Investigating Nutritional Status in Moderate to Severe Alzheimer’s Disease Patients Enrolled in a Randomized Controlled Trial with Nabilone

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

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Abstract

Nutritional status is of great clinical significance in Alzheimer’s disease (AD) patients as malnutrition can increase risk of morbidity, mortality and severity of neuropsychiatric symptoms. Due to a lack of pharmacological treatments for malnutrition, we investigate the use of nabilone, a synthetic cannabinoid, for the improvement of nutritional status. Patients were recruited from a clinical trial in AD patients with clinically significant agitation. Patients treated with nabilone did not have improved nutritional status over time as assessed by the Mini Nutritional Assessment-Short Form \( (b=-0.020 \ (95\%CI\ -0.27\ to\ 0.23),\ p=0.87) \) and body mass index \( (b=0.020 \ (95\%CI\ -0.13\ to\ 0.17),\ p=0.79) \). Safety outcomes did not significantly differ with respect to nutrition for patients receiving nabilone treatment. By identifying efficacious interventions to manage nutrition in an at-risk population, there may be potential to improve quality of life for AD patients.
Acknowledgements

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<tr>
<td>MNA</td>
<td>Mini Nutritional Assessment</td>
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<tr>
<td>MNA-SF</td>
<td>Mini Nutritional Assessment-Short Form</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>NPS</td>
<td>Neuropsychiatric Symptoms</td>
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<tr>
<td>THC</td>
<td>Tetrahydrocannabinol</td>
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<tr>
<td>CB1</td>
<td>Cannabinoid Receptor 1</td>
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<td>Cannabinoid Receptor 2</td>
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<td>CBs</td>
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<td>CB</td>
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<td>CMAI</td>
<td>Cohen Mansfield Agitation Inventory</td>
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<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders – 5</td>
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<td>MUST</td>
<td>Malnutrition Universal Screening Tool</td>
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<td>ChEIs</td>
<td>Cholinesterase Inhibitors</td>
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<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<td>ONS</td>
<td>Oral Nutritional Supplements</td>
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<td>ECS</td>
<td>Endocannabinoid System</td>
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<tr>
<td>Anandamide</td>
<td>Arachidonyl Ethanolamide</td>
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<tr>
<td>2-AG</td>
<td>2-arachidonoyl glycerol</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>sMMSE</td>
<td>Standardized Mini Mental State Examination</td>
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<tr>
<td>BID</td>
<td>Twice a Day</td>
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<tr>
<td>NPI-NH</td>
<td>Neuropsychiatric Inventory-Nursing Home</td>
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1 Introduction

1.1 Statement of problem

Alzheimer’s disease (AD), a neurodegenerative disorder marked by cognitive deterioration is the most prevalent form of dementia, responsible for 60% to 80% of cases (Alzheimer’s 2016). Nutritional status, or the extent to which nutrients are available to meet metabolic needs, is of great relevance in the care of patients with severe AD (Marino, Ramos et al. 2015). Malnutrition has been defined as a deficient or imbalanced state of energy, protein or nutrients that can negatively impact an individual (Ahmed and Haboubi 2010). Malnutrition in AD has been associated with a lower quality of life, higher rates of infection, greater morbidity, mortality (Meijers, Schols et al. 2014) and caregiver distress (Brocker, Benhamidat et al. 2003). Prevalence rates of malnutrition in AD and related dementias may vary depending on whether an individual resides in a community or long-term care setting. Tombini et al. found that 54% of outpatients with AD assessed with the Mini Nutritional Assessment (MNA) were found to be malnourished, while 41% were at risk of malnutrition (Tombini, Sicari et al. 2016). Among long-term care patients with dementia, 60% and 29% were found to be at risk of malnutrition or malnourished, respectively (Suominen, Muurinen et al. 2005). Chang et al. found 21.6% of long term care residents to be malnourished, based on a body mass index (BMI) of less than 18.5 kg/m² (Chang, Lin et al. 2017), while Faxen-Irving et al. identified 28% of dementia patients as underweight based on a BMI less than 22 kg/m² (Faxen-Irving, Fereshtehnejad et al. 2014).

