervention in this proposal. Neuronal circuits in the brain are shaped during critical periods of development. Therefore, effective intervention during a circumscribed period of increased susceptibility (i.e., the UHR stage) can have longer-term effects. UHR patients are in a critical developmental stage (i.e., adolescence) during which pathophysiological conditions (for example, oxidative stress) are potentially more harmful since they are affecting the developing brain. At the same time, this critical period provides a window of opportunity for intervention, when relatively brief treatment can lead to transformative benefits. This view that a brief intervention during a critical period can change the developmental trajectory, ultimately leading to a different outcome in adulthood, is supported by one of our previous RCTs in UHR patients (Amminger et al., 2015). In this study, a 12-week intervention with omega-3 fatty acids prevented transition to full-threshold psychotic disorder and led to sustained symptomatic and functional improvements for 7 years (median). Furthermore, CBD has antidepressant-like and anxiolytic-like properties (Blessing et al., 2015; Sales et al., 2018). This suggests that it may be effective for treating the depression and anxiety symptoms typically experienced by UHR patients, irrespective of transition to psychosis.

The follow-up assessment at 6 months will allow us to determine if therapeutic effects are sustained after the study medication has been ceased, or if longer treatment is needed. Addressing this question is relevant to young people who usually prefer a short intervention period. Based on our follow-up data, UHR patients are at longer-term risk for psychotic disorder, with the highest risk in the first 2 years (Nelson et al., 2013). We have previously found that retention for 6–24 months in clinical trials is challenging and usually not feasible (i.e., due to drop out, resulting in an unrepresentative sample). Therefore, the primary outcome in our trial is not transition to psychosis but impact on a crucial proximal target i.e., severity of positive symptoms, a continuous measure that is sensitive to short-term changes. We have shown that if these are studied over multiple time points, the “dynamic of response” to treatment is highly predictive for future mental health outcomes and need for care (Nelson, McGorry, Wichers, Wigman, & Hartmann, 2017b).

3 STUDY AIM

The main study aim is to test if subthreshold psychotic symptoms in an UHR group (using criteria by (Yung et al., 2005)) can be effectively treated with cannabidiol (CBD), a non-

psychoactive compound of the plant *Cannabis sativa*. Since the therapeutic action of CBD does not appear to depend on dopamine receptor antagonism (Leweke et al., 2012; McGuire et al., 2018), this agent may represent a new class of treatment for UHR patients when treatment with conventional antipsychotic medication is controversial and has no good evidence base. A secondary aim is to test biological markers that may moderate and mediate response to this treatment.

4 STUDY DESIGN

Multi-centre, three-arm, 12-week RCT of 2 doses of CBD and placebo in UHR patients. The study treatments will be provided in addition to bi-weekly cognitive behavioural case management (CBCM; 6 sessions) in both groups. Participant, researcher and clinician will be 'blind' to treatment group allocation ('triple blind'). All participants will be engaged with a therapist/case manager for the duration of the trial, and if taking antidepressant medication at study entry, will continue on a stable dose for the duration of the study. The primary outcome (severity of positive symptoms) will be at the end of week 12, with a further assessment at 6 months to assess whether treatment effects are sustained. Additional longer-term follow-up data will be collected in participants who reach 12 and 24 months from baseline during the study period. The study will have a 6-week lead in period to ensure symptom stability prior to drug exposure during which potential participants will be offered basic supportive counselling, as in the initial 6 weeks of our current sequential multiple assignment randomised trial (Nelson et al., 2017a). Based on findings from this trial, 90% UHR individuals are expected to still meet inclusion criteria after the lead in period. After the 12-week intervention period all participants will routinely be offered "treatment as usual" at the study sites to assure continuation of evidence based state-of-the-art care. Blinding to allocation will be maintained until the entire study period is completed and the dataset is locked – for participants, clinicians, and staff administering study instruments. Participants will be informed that they will be entering a controlled trial and will receive an active drug or placebo. The trial protocol will adhere to the 'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT-PRO)(Calvert et al., 2018) and findings will be reported according to the CONSORT statement (Schulz, Altman, Moher, CONSORT Group, 2010).

