

Examining the use of Cannabinoid-based Medicine among older residential care recipients diagnosed with dementia: A study protocol for a double blind randomised cross-over trial

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Abstract

Background: Dementia is a neurological condition that affects the cognitive and functional ability of the brain and is the leading cause of disability among those aged 65-years and above. More effective ways to manage dementia symptoms are needed as current treatment options (anti-depressant and antipsychotic) can be ineffective and associated with substantial side-effects, including increased rate of mortality. Cannabinoid-based medicines (CBM) has shown to inhibit some symptoms associated with dementia and the adverse effects are often minimal, yet little research has explored the use of CBM among this population.

Aim. To monitor the safety of a purified dose of CBM oil (3:2 THC:CBD) on behaviour symptoms, Quality of life (QOL), and discomfort caused by pain.

Methods/Design: We will carry out an 18-week randomised, double-blinded, crossover trial that consists of a 2-week eligibility period, two, 6-week treatment cycles and two, 2-week washout periods (between both cycles, and after the second treatment cycle). We aim to recruit 50 participants with dementia who are living in residential aged-care facilities. The participants will be randomised into two groups, and receive a dose of either CBM oil or placebo for the first treatment cycle and receive the opposite medication for the second. The Neuropsychiatric Inventory Questionnaire, Cohen Mansfield Agitation Inventor, Quality of Life-Alzheimer's Disease questionnaire, and the Abbey Pain Scale will be collected on seven occasions, and completed by the participants, aged-care staff, and nominated next of kin or family member. The participant's heart rate and blood pressure will be monitored weekly and their body composition and weight will be monitored fortnightly by a research nurse to assess individual dose response and frailty. In addition, pre- and post-surveys will be administered to aged-care staff and family members to understand their perceptions towards CBM, and to inform proposed focus groups consisting of the aged care staff and next of kin.

Discussion: The study design has been informed by medical professionals and key stakeholders including those working in the residential aged-care industry to ensure patient safety, collection of non-invasive measures, and methodological rigor and study feasibility. T

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<https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375128&isClinicalTrial=False>

Background

Dementia is a collection of symptoms that progressively reduces the cognitive and functional ability of the brain (1) and affects memory, intellect, rationality, social skills, and physical functioning (2). The symptoms associated with dementia present themselves in a variety of ways and can include depression, frustration, clinginess, forgetfulness, wandering, sexual aggression, hoarding, sleep disturbances and 'the sundowner effect' (increased manifestations of challenging behaviours at the end of the day; 3). Severe cognitive fluctuations in patients with dementia have been associated with an individual's impaired

ability to engage in activities of daily living including social interactions and poorer quality of life (QOL; 4). The slow progression and degeneration of dementia requires additional support and assistance to remain at home or ultimately admission into residential aged-care facilities with 24-hour care.

Dementia is the second leading burden of disability among Australians aged 65-years and older and the burden of disease is expected to exponentially increase over the next 30 years (5). Alzheimer's disease is the most common cause of dementia and affects approximately 50 to 70% of the elderly with dementia. Pharmacological management of behavioural and physical symptoms of dementia is currently the most common treatment option, and many are prescribed medications such as off-label antipsychotics, sedative/hypnotics, anxiolytics, acetylcholinesterase inhibitors, and antidepressants to mask and alleviate the array of dementia symptoms (6, 7). Medications such as Aripiprazole, Olanzapine, Risperidone, and Memantine have been shown to reduce troublesome behaviours (8), although unclear guidelines are often provided for administration (2, 7). This results in polypharmacy and its inherent risks, with numerous medications being prescribed for a longer duration than recommended (9). Many of these medications lead to a number of substantial side-effects (10), including increased rate of stroke and mortality (11).

Cannabinoid-based Medicines (CBMs) have been shown to improve dementia symptoms such as aggression and agitation (12, 13), and appears safer to prescribe compared to other pharmacotherapies (3) as the adverse effects are often minimal (14). For example, Weier and Hall (15) found sedation to be the only adverse effect among dementia patients prescribed either cannabinoids or pharmacotherapies. While periods of euphoria, somnolence, and tiredness were observed among those prescribed Dronabinol [a synthetically derived delta-9-tetrahydrocannabinol (THC); 16]. There were only a small number of adverse events (6 out of 98) related to the administration of the synthetic THC similar to those manifested by the placebo (14). However, well-designed randomised, double-blinded, placebo-control trials need to be completed to understand the most efficacious formulation, safety profile, drug-drug interactions and true effect to determine the place of CBM in dementia (17, 18), allowing for greater generalisability of these outcomes (19).