To evaluate nutritional status, a combination of biochemical and anthropometric measures as well as clinical assessments are often utilized (Knox, Zafonte-Sanders et al. 2003). However, there is no gold standard assessment for evaluating malnutrition in AD. The MNA and MNA-SF have been validated for the assessment of nutritional status in geriatric patients (Kaiser, Bauer et
al. 2009). The creation of the MNA served to address a gap in geriatric research with respect to evaluating nutritional status in the elderly (Vellas, Villars et al. 2006). According to the MNA-SF, components of nutritional status include food intake, weight loss, mobility, whether a patient has suffered a recent episode of psychological stress or acute disease, neuropsychological problems and BMI (Rubenstein, Harker et al. 2001, Kaiser, Bauer et al. 2009). BMI has also frequently been utilized as an independent and objective measure of nutrition and lower BMI has been associated with increased mortality (Garcia-Ptacek, Faxen-Irving et al. 2014). Innate characteristics such as age and gender have been shown to play an influential role in nutritional status (Sanders, Behrens et al. 2016). As well, polypharmacy has been indicated as having a negative impact on nutritional status in the elderly (Griep, Mets et al. 2000), while psychotropic medications and cognitive enhancers have been shown to impact weight (Agostini, Han et al. 2004, Ellis 2005).

Poor nutritional status may be particularly important in AD sufferers with concomitant neuropsychiatric symptoms (NPS). White et al. found a negative correlation between BMI and NPS such as agitation and aggression, irritability and aberrant motor behaviour (White, McConnell et al. 2004). Similarly, Spaccavento et al. found NPS such as irritability and agitation to be associated with changes in eating patterns (Spaccavento, Del Prete et al. 2009). As malnutrition and its associated components have been linked with numerous psychological and functional impairments in an already at-risk population, elucidating safe and efficacious interventions in a population with clinically significant agitation is of great clinical importance.

Current treatment recommendations directed towards improving weight or BMI may include soothing mealtime music (Wong, Burford et al. 2008) or oral nutritional supplements (ONS) (Faxen-Irving, Andren-Olsson et al. 2002). However, little attention has been paid to
pharmacotherapeutic interventions. When utilizing pharmaceuticals, the presence of treatment emergent adverse events (TEAEs) must be closely monitored, as patient safety is the first priority. TEAEs are considered adverse events that occur following the onset of treatment or symptoms present prior to treatment that worsen in severity following treatment. A small randomized controlled trial (RCT) evaluated the use of the cannabinoid (CB) dronabinol, in a severe AD patient population (Volicer, Stelly et al. 1997). A related treatment measure involves the administration of nabilone, a synthetic CB wherein the central component is a tetrahydrocannabinol (THC) analogue. Nabilone, a cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) partial agonist may have the potential to improve nutritional status as studies have shown that ligands that act on CB1 can increase food intake and weight gain. The use of nabilone as a pharmacotherapy for the management of nutritional status in AD has yet to be thoroughly examined. Therefore, by conducting a placebo-controlled crossover trial, we hope to evaluate the safety and efficacy of nabilone for the improvement of nutritional status in AD patients with clinically significant agitation.

1.2 Purpose of Study and Objective

The primary objective of this study was to determine whether nabilone, a synthetic CB could improve nutritional status and therefore elucidate a pharmacological intervention that may be used to target malnutrition in patients with moderate to severe AD and clinically significant agitation. The study investigated the nutritional status of each patient by monitoring MNA-SF scores and BMI values overtime. Additionally, safety outcomes were monitored over the duration of the trial to determine whether the presence of adverse events during nabilone treatment might be contributing to a decline in nutrition.
1.3 Statement of Research Hypotheses and Rationale for Hypotheses

1.3.1 Primary Hypothesis

| Compared to placebo, patients treated with nabilone will have improved nutritional status, as indicated by increased scores on the MNA-SF over time. |