4.1 Study criteria

Study inclusion and exclusion criteria, UHR criteria, and discontinuation criteria are shown in Tables 1-3.

4.2 Randomisation

Participants will be randomised to receive either 600 mg or 1000 mg of CBD per day or

placebo in a ratio of 1:1:1, stratified by trial site and antidepressant treatment (on stable dose). The stratified randomisation will be computerised and will be conducted with permuted blocks within each stratum. The clinical trial supply company will prepare the product specification file and prepare and label all trial drugs for study sites based on the randomisation sequence. All personnel involved in the study will be blinded to the randomisation sequence throughout the trial, except for the trial pharmacists at each site. Blinding of participants and raters will be assessed after the first treatment session (on day 0) and at primary outcome (week 12).

4.3 Measures

4.3.1 Primary outcome measure

The primary outcome is severity of positive psychotic symptoms determined by the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005). Symptom severity will be operationalised, as described by Morrison et al (Morrison et al., 2012), as the summed scores of the product of global rating scale score (0-6) and frequency (0-6) of the four positive symptom subscales ranging from 0 to 144, with higher scores representing a composite score of greater symptom severity and frequency. The CAARMS is sensitive to change and has been specifically designed for the assessment of UHR patients (Yung et al., 2005). While other symptomatic and functional outcomes are hypothesised to be impacted by CBD, in this study we are particularly interested in the antipsychotic properties of this novel agent.

4.3.2 Secondary outcome measures

All instruments are widely used clinical scales for UHR patients and guarantee standardized assessment when used with interview guides and operationalized anchor points. The secondary measures used are:

- Transition to psychotic disorder, negative symptoms and distress associated with positive psychotic symptoms will be assessed using the CAARMS.
- Depression will be assessed by the Montgomery Asberg Depression Rating Scale (MADRS).
- Anxiety symptoms will be assessed by the Hamilton Anxiety Rating Scale (HAM-A) and the Overall Anxiety Severity and Impairment Scale (OASIS).
- General psychopathology will be assessed using the Positive and Negative Syndrome Scale (PANSS).
- Functioning will be assessed by the Social and Occupational Functioning Assessment Scale (SOFAS).

- Overall clinical improvement will be assessed by the Clinical Global Impression-Improvement (CGI-I) scale, which ranges from 1 to 7, with lower scores indicating more improvement, as compared with baseline. A score of 1 or 2 reflects a substantial, clinically meaningful improvement.
- Quality of life will be measured using the Assessment of Quality of Life – six dimension (AQoL- 6D) which can be used in both adolescents and adults. The advantage of this measure is that it also allows the calculation of quality-adjusted life years (QALYs). QALYs are the preferred outcome metric of economic evaluations as they allow practical 'value-for-money' judgements to be made (e.g., $50,000/QALY is a commonly used threshold in Australia).
- Costs will be measured using Medicare and Pharmaceutical Benefits Scheme service use data (with participant consent), supplemented by collaborator Mihalopoulos' Resource Use Questionnaire, developed for mental health economic evaluations undertaken in Australia.

4.3.3 Additional measures

- **Demographic variables** will include age, living situation, years of education, employment status, marital status, source of income and neighbourhood socioeconomic status.
- **Diagnostic:** The Structured Diagnostic Clinical Interview for DSM-5 (SCID) measures the full range of Axis I psychiatric disorders.
- **Substance use:** The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) will be used to assess tobacco, alcohol and illicit substance use.
- **Physical examination:** Weight, height, blood pressure, pulse, waist and hip circumference.
- **Laboratory measures:** (1) Routine blood tests for exclusion criteria and safety will comprise urea/electrolytes, glomerular filtration rate, liver/thyroid function test, full blood examination, clotting and pregnancy test (only at baseline); (2) Plasma and urine levels of CBD and three of the major CBD metabolites: 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD; (3) Inflammatory cytokines including, TNFα, IL-1A, IL-1β IL-6, and IL-10, high-sensitivity C-reactive protein, growth factors (BDNF) and oxidative stress measures (e.g., 3-nitrotyrosine, malondialdehyde) will be assessed in plasma; (4) To verify substance use objectively, we will assay urine samples (see Table 4) for presence of cannabinoids, opioids, cocaine, methamphetamine and its major metabolite amphetamine, benzodiazepines and MDMA.