A range of CBMs (synthetic compounds such as Dronabinol or Nabilone or pure cannabinoids) are available, however the combination of Cannabidiol (CBD; the non-psychoactive compound) and THC (the psychoactive compound; 20) appear to be most effective, as both compounds improve psychomotor activity, mood, sleep-wake cycles and eating behaviours (14, 21, 22). THC and CBD interact with the endogenous cannabinoid (CB) systems CB1 and CB2 receptors (18, 22, 23) producing symbiotic neuroprotective effects. For example in pre-clinical trials, THC is found to be a partial CB1 antagonist and improves immune function (24), encourages amyloidogenesis (14, 21, 22, 25, 26), reduces neuropsychiatric symptoms, pain sensation (27), stimulates appetite (20-22, 28) and inhibits acetylcholinesterase, similarly to cholinesterase inhibitors such as Donepezil (29). CBD is an inverse CB1 agonist (30) that promotes neurogenesis and vasodilatation within the brain, increases neuronal plasticity and cerebral blood flow (31), prevents cell destruction, and holds anti-inflammatory (neuro and peripheral inflammation), analgesic, anticonvulsant and anxiolytic properties (24). CBD is an important

compound as it reverses the negative consequences on cognition and ameliorates the psychoactive properties of THC (20–22, 28).

Studies assessing the safety and efficiency of CBMs have shown many benefits among other neurodegenerative diseases, such as Parkinson's disease (32, 33), epilepsy, Post-Traumatic Stress Disorder (17, 34), anxiety (12), and spasticity due to Multiple Sclerosis (35) with the use of CBM reducing Benzodiazepine prescriptions by 45% (36). However, only a handful of studies have investigated the use of CBM in dementia patients (13, 14, 22). Recently, an observational study monitored the use of a CBM medication over a 2 month period among 10 females with severe dementia and found a 40% reduction in behavioural problems and 50% reduction in rigidity (37).

The pharmacodynamics and pharmacokinetics of THC (weeks 1–6; 0.75 mg, weeks 7–12; 1.5 mg) administered to 10 participants with dementia was safe and well tolerated (14), with positive effects in mental state, dementia severity, behavioural symptoms such as delusions, irritability, and sleep and caregiver distress observed with THC (2.5mg) administration among 11 dementia patients (22). Studies reporting the use of Dronabinol (2.5mg daily) found improvements in anorexia and body weight, and less disturbed behaviours (16), such as agitation and motor behaviours with no adverse effects observed (38). Retrospective observations of Dronabinol administration among 40 hospitalised patients' indicated improvements in agitation and aggression, sleep duration, and meal consumption (13). Two independent case studies monitoring the effects of Nabilone (maximum dose of 0.5mg, twice daily for six weeks) among elders with dementia found improvements in severe agitation and aggression (39), psychomotor activity, smiling, as well as positive experiences from family members (40). No changes in the number of falls or balance (with eyes open) were reported among 18 participants administered 1.5mg of oral THC twice daily (41), with recommendations suggesting higher doses (THC 1.5mg three times daily) and longer study durations (greater than three weeks) are needed to understand the true effects on behavioural symptoms including QOL and activities of daily living (42). Therefore, further research in this area is needed as many beneficial outcomes have been reported, although dosing, samples size, patient cohort (two to 50 participants) and outcomes have varied in what are generally small studies with poor experimental design.

Aims

The primary aim of the present study will be to see if a purified CBM oil is safe and improves behavioural and neuropsychiatric symptoms of dementia (BPSD). In addition, two secondary aims of this study will include examining QOL and discomfort caused by pain among dementia patients taking CBM oil.

Methods And General Study Design

This study has approval from the Human Ethics Research Committee at the University of Notre Dame Australia. The study will utilise a parallel mixed methods study design. The research methodology for this study is a Phase II randomised placebo-control cross over trial. The design will include, a 2-week eligibility

(assessment) period, two, 6-week-treatment cycles to allow for each participant to take part in both the control and the treatment cycles, and two, 2-week washout periods (one between both treatment cycles and the other after the second treatment cycle). The 6-week treatment cycles have been selected based on the safety, pharmacodynamics, and pharmacokinetics completed by Ahmed et al. (14), and a 2-week washout period has been shown to be safe and an appropriate length of time for cannabis to metabolise in older individuals (43).