Rationale: The MNA-SF is a validated and widely used measure of nutritional status (Kaiser, Bauer et al. 2009). The MNA-SF categorizes geriatric patients into those of normal nutritional status, at risk of malnutrition or malnourished (Guigoz 2006, Kaiser, Bauer et al. 2009). Poor nutritional status may be the result of involuntary weight loss, low BMI (Wells and Dumbrell 2006), deficient caloric or nutrient intake (Johansson, Wijk et al. 2017). Consistent with its role as a risk stratification tool, the MNA-SF also includes the patients’ neuropsychological status, mobility and the presence of acute disease. Cannabinoids (CBs) have been shown to improve food intake and result in weight gain in several clinical populations (Sallan, Cronin et al. 1980, Gorter 1991, Struwe, Kaempfer et al. 1993). Nabilone, a CB with CB1 partial agonist activity, may have the potential to improve scores on several domains of the MNA-SF by stimulating an increase in appetite, thereby increasing food intake, and ultimately, increasing weight gain. A small placebo-controlled crossover trial found that AD patients receiving dronabinol, a CB1 and CB2 agonist demonstrated significant increases in body weight (Volicer, Stelly et al. 1997). While those results suggest that CBs might be effective, a partial agonist has the potential advantage of binding to CB receptors with reduced risk of promoting side effects that may occur with a full agonist. Therefore, the primary goal of this study was to determine whether nabilone,
a CB1 and CB2 partial agonist might have beneficial effects for nutritional status in a cohort of AD patients with clinically significant agitation

1.3.2 Secondary Hypothesis

| Compared to placebo, patients treated with nabilone will have improved BMI values over time. |

Rationale: Nabilone, a CB with chemical properties similar to that of THC (Jager and Witkamp 2014) may have the potential to improve BMI, a measure of nutrition. Wiley et al. investigated feeding behaviours in mice receiving the CB1 agonist THC and a CB1 antagonist. Increased food intake was observed in mice receiving THC, while the CB1 antagonist significantly reduced food intake (Wiley, Burston et al. 2005). Similarly, Woodward et al. investigated the CB1/2 agonist dronabinol in dementia patients and found that patients had a significant increase in food intake at each meal (Woodward, Harper et al. 2014). As BMI is a measure of weight divided by height, these findings suggest that there may be potential for improved BMI resulting from an increased food intake. Volicer et al.’s placebo-controlled crossover trial demonstrated an increase in BMI following dronabinol treatment relative to placebo in AD patients. However, due to several study limitations, further exploration into the benefits of CBs on BMI are warranted. Therefore, the secondary goal of this study was to investigate whether nabilone would result in improved BMI values.
1.3.3 Exploratory Hypothesis


Rationale: Monitoring safety outcomes in a clinical trial is of crucial importance. Prior trials utilizing synthetic CBs in dementia patients have noted that reactions such as tiredness and somnolence may be common side effects (Volicer, Stelly et al. 1997, Woodward, Harper et al. 2014) in addition to dry mouth and dizziness (Tsang and Giudice 2016). If a medication does not demonstrate a safe side effect profile, its use will be limited regardless of efficacy. Few studies investigate the effects of safety outcomes as they pertain to nutritional status, an important domain in patients with AD. Therefore, by investigating safety outcomes in regards to nutritional status, it will be possible to evaluate if treatment emergent side effects contributed to nutritional changes in this cohort.

1.4 Review of Literature

1.4.1 Alzheimer’s disease

Alzheimer’s disease (AD), the most prevalent form of dementia, is responsible for 60% to 80% of cases (Alzheimer's 2016) and is marked by the presence of cognitive and functional deterioration and NPS such as anxiety, agitation and sleep disturbances (Selbaek, Engedal et al. 2013, Alzheimer's 2016). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the diagnosis of AD requires symptoms of memory impairment in addition to aphasia, apraxia, agnosia or a disturbance in executive functioning (Association 2013). The
presence of apolipoprotein E4 has been identified as a genetic risk factor for the development of AD (Carmona, Hardy et al. 2018) and has shown to be a strong predictor of clinical progression of the disease (Liu, Liu et al. 2013). Contributing factors to the neuropathology of AD development include the accumulation of beta amyloid protein and neurofibrillary tangles, aggregates of phosphorylated tau protein (Serrano-Pozo, Frosch et al. 2011). A likely consequence of these events includes synaptic dysfunction and neuronal loss (Niikura, Tajima et al. 2006, Serrano-Pozo, Frosch et al. 2011).