- All laboratory measures except for routine tests will be used in secondary exploratory analyses testing associations between biomarkers and clinical outcomes.
- **Treatment compliance:** Treatment adherence will be assessed by monthly pill counts over the course of the study and objective quantification of cannabinoid levels in regular urine samples throughout treatment.

The schedule of visits and assessments is shown in Table 4.

5. STUDY INTERVENTIONS

5.1 Experimental intervention

Doses between 800 and 1280 mg/day of orally administered CBD have been found effective and well-tolerated in clinical studies of people with schizophrenia (Leweke et al., 2012; McGuire et al., 2018; Zuardi et al., 2006) while in UHR patients, a single dose of 600 mg CBD was found to partially normalise alterations in brain activity in regions critical to the pathophysiology of psychosis (Bhattacharyya et al., 2018). Based on these existing studies (Leweke et al., 2012; McGuire et al., 2018; Zuardi et al., 2006), participants will be randomly assigned in a 1:1:1 ratio to receive CBD (per oral) doses of 600mg or 1000 mg per day (fixed schedule – 2x capsules in the morning and 3x capsules in the evening) for 12 weeks. All CBD capsules contain 200mg active CBD. For the 600mg group, one capsule in the morning and one capsule in the evening will be placebo capsules. Participants in the third arm of the trial will receive a matching placebo for all capsules.

5.1.2 Toxicity and overdose: CBD is safe at high doses and non-toxic based on animal studies (Bergamaschi et al., 2011; Iffland & Grotenhermen, 2017; Sachs, McGlade, & Yurgelun-Todd, 2015). Any overdose in the trial will be managed as an adverse event, in accordance with GCP (R2) requirements.

5.2 Control intervention

Control participants will be administered a placebo. To ensure blinding, placebo capsules will be carefully matched in appearance, flavour and packaging with the active treatment.

5.3 Cognitive behavioural case management

Cognitive behavioural case management (CBCM) consists of CBT embedded within case management, as successfully developed and implemented in our previous UHR studies (e.g., NEURAPRO (Markulev et al., 2015). The CBT consists of four modules addressing attenuated psychotic symptoms, stress management, negative symptoms/depression and other comorbidities. All modules consist of psychoeducation, behavioural strategies/experiments and cognitive restructuring. The treatment approach is modular and

based on shared formulation with the individual client; it therefore does not prescribe which module should be delivered or for how long. The treatment components are provided within a case management framework addressing practical issues. The standard will be to deliver CBCM sessions fortnightly for 12 weeks (6 sessions), but frequency of sessions will be flexible depending on the participant's needs. Sessions will be 30-50 minutes in duration.

5.4 Concomitant medication

Benzodiazepines and zolpidem (as clinically indicated) will be allowed, as will the continuation of a prescribed antidepressant if compliant with study exclusion and discontinuation criteria. Concomitant medications will be collected at each assessment time point. All treatments administered to 12 weeks will be recorded.

5.5 Safety

A record will be made of any adverse event that arises during the trial. Any adverse event will be managed and reported according to National Health Medical Research Council, Australia, standards, following good clinical practice. In this study, any undesirable medical condition occurring from the time of signing consent (even if no study treatment has been administered) will be considered to constitute an adverse event.

6 BIOMARKER ANALYSES

The CanARY trial provides an opportunity for an authoritative biomarker study of CBD's effects, with clarification of its mechanisms of action and identification of predictors of response in UHR patients. Biomarkers analysed in the study include: (1) cannabinoids; (2) immuno-inflammatory and oxidative stress measures; and (3) hair cortisol. The rational and methods of the biomarker analyses will be provided in a separate paper.