In addition, residential aged-care staff and next of kin perceptions towards the use of CBM oil will be evaluated via surveys administered prior to, and on completion of the study. At the end of the second treatment cycle the residential aged-care staff and family members will be asked to participate in a follow-up focus group to gather more in-depth information around individual's perceptions before and after the administration of CBM. Each participant will be in the trial for approximately 4 months (18-weeks), but the duration of the study will last over 12 months in order to recruit participants from a number of aged care facilities.

Participants and setting

Participants will be recruited through residential aged-care facilities. Residential aged-care facilities within Australia are government funded organisations that provide additional support for families who may have a family member suffering from dementia whereby many move from their residential homes into a residential aged-care facility so they can be monitored and provided with additional care. A two-sided calculation, using the Neuropsychiatric Inventory Questionnaire–Nursing Homes (NPI-NH) as the primary outcomes measure, achieves 81% power when the total sample size of a 2x2 cross-over design is 40 [*Mean (M) = 6, Standard Deviation (SD) = 13*], and the significance level is 0.05. Fifty participants will be recruited to allow for a 20% attrition rate. Participants will be eligible to participate if they live in a residential aged-care facility, are aged 65-years or older, have a mild diagnosis of dementia [indicated by a score of >20 on the Mini Mental State Assessment (MMSE)], able to speak English, are known as compliant to taking medication, are not bed ridden, and are able to provide informed consent. Participants will be excluded if they have certain health conditions such as Frontotemporal or Lewy body dementia, other comorbidities such as epilepsy, anorexia nervosa, comorbid psychiatric conditions, Parkinson's disease, congestive heart failure, history of myocardial infarction or anginal pain, history of stroke, liver disease, renal disease or taking medications such as Primidone, Phenobarbital, Carbamazepine, Rifampicin, Rifabutin, Troglitazone, Hypericum perforatum, and valproic acid that may interact with cannabis metabolism.

The pre-/post-surveys and focus group discussions are an exploratory qualitative component of this study and thus a definitive sample size calculation cannot be determined at this stage. We estimate that six focus groups comprising of six to eight participants, including two groups of residential care staff, activity staff (care staff who monitor daily activities and social engagement), and family members will

ensure data saturation has been reached. Written informed consent will be obtained from all participants, including the residential aged-care staff and the next of kin.

Rigor

Residential aged-care staff usually work within the aged-care setting for at least three months and therefore are likely to be working in the same facility for the duration of the 4-month trial. The same aged-care staff will monitor the same participant(s) for the duration of the study and report any changes on the participant's behalf. To be classified as a residential care staff, the individual must spend at least two occasions per week with the participant. The same registered nurse will administer the medication for both treatment cycles.

Recruitment

The residential aged-care clinical and general managers who have established relationships with the participants and their next of kin will promote the study to those they feel would be eligible to participate. This will be performed through face to face conversations.

Randomisation

The randomisation process for this study will be done by creating a random number list using a 1:1 ratio allocation to ensure equal number of cases in the both the placebo (n = 25) and treatment group (n = 25) using Microsoft Excel. The determination of participant allocation will be completed by the laboratory manager in the drug manufacturing laboratory with each case being provided with a unique identification (ID) number (1–50). The primary researcher, who is responsible for recruitment, will provide the lab manager with the participants name to be sequentially matched again the next available ID number. The laboratory will provide the pharmacy with both CBM and placebo in identical bottles labelled with the ID but the medical practitioner and research team members will not know the order of treatment until the completion of the study. The pharmacist will place the participants name on the bottle before distributing the bottles to the aged care facilities.

Blinding

This is a double-blinded study. Therefore, the lab technician will be the only individual who will know the group allocation for the participants. This is to ensure that the pharmacist, aged-care staff, medical practitioners, research nurse, family members/next of kin, participants, and researchers are all blinded to the participant's group allocation. Once the study is complete, the lab technician will un-blind the information by providing the primary researcher with a list of participants and their group allocation in order to conduct the analysis.

Procedure

The study will run for 18-weeks comprising of a 2-week '*Eligibility period*' for screening and clinical assessment, and a 16-week "*Experimental phase*" comprising of two, 6-week cycles of treatment and placebo separated by a 2-week washout period between the treatment cycles, and a 2-week washout period following the completion of the second arm (Figure 1).

Insert Figure 1 about here.