With the rising prevalence rate of AD, the number of individuals affected by this disease is expected to reach roughly 106.8 million cases by 2050 (Brookmeyer, Johnson et al. 2007). AD is a leading cause of morbidity and mortality in individuals over the age of 65 years old (Alzheimer's 2016), reinforcing the substantial need for safe and efficacious therapies that may delay onset of disease, slow disease progression and manage symptoms that help to improve quality of life.

1.4.2 Nutrition in Alzheimer’s disease

The world health organization defines nutrition as the intake of food, relative to an individual’s dietary needs (Organization 2018). In conjunction with the cognitive and behavioural decline that accompanies the disease process, identifying, monitoring and management of nutritional deficits are of critical importance. A common finding among the literature reveals that age is a risk factor for the development of malnutrition (Ahmed and Haboubi 2010). Additionally, insufficient food intake and weight loss are highly prevalent in patients with AD. Factors that may contribute to a decrease in food intake include difficulty chewing or swallowing
as well as an overall discomfort during food consumption, all of which may be a result of unrecognized pain, poor oral hygiene or poor fitting dentures (Murphy, Holmes et al. 2017).

While malnutrition is considered to be an imbalance of energy and may refer to a deficient or excess state of nutrients, it is often used synonymously with the term undernourished (Shetty 2003, Shetty 2006). However, undernourishment specifically refers to an inadequate consumption of food and energy to meet the body’s needs (Shetty 2006). A proposed definition of malnutrition in the elderly categorizes it as a state of excess or imbalance of energy, protein or other nutrients, which may result in negative consequences on functional or clinical outcomes (Ahmed and Haboubi 2010). Meijers et al. stated that malnutrition may be classified as cachexia, the involuntary loss of fat free mass, sarcopenia, the loss of muscle mass and strength or involuntary weight loss within an elderly population (Meijers, Schols et al. 2014). Koyama et al. proposed a quantitative definition of malnutrition as total protein level less than 6.5 g/dL and serum albumin less than 3.5 g/dL (Koyama, Hashimoto et al. 2016).

Frequently used scales to assess nutritional status in geriatric patients include the MNA, MNA-SF, and the malnutrition universal screening tool (MUST). The MNA is a well-validated comprehensive tool and is highly correlated with clinical and objective measures of nutrition (Guigoz 2006). The MNA-SF has been validated with the MNA and is a practical and accessible means of assessing nutritional status in geriatric medicine (Kaiser, Bauer et al. 2009). The MUST, although also a short screening tool was not specifically designed for clinical use in a geriatric population and is better suited for adults in a community setting (Kondrup, Allison et al. 2003, Anthony 2008). In addition, BMI has been utilized as an objective measure of nutritional status in various populations (Bailey and Ferro-Luzzi 1995, Barao and Forones 2012).
Malnutrition and weight loss are common occurrences associated with AD. Prevalence rates of malnutrition and those at risk of malnutrition often vary based on patient setting, as elderly living in long term care frequently have higher rates of malnutrition compared to community dwelling elderly. A review conducted by Guigoz identified mean prevalences of malnutrition of 1% in healthy elderly living in the community, 5% in AD patients residing at home, and 37% of institutionalized elderly using the MNA (Guigoz 2006). Tombini et al. identified 41% of patients at risk of malnutrition and 54% as malnourished among outpatients with AD using the MNA (Tombini, Sicari et al. 2016). Medication compliance may vary between patients residing in long-term care and those in a community setting as the likelihood of receiving an incorrect dosage of a prescription, receiving medication at the improper time and non-adherence rates have been shown to differ based on a patients living environment (Jin, Sklar et al. 2008). Saragat et al. found 27% and 54% of men and women, respectively to be at risk of malnutrition, while 7% of women were found to be malnourished among long term care residents with AD (Saragat, Buffa et al. 2012). Agarwalla et al. assessed factors associated with worsening of nutritional status in an elderly cohort and found that females were at significantly greater risk of being malnourished and at risk of malnutrition, compared to their male counterpart (Agarwalla, Saikia et al. 2015).