7 STATISTICAL ANALYSIS

7.1 Sample size and power

The power calculation is based on applying analysis of variance to compare the three treatment groups on the primary outcome measure and then conduct Fisher's LSD test for pairwise comparisons. There is no previous data of the effect of CBD on CAARMS positive symptoms. As the range of the CAARMS positive symptom score is 0 to 144, it is reasonable to assume that the range of the within treatment SD to be 15 to 20. This assumption is consistent with a study using CAARMS positive symptom score as an outcome (Morrison et al., 2012), which indicated a within treatment SD of about 17. Using this assumption on the within treatment SD, a sample size of 135 per group would be able to detect an effect size

of 0.4 with 80% power and a 5% significance level, allowing for a 20% drop-out rate. This effect size would correspond to a detectable difference of 6 to 8 in CAARMS positive symptom score in a pairwise treatment comparison. Such a difference would be clinically relevant. Since the study has a lead-in phase during which 10% of UHR individuals are expected to experience symptom remission, 450 UHR individuals will need to be recruited to yield a sample of 405 UHR individuals to randomise in this trial.

7.2 Data analysis

The primary analysis will adopt the intention-to-treat approach and employ analysis of variance to conduct an overall comparison of the three treatment groups in terms of the primary outcome measure, which is severity of positive psychotic symptoms. If this overall comparison is significant, pairwise comparison of the treatments will be conducted using Fisher's LSD test. As a secondary analysis, baseline outcome score, site, antidepressant treatment (the two stratifying variables in randomisation) and compliance level will be included as covariates. To compare the treatment groups for the secondary outcomes, survival analysis will be used for transition to psychosis, general linear model analysis for psychopathology measures, functioning and quality of life and logistic regression for clinical improvement (dichotomised as yes or no). Generalised linear mixed-effects model analysis will also be used to compare the treatment groups in terms of the longitudinal trajectories of the outcomes. If the amount of missing data is non-trivial, multiple imputation will be considered.

7.3 Economic Evaluation

An important secondary aim of this study is the determination of the cost-efficacy of CBD from a societal perspective. A cost-consequences analysis will compare the incremental costs of CBD to the full spectrum of outcomes via a series of cost-effectiveness ratios. This approach has been found to be useful for decision-makers. The AQoL-6D will allow a cost-utility analysis to be undertaken (cost/QALY). Intervention and other costs will be estimated from the study financial records, PBS/MBS data and the Resource Use Questionnaire (including health care, welfare, and employment (including unpaid work) productivity). Standardised economic evaluation techniques including incremental analysis of mean differences, generalised linear modelling techniques and bootstrapping to determine confidence intervals will be used. If the intervention is found to be effective, modelling techniques will be used to assess its cost-effectiveness.

8 SUMMARY

Early intervention and specialised care can improve outcomes in people with schizophrenia or other psychotic disorders (Correll et al., 2018; Henry et al., 2010). Significant progress has been made over the last twenty-five years by reducing the rate of progression to psychosis in people with subthreshold symptoms identified as being at UHR of psychosis (Amminger et al., 2015; Nelson et al., 2016; van der Gaag et al., 2013), as well as by reducing the duration of untreated psychosis (Marshall et al., 2005) and optimising care and relapse prevention for individuals with first-episode psychosis (Alvarez-Jimenez et al., 2012). However, no biological intervention has been firmly established for the UHR stage (Amminger et al., 2017) and more effective treatments are still needed to further improve short and longer-term outcomes, including onset of psychotic illness, other psychopathology and functional outcomes. If successful, this study can establish a novel biological treatment for young people at UHR of psychosis that can be used in a wide variety of settings, from primary care to specialist, and be easily translated to longer-term treatment.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Table 1: Inclusion and exclusion criteria