Eligibility period

Individuals who express interest in participating in the study will initially be screened based on the inclusion criteria (described above). Following the initial screening process, potential participants will then undergo a thorough clinical investigation by a geriatrician to ensure they have the cognitive capacity to provide informed consent using the MMSE. The MMSE (44) is the most widely used cognitive outcome measure to assess the severity of cognitive performance. It comprises of 11-items, where a total score out of 30 can be calculated to assess the severity of dementia (25–30 questionably significant, 20–25 mild, 10–20 moderate, 0–10 severe). Those who seem suitable, will be revisited by the geriatrician one week after the cognitive tests and will confirm the participant has understood the purpose of the trial and recalled the details of the study. Then the primary researcher will invite the eligible participants into the study and ask them to complete the Consent Form and provide some demographic and baseline details including age, sex, education level, weight, medical history including comorbid illnesses, and prescribed medication. The participants will then be randomly allocated into treatment Group A or B and receive either CBM oil or placebo for the first 6-week treatment cycle. No adjustments will be made to the participants currently prescribed medications.

Experimental phase

This phase of the study will take 16-weeks to complete. To minimize the risk of adverse events and variation in the maximum tolerated dose of CBM oil, each participant will receive one dose on the first and second days (2pm) and two doses (9am and 2pm) for the remainder of both treatment cycles. The dose will be administered by a registered nurse along with a small meal (e.g. morning and afternoon tea) and the rate of titration will be monitored by the pharmacist to ensure it is appropriate for each individual. The participant will gradually receive an increased dose (titration) of the medication over several weeks as shown in Table 1. During these weeks, the participant along with the care staff will record the presence of, and change in, any potential adverse events that may be associated with the medication after the first dose, each afternoon where the dose is increased, and again on their final day of medication. If an adverse event is noted, the participant will revert to their previous, best tolerated dose using the adverse events and safety protocol listed below.

An upper limit of 50mg/day of THC will be permitted in those who do not have any adverse events from the medication. Once a participant has reached their maximum tolerated dose (or a total of 50mg/daily of THC), they will continue to receive that dose until the cessation of the 6-week period. The placebo group will follow a similar titration process using the indicated volumes shown in Table 1. They will continue to receive an increase in the volume of medication until they record an onset of an adverse event, at which time they will continue to take that volume of placebo until the end of the 6-week placebo cycle.

Insert Table 1 about here.

Management and administration of medication

The CBM oil, "*CogniCann*", will be provided in a sealed 10ml glass spray bottle which contains a mix of THC and CBD in a 3:2 ratio (25 mg/ml THC, 17 mg/ml CBD) in a Medium-Chain Triglycerides oil base. Each press of the vial will accurately dispense 100 µl of oil that contains 2.5mg of THC. A total of 50mg/day of THC and 34mg/day of CBD can be administered for 4–5 days from one 10ml glass spray bottle. *CogniCann* can be stored at room temperature (below 25°C) for a total of 4 weeks. A certificate of analysis will be provided for each batch upon delivery.

The placebo will be administered in the same 10ml glass spray bottle and collected following the procedures describe above. The placebo will comprise of a Terpene based oil that contains Esters that mimic the smell and taste of CBM.

The bottles of medication will be provided to the residential aged-care facilities by the affiliated pharmacist. The bottles will be delivered every week and collected again after 7 days of use (even if they are half full) and returned to the pharmacy where they can determine how much was used (or left) and then dispose of the bottles to meet Therapeutic Goods Administration (TGA) requirements. At the start of the titration phase, 1 bottle will be administered for each participant (as the lower dose of 2.5mg of THC allows for each bottle to hold 2–3 weeks of the medication). As participants begin to reach a higher dose (titration phase, see Table 1 above), 2 bottles will be provided on a weekly basis, so each participant will have sufficient medication to last for 7 days.

Data collection

The aged-care staff, resident participants with dementia, and nominated next of kin will complete a total of four outcome measures on seven occasions throughout the study. The questionnaires take approximately 20 minutes to complete, and will be completed three times during the first treatment arm [baseline (Day 0), after maximum tolerated dose has been reached (Day 24), and the end of the treatment cycle (Day 42)], three times during the second treatment arm [baseline (Day 56), after maximum tolerated dose has been reached (Day 80), and the end of the treatment cycle (Day 97)] and once following the two-

week washout period after the second treatment arm (Day 112). The questionnaires will be administered by the primary researcher.