There are several modifiable nutritional risk factors that may contribute to the onset of the disease process. Diets high in saturated fat may contribute to high plasma cholesterol levels and ultimately, a greater risk of AD development (Morris, Evans et al. 2003, Morris 2009). In contrast, diets high in fish, omega-3 fatty acids and antioxidants such as vitamin E have been associated with lower risk of cognitive decline and AD (Ortega, Requejo et al. 1997, Morris 2009, Smith and Blumenthal 2016). Patient demographics such as age (Ahmed and Haboubi
and gender (Agarwalla, Saikia et al. 2015) are also important factors in nutritional decline as food intake and appetite have been shown to decline with increasing age (Ahmed and Haboubi 2010), and were found to be lower for females in a recent study by Yildiz et al. (Yildiz, Buyukkoyuncu Pekel et al. 2015). Conversely, nutritional deficits and malnutrition are also a consequence of AD progression. A study examining the relationship between malnutrition and dementia in long term care residents found a significantly higher prevalence of malnutrition in those with dementia compared to those without over a 4-year duration (Meijers, Schols et al. 2014). Factors that may contribute to this decline include worsening of cognitive function and behavioural disturbances (Spaccavento, Del Prete et al. 2009), dysphagia (Gillette-Guyonnnet, Nourhashemi et al. 2000) and prescribed medications (Meijers, Schols et al. 2014). Studies have found an inverse relationship between polypharmacy and nutritional status among the elderly, indicating that a higher number of prescriptions may put a patient at greater risk of poor nutritional status (Griep, Mets et al. 2000, Schilp, Wijnhoven et al. 2011). Medications that may induce weight loss in elderly patients include non-steroidal anti-inflammatory drugs (Ahmed and Haboubi 2010), frequently used for pain management (Guerriero, Bolier et al. 2016), and cholinesterase inhibitors (ChEIs), one of the most commonly used cognitive enhancers in dementia patients (Ellis 2005, Sheffrin, Miao et al. 2015). Sheffrin et al. found that there was greater risk of clinically significant weight loss over a 12-month period for dementia patients taking ChEIs, compared to those who were not on the medication (Sheffrin, Miao et al. 2015). Additionally, the antidepressant fluoxetine has been shown to induce weight loss in elderly patients (Brymer and Winograd 1992). Conversely, many other types of antidepressants and second-generation antipsychotics have been shown to promote weight gain (Fava 2000, Bak, Fransen et al. 2014).
Weight loss is a common occurrence with the onset of dementia and becomes more prominent with disease severity (Volkert, Chourdakis et al. 2015). Changes in weight may be due to multiple factors including atrophy to the mesial temporal cortex (Volkert, Chourdakis et al. 2015), nutrient deficiencies (Morley 2010), NPS (Spaccavento, Del Prete et al. 2009) as well as a dependency on caregivers for assistance with activities of daily living (Volkert, Chourdakis et al. 2015). Malnourished dementia patients as well as those at risk of malnutrition face a multitude of concerns such as increased frailty and risk of hospitalization, worsening of agitation and poor mobility (Yildiz, Buyukkoyuncu Pekel et al. 2015), a component of nutritional status (Kaiser, Bauer et al. 2009). Therefore, monitoring and working to improve the nutritional status of patients with AD is of great clinical relevance to ensure optimal nutrition as well as reduce modifiable symptoms in an already vulnerable population.