Inclusion Criteria	1. Age 12-25 years (inclusive) at entry. 2. Sufficient fluency in English (for assessment purposes). 3. Ability to provide informed consent (parental/guardian consent will be obtained for participants aged <18 years) 4. Meeting one or more UHR for psychosis groups as defined in Table 2.
Exclusion Criteria	1. UHR symptoms only present during acute intoxication 2. If prescribed psychotropic medication (e.g., antidepressant medication) the individual must have been on a stable dose for a minimum of 6 weeks prior to randomisation* 3. Pregnancy, lactation, or if sexually active, no effective contraception (applies to both male and female participants) 4. Clinical blood test findings that might compromise participant safety or confound the trial results 5. Acute or unstable systemic medical disorder 6. Psychiatric condition due to a medical condition 7. Severe disturbance, such that the person is unable to comply with either the requirements of informed consent or the treatment protocol 8. Current acute suicidality/self-harm or aggression/dangerous behaviour (indicated by a CAARMS severity score of 6 on items 7.3 and/or 5.4). Diagnosis of a serious developmental disorder or a documented history of developmental delay or intellectual disability 9. History of a psychotic episode of one week or longer **Antipsychotic medication is not an exclusion criterion. In the case of current antipsychotic use, medication will be tapered and ceased at entry to the study.*

Table 2: Operationalised UHR intake criteria

Group 1: Vulnerability Group

Family history of psychosis in first degree relative OR Schizotypal Personality Disorder (as defined by DSM V) in identified patient
AND
Drop in Functioning:
Recency: Change in functioning occurred within last year
Impact: SOFAS score at least 30% below previous level of functioning and sustained for at least one month.
OR
Sustained low functioning:
Recency: For the past 12 months or longer
Impact: SOFAS score of 50 or less.

Group 2: Attenuated Psychotic Symptoms Group

2a) Subthreshold intensity:
Intensity: Global Rating Scale Score of 3-5 on *Unusual Thought Content* subscale, 3-5 on *Non-Bizarre Ideas* subscale, 3-4 on *Perceptual Abnormalities* subscale and/or 4-5 on *Disorganised Speech* subscales of the CAARMS
Frequency: Frequency Scale Score of 3-6 on *Unusual Thought Content*, *Non-Bizarre Ideas, Perceptual Abnormalities* and/or *Disorganised Speech* subscales of the CAARMS
Duration: symptoms present for at least one week
Recency: symptoms present in past year
2b) Subthreshold frequency:
Intensity: Global Rating Scale Score of 6 on *Unusual Thought Content* subscale, 6 on *Non-Bizarre Ideas* subscale, 5-6 on *Perceptual Abnormalities* subscale and/or 6 on *Disorganised Speech* subscales of the CAARMS
Frequency: Frequency Scale Score of 3 on *Unusual Thought Content*, *Non-Bizarre Ideas*, *Perceptual Abnormalities* and/or *Disorganised Speech* subscales of the CAARMS
Recency: symptoms present in past year

Group 3: BLIPS Group

Intensity: Global Rating Scale Score of 6 on *Unusual Thought Content* subscale, 6 on *Non-Bizarre Ideas* subscale, 5 or 6 on *Perceptual Abnormalities* subscale and/or 6 on *Disorganised Speech* subscales of the CAARMS
Frequency: Frequency Scale Score of 4-6 on *Unusual Thought Content*, *Non-Bizarre Ideas, Perceptual Abnormalities* and/or *Disorganised Speech* subscales
Duration: Symptoms present for less than one week and spontaneously remit on every occasion.
Recency: symptoms present in past year

Table 3: Discontinuation criteria

A participant will be considered 'discontinued' from the study in cases where the study treatment is ceased. However, the participant may continue to complete other aspects as per the study schedule.