Adverse Events and safety protocol

An adverse events protocol will be put into place to minimise any potential harm or risks of receiving additional medication (14). This will include participants reporting if they have experienced any adverse events one hour after the increased dose has been administered (Appendix A). If moderate to severe adverse events are recorded [determined as *'Somewhat worse'* (moderate) or *'Much worse'* (severe) on the participants adverse event record] and these events have not ameliorated by the time for the next dose, the participant will receive the previous, best tolerated dose. If the effects of the adverse event(s) have disappeared or become milder, and do not interfere with the participant's daily function or well-being, the registered nurse may increase their dose at the indicated rate. Recurrence of adverse events after two attempts to increase the dose will result in the participant remaining at their previous best tolerated dose for the remainder of the intervention period. If a participant experiences an adverse event they will stay on the previous dose for another two days before the next dose is increased. At the beginning of the titration phase a staff member at the aged care facility will be vigilant in monitoring any acute adverse events such as dizziness, discoordination with a danger of falls and injury and extreme fatigue. Any adverse events recorded will be reported to a facility line manager, which will then be communicated to staff during shift changes.

Additional safety monitoring will be completed by a research nurse who will meet with each participant to discuss their adverse event records and measure their heart rate and blood pressure twice a week. In addition, the participants weight and non-invasive body composition measures such as lean body mass, bone mass and body fat percentage and fat mass will be measured once a week using a portable scale. In addition, a nurse-led review will be completed two days into the washout periods to monitor the participant's withdrawal symptoms once no more medication is being administered.

Measures

The Neuropsychiatric Inventory Questionnaire–Nursing Homes (NPI-NH; 45) is a questionnaire that measures 12 neuropsychiatric symptoms (delusions, hallucinations, agitation, depression, anxiety, euphoria/ elation, apathy/indifference, disinhibition, irritability, aberrant motor behaviour, night time disturbances, and appetite changes). The frequency and severity of each symptom is rated (4-point and 3-point Likert scales). A total score can be calculated by adding the first 10 domains together, all 12 domain scores can be summed in special circumstance where neurovegetative symptoms are of interest, and a carer disruptiveness score [summing the disruptiveness score of the 10 (or 12) behavioural domains] can be calculated. The NPI-NH can be completed in approximately 10 minutes.

Cohen Mansfield Agitation Inventory (CMAI) is designed to assess agitation across three domains. Namely, physically aggressive behaviour, physically non-aggressive behaviour and verbally agitated behaviour (46). The CMAI comprises of 29-items and uses a 7-point Likert scale [Never (1), Less than once a week (2), Once or twice a week (3), Several times a week (4), Once or twice a day (5), Several times a day (6), Several times an hour (7)] and measures four subscales: Aggressive Behaviour, Physical Non-aggressive Behaviour, Verbally Agitated Behavior, and Hiding and Hoarding. A total score of 203 is calculated, with a higher score indicating a higher frequency in behavioural occurrence and takes approximately 5 minutes to complete.

The Quality of life-Alzheimer's Disease (QOL-AD) is designed to measure aspects important towards an individual's QOL. The QOL-AD consists of 13-items, using a 4-point Likert scale [poor (1), fair (2), good (3) and excellent (4)] and is designed for both self and proxy report (47). The QOL-AD measures four domains (Physical, Mental Health, Social, and Function) and can be completed with people with a wide range of dementia severity (48). A total score out of 52 is calculated, with a larger score indicating a higher QOL. The self-report version can be completed in about 10–15 minutes, and the proxy-report in about 5 minutes. A composite score can also be calculated (participant QOL-AD x 2 + carer QOL-AD x 3).

The Abbey Pain Assessment Scale comprises of six items, assessing vocalization, facial expression, change in body language, and behavioural, physiological, and physical change (49). This questionnaire uses a 4-point Likert scale [Absent (0), Mild (1), Moderate (2), Severe (3)] and a total score of 18 is calculated. The severity of pain is indicated as mild (3–7), moderate (8–13) and severe (14+) and can be completed in less than 5 minutes.

Process evaluation outcomes:

The one page pre- and post-surveys will be administered to aged-care staff and next of kin at the beginning of the first treatment cycle and at the end of the second treatment cycle. These surveys comprise of seven to nine questions regarding individual's perceptions towards CBM oil use and the symptoms of dementia they find most challenging. A total of six questions will be asked during the focus group discussions. These questions relate to positive and negative observations among those taking CBM oil, changes in perceptions, knowledge and benefits around the use of CBM use.

Data Analysis

Quantitative

The questionnaire results completed on behalf of the aged-care staff, participants and family members will be analysed using SPSS version 25 (IBM Inc. 2018). The responses from the aged-care staff will be the main responses considered for analysis. Where available, participants and family responses will be included for secondary analysis. To examine group differences, the participants will be categorised

according to their treatment cycle group allocation (Group A or Group B). Descriptive statistics will be derived. Each variable will be tested for normality, with t-test or ANOVA being used if appropriate or non-parametric tests such as Wilcoxon Signed Rank Test and Friedman test if the data is skewed. Within subject differences between both treatment cycles will be done using independent t-test to ensure the washout phase is long enough to rule out a carryover effect (50, 51). The seven data collection points will be examined using general linear modelling techniques, in a single repeated measure model controlling for weight and the average dose of medication to see if any changes in behaviour, QOL or pain have occurred over the duration of both treatment cycles. Differences between CBM, placebo and occurrence of AEs will be compared using paired t-tests. NPI-NH is the primary outcome measure for this study. All other measures (CMAI, QOL-AD, and Abbey Pain Assessment) have been included for secondary analysis. The CMAI will be analysed using the reliability change methodology in comparison to the NPI-NH to allow for small changes to be reported (52). Alpha will be set at .05. In the instance where a participant withdraws half-way through a treatment cycle, the information collected prior to their withdrawal will be retained within the study as their personal information will have been de-identified. The data management of the information collected will follow standard university procedures, be stored in a locked cabinet for a period of 15 years, stored on a password protected computer, and backed up regularly in a secured format.

Qualitative

QSR NVivo 12 will be used for qualitative data management and assistance in the analysis of both of the pre-and post-surveys and focus groups. Qualitative content analysis will be used to analyse the surveys to assess similarities and differences between responses. The focus groups will be transcribed verbatim and the transcripts will be thematically analysed by repeated readings and subsequent open coding process followed by line by line coding to identify key themes. To avoid bias, a triangulated approach including reflectivity by the primary researcher during the interview process, member checking to establish confirmability and verbatim quotes to establish credibility will be used. The primary researcher and the research team at the University of Notre Dame Australia will only have access to the final data set. The data will be stored on the University computers on a locked storage drive.

Discussion

To our knowledge, this is one of the first trials within Australia to evaluate the use of a purified CBM oil at the individual level among those with dementia to examine behavioral effects, QOL, and pain and discomfort. Only a handful of crossover trials have been conducted (14, 16, 40, 41, 53), although the majority have used fixed doses and have not incorporated an individual tailored dosing regimen. Soto et al. (27) reviewed 18 randomised clinical trials examining drugs prescribed for agitation and aggression and found large variations not only in the chosen questionnaires to measure these symptoms, but also in the inclusion criteria. Based on their results, Soto et al. (27) suggested trials lasting 9- to 12-weeks were adequate for assessing an acute response, whereas longer trials (6- to 12-months) were effective for

assessing the stability of a response. The 18-week duration of this study is appropriate to assess the initial dose response (27), and the trial design is also reflective of other protocols conducting crossover studies, and includes two, 2-week washout periods to ensure patient safety and a chance for the medication to metabolise out of the body. For example, Balestrino et al. (30) designed a protocol to examine the use of THC:CBD oromucosal spray among post-stroke spasticity patients and included two, 4-week treatment cycles, with a 2-week washout period between both cycles.

There are a number of strengths in our study. First, all participants will have a medical diagnosis of dementia. This ensures that the diagnosis is in line with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V; 54). Second, the residential aged care staff spend a large amount of time with the participants, so they will be able to observe small changes and lead to accuracy in recording of the results. Where possible, these results will also be compared with the participant and their next of kin to examine similarities and differences. Beattie et al. (55) published a protocol paper outlining a national project to collect multiple QOL perspectives from the care staff, family members and those living with dementia. Comparisons between care staff, family members and self-report QOL scores showed a linear relationship between reporters, with the residents often rating their QOL higher than the care staff (56, 57).

As an additional precautionary step, two separate questionnaires assessing behavioural symptoms have been included to ensure the smallest effects of CBM oil are observed. A strict safety protocol, monitoring of adverse events and nurse led reviews during the washout periods will also be followed to ensure participant safety, which has been included due to the average age of the participants, additional medications currently prescribed, and the likelihood of having a comorbid condition. Weier and Hall (58) suggest the therapeutic benefits of CBM are observed among dementia patients when administered alongside adjacent therapy or medication. In addition, the dose of medication will be titrated to ensure each participant receives their best, tolerated dose and minimizes the onset of any adverse events. This process of 'start low and go slow' is reflective in other studies as well as government documentation from Queensland Health (59, 60). Educational training with the aged-care staff will be completed before the first participant is recruited to prevent unexpected issues arising during the trial, and to make sure they are familiar with the structure of the overall research protocol as well as the questionnaires.