A participant will be discontinued in the following cases:

(1) Participation interferes with the appropriate clinical management of risk to self or others

(2) An adverse event or serious adverse event leads to a request for discontinuation by participant or investigator

(3) A participant becomes pregnant

(4) Participant is not compliant with the intervention (i.e., returns more than 50% of capsules at Week 2 or Week 4)

(5) A participant starts non-trial psychotropic medication or changes dose of existing psychotropic medication

(6) The randomisation code is broken

(7) Severe non-compliance to protocol as judged by the Investigator

(8) Transition to psychosis or mania. Transition is operationally defined via the CAARMS, as frank positive psychotic symptoms occurring daily for 1 week or longer. These cases may be offered treatment as inpatients or via intensive community care, as per early psychosis guidelines. Data collected after meeting the discontinuation criterion will not be included in the primary analysis.

Table 4: Schedule of assessments and endpoint measures

VISIT NUMBER	1	2	3	4	5	6	7	8****	9****	10****
Eligibility and safety measures	**Lead-In Day -63 to -42***	**Screening Day -21 to 1***	**Week 0 Day -7 to 1 (baseline)***	**Week 4 Day 21 to 35***	**Week 8 Day 49 to 63***	**Week 12 Day 77 to 91***	**Week 26 Day 175 to 189***	**Week 52 Day 354 to 394***	**Week 78 Day 516 to 576***	**Week 104 698 to 748***
Informed consent	X									
Inclusion/exclusion criteria	X	X	X							
Demographics	X									
Medical & psychiatric history		X								
Pregnancy blood test		X								
Fasting blood test (main study research and clinical)		X		X		X				
Urine test		X		X	X	X				
Hair sample & finger prick test			X			X				
Physical examination			X	X		X				
Telehealth appointment with study doctor			X	X	X	X				
Intervention										
Randomisation**			X							
Intervention (CBD or placebo) administered			X	X	X					
Blinding assessment (participant and rater)			X			X				
Adverse events review			X	X	X	X	X	X	X	X

VISIT NUMBER	1	2	3	4	5	6	7	8****	9****	10****
Eligibility and safety measures	**Lead-In Day -63 to -42***	**Screening Day -21 to 1***	**Week 0 Day -7 to 1 (baseline)***	**Week 4 Day 21 to 35***	**Week 8 Day 49 to 63***	**Week 12 Day 77 to 91***	**Week 26 Day 175 to 189***	**Week 52 Day 354 to 394***	**Week 78 Day 516 to 576***	**Week 104 698 to 748***
Concomitant medication review			X	X	X	X	X	X	X	X
Treatment adherence				X	X	X				
Primary outcome measure										
CAARMS (positive symptoms + aggression 5.4 and suicidality items 7.3 items)***	X	X	X	X	X	X	X	X	X	X
Secondary outcome measures										
MADRS			X	X	X	X	X	X	X	X
HAM-A			X	X	X	X	X	X	X	X
OASIS			X	X	X	X	X	X	X	X
PSQI			X	X	X	X	X	X	X	X
PANSS			X	X	X	X	X	X	X	X
SOFAS	X		X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X
AQoL- 8D			X	X	X	X	X	X	X	X
RUQ			X			X	X			
ASSIST			X	X	X	X	X	X	X	X
SCID-I^			X			X	X			
SCID-II Schizotypal PD	X									

**Assessments will be conducted within the specified timeframes indicated in the schedule of assessments. Due to the spread of assessments, the assessment window changes over time.*

***Randomisation will occur at the baseline time point only after all inclusion/exclusion criteria have been completed and confirmed.*

****CAARMS positive symptoms will be assessed at each time point. The full CAARMS will not be administered; however, the aggression/dangerous behaviour (item 5.4) and suicidality/self-harm (item 7.3) items in the CAARMS will be used to assess exclusion criteria at screening/baseline and risk throughout the study. Wherever the CAARMS is referred to in this document, it refers to these three elements unless otherwise specified.*

*****Given the study duration of 3.5 years including a recruitment period of 3 years, not all participants will have week 52, week 78 or week 104 data collected.*

^The full SCID with the exception of externalising disorders will be completed at baseline. At week 12 and week 26, only the mood and psychosis modules will be completed.