This study has utilised a holistic approach to gain more in-depth information around BPSD and to capture staff and family member's perceptions towards CBM. The inclusion of the qualitative phase is important as little research has been completed to understand personal views towards CBM use and the effects thereof in this setting. This approach allows the researchers to understand the perceived strengths and challenges around the use of cannabis within an institutional setting. Many symptoms associated with dementia such as wandering, agitation, aggression, and psychotic behaviours contribute to fatigue and burnout experienced by many caregivers (61). Feast, Moniz-Cook, Stoner, Charlesworth, and Orrell (62) reviewed the relationship between BPSD and informal caregivers (child-adult or spousal caregivers) well-being and found depressive behaviours, agitation and aggression, apathy including irritability, aberrant motor behaviours and delusions were the most distressing symptoms for caregivers.

A number of challenges have been identified in the proposed study. It may be difficult to find those with a dementia diagnosis who have the cognitive capacity to give informed consent as many experience a loss of short-term memory, intellectual reasoning, rationality, and social skills (1, 2). This may lead to difficulty in recruiting participants into the trial and excluding those who do not have the capacity to give informed consent, yet they are potentially the ones who exhibit a greater number of behavioural occurrences. Those who experience mild to moderate dementia still exhibit symptoms such as depression and anxiety, and both verbal and physical agitation (2). However, due to the limited legislation around including those who do not have the cognitive capacity to give informed consent in research projects, this limits who can be included within this study. The replication of this study design to include those with a moderate to severe diagnosis would warrant further generalizability of the results. Irreversible progression of cognitive impairment, the associated complications and comorbidities, and frailty of the participants, may lead to participants dropping out of the study. To accommodate this, we have included a 20% increase to the sample size. It is also difficult to know if the selected questionnaires chosen for this study are suitable and sensitive enough to measure the changes attributed to the use of CBM oil, as no 'gold standard' exists to measure BPSD. Therefore, both the NPI-NH and the CMAI have been selected to account for the small effects. The pharmacodynamics of the medication will be monitored during the treatment cycles through the use of non-invasive body composition measures, and monitoring heart rate, blood pressure and weight. These measures will be collected by a research nurse external to the aged care facilities to improve the feasibility of the study, to avoid additional workloads placed onto the aged-care staff and ensure that each participant is receiving their best tolerated dose. In addition, only one residential staff member has been selected to complete the questionnaires, as they spend a great deal of time with the residents, they can report symptoms easily. Independent reviews have not been selected for this study, as they are unfamiliar to the participants, which may lead to inaccuracy in recording of the results.

Trial Status

The trial has been registered with the Australian New Zealand Clinical Trials Registry. The registration number is ACTRN12619000474156 and was registered in 21 March 2019. Recruitment will begin in July, 2019. The approximate date that the recruitment will be completed is 30 September 2019.

List Of Abbreviations

QOL: Quality of Life; CBD: Cannabidiol; THC: delta-9-tetrahydrocannabinol; MMSE: Mini-Mental State Examination; NPI-NH: Neuropsychiatric Inventory Questionnaire—Nursing Homes; CMAI: Cohen Mansfield Agitation Inventory; QOL-AD: Quality of Life –Alzheimer's disease

Declarations

Ethics approval has been granted by the Human Research Ethics Committee at the University of Notre Dame Australia (UNDA; approval number: 018091F). All participants including the residents and their family members will need to consent to participate. The results gathered beyond this protocol paper will

be presented on the total sample, not on individual cases and all participants will be given a unique identification number to de-identify their information.

Availability of data and materials

Not applicable.

Supplementary Files

Appendix A

Acknowledgements

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Authors contributions

AT, CB, MB and JC designed the trial protocol alongside MGC pharmaceuticals Ltd. AT drafted the manuscript and CB, MC, AV, JS and JC contributed to the manuscript. All authors read and approved the final manuscript.

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This project has been full funded by MGC Pharmaceuticals. MGC Pharmaceuticals informed the design of the study. They will not be involved in the data collection, analysis or interpretation of the data. Meetings held between UNDA and MGC during the collection and analysis of data will only be outlined in a general sense. No specific information about the results will be shared.

Competing interests

The authors declare there may be a perceived conflict of interest of undertaking research funded by MGC Pharmaceuticals, the manufacturer of the drug used in the trial, a number of precautionary steps have been implemented to minimise these. These include input on study design and drug doses was obtained in the development of the research protocol, and obtaining TGA approval for provision of the drug, all MGC Pharmaceutical staff will be excluded from the trial itself including the data collection, analysis an interpretation of the data. Joint management meetings will only discuss the progress of the study in

broad terms to ensure compliance with budgetary issues and appropriate responses to any serious adverse events. UNDA has written permission from MGC Pharmaceuticals Ltd for a worldwide non-exclusive, royalty free license to use the Project Intellectual Property for non-commercial research purposes including consent to publish research findings regardless of the results. The results will be disseminated via brief reports provided to the participating aged care facilities, through manuscript publications and conference presentations.

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Tables

Table 1: *Titration administration including dose and number of sprays*

Day(s)	week	Dose administered (daily)		Number of Spray(s) per dose	Adverse events recorded (time)
		9am	2pm		
1, 2	1	---	2.5mg	1	3pm
3, 4	1	2.5	2.5	1	
5, 6	1	2.5	5	1 - 2	3pm
7, 8	1	5	5	2	
9, 10,	2	5	10	2 - 4	3pm
11, 12,	2	10	10	4	
13, 14	2	10	15	4 - 6	3pm
15, 16	2/3	15	15	6	
17, 18	3	15	20	6 - 8	3pm
19, 20	3	20	20	8	
21, 22	3/4	20	25	8 - 10	3pm
23, 24	4	25	25	10	3pm

AE will be recorded one hour after drug administration on days of dose increase (days highlighted in red) and on the last day of the treatment period

Figures

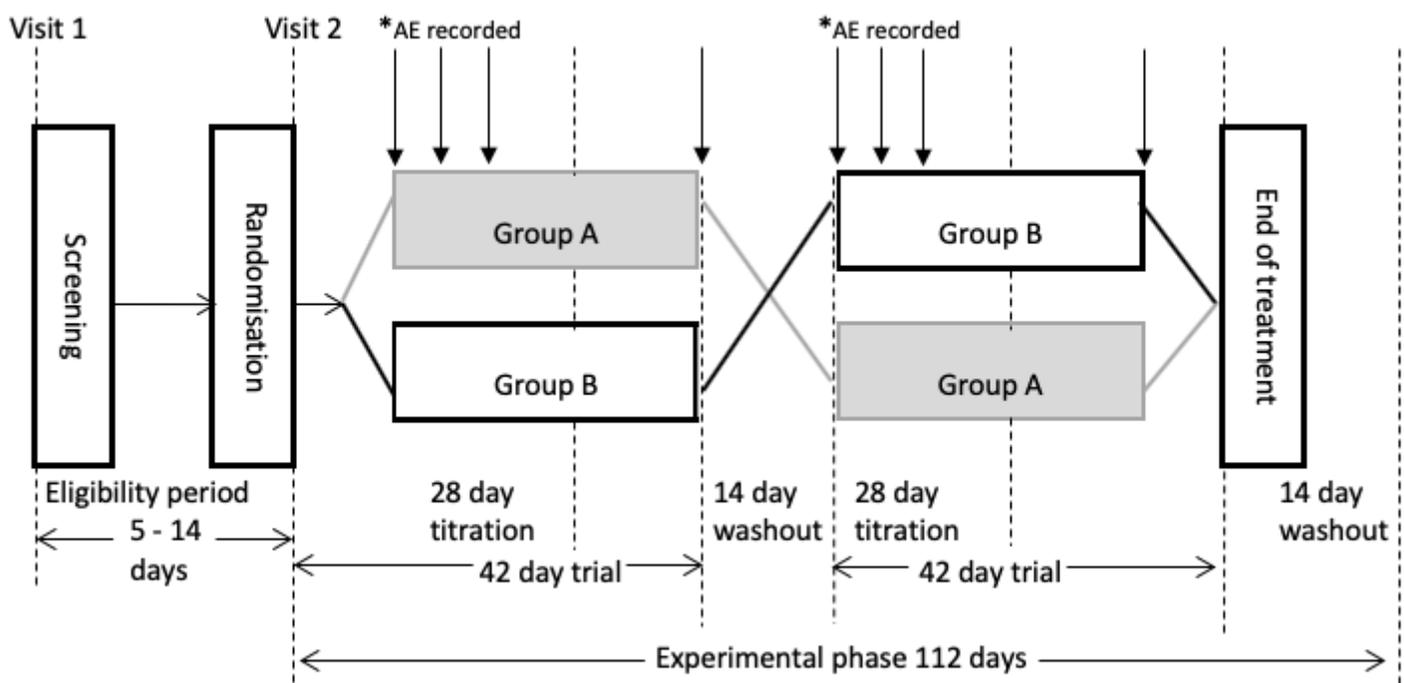


Figure 1

*Adverse events (AE) will be recorded with each dose increase during the titration phase and on the last dose during the intervention phase

Supplementary Files

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