1.4.3 Nutrition and Agitation in AD

Risk of malnutrition and behavioural disturbances have been shown to be associated with dementia severity (Srikanth, Nagaraja et al. 2005, Volkert, Chourdakis et al. 2015) and therefore warrant exploration for potential treatments to lessen symptoms and improve quality of life. Treating malnutrition may be an essential component in mitigating AD symptoms, as poor nutritional status has also been associated with NPS severity, and NPS prevalence has been shown to range from 50-80% among patients with AD (Lyketsos, Lopez et al. 2002). The REAL-FR study revealed that nutritional decline, demonstrated through a decrease in MNA score was associated with an increase in neuropsychiatric inventory (NPI) scores from baseline to two year follow up (Cortes, Nourhashemi et al. 2008). Of the many NPS present in AD, agitation is highly prevalent, found in 20-50% of patients (Lyketsos, Carrillo et al. 2011). Guerin et al. investigated
risk factors for weight loss in patients with AD and identified higher scores on the CMAI, indicative of greater agitation to be a significant variable (Guerin, Andrieu et al. 2009). In patients with dementia, the perception of pain may also be a contributing factor to a decline in nutrition and NPS. A lack of communicative abilities in this patient population may result in symptoms of pain left untreated or expressed in the form of NPS such as agitation (Booker and Booker 2017).

BMI, a component of nutritional status, has been negatively correlated with NPS such as agitation and aggression (White, McConnell et al. 2004); while agitation has also been associated with inadequate protein intake and alterations to food preference (Spaccavento, Del Prete et al. 2009). It is possible that greater levels of agitation result in increased energy expenditure and/or a decrease in daily nutrient consumption, increasing the risk of malnourishment among patients (White, McConnell et al. 2004). Malnutrition and weight loss in AD are also associated with a greater risk of falls and poorer quality of life, both of which may contribute to higher levels of agitation (Guerin, Andrieu et al. 2009). Therefore, the literature suggests that there is a strong association between several components of nutritional status such as weight, BMI and food intake with agitation. As a result, it is possible that treating and improving nutrition in this cohort will also reduce symptoms of agitation.

1.4.4 Subjective versus objective measures of nutrition

Although there is no gold standard for evaluating nutritional status in moderate to severe AD, the MNA-SF has been validated as a subjective measure of nutrition in a geriatric population, while BMI is frequently used as an objective measure of nutrition. Evaluating
nutrition through the use of the MNA-SF and/or BMI both present with unique benefits and challenges. The MNA-SF is an accessible and realistic tool to use in clinical practice and nursing home settings (Kaiser, Bauer et al. 2009). By using the MNA-SF, healthcare providers have the ability to assess a combination of factors that influence nutrition, and ultimately create a composite score of nutritional status. However, as a result of being a subjective measure and the particular framing of certain questions on the MNA-SF, the scale must be thoughtfully interpreted. For example, many questions are asked in reference to a 3-month period. As a result, this has the potential for varied interpretations depending on the caregiver completing the scale. Additionally, the MNA-SF has been validated as a screening tool for nutritional status within a geriatric population, but has not specifically been validated as a diagnostic tool for individuals with moderate-to-severe AD. Taking this into consideration, the MNA-SF is still the most suitable scale available, based on its prior use in a geriatric specific sample.

Using an anthropometric measure of nutrition such as BMI provides the advantage of being a quantitative measurement and may reveal important physical changes before they would be accurately detected though clinical evaluation (Bailey and Ferro-Luzzi 1995). Ferro-Luzzi et al. claimed that BMI might be an accurate independent measure for assessing dietary deficiencies (Ferro-Luzzi, Sette et al. 1992). However, using BMI as an independent marker of nutrition in a geriatric population may have some limitations. BMI is calculated by dividing weight in kilograms by height in meters squared (Garrow and Webster 1985). In a geriatric population, particularly with AD, obtaining an accurate measure of height can be challenging as a result of poor posture and loss of muscle tone (Ahmed and Haboubi 2010). In addition, measures of weight may be recorded inaccurately if a patient is in a wheelchair (Sherrod, Dew et al. 2017).
bedridden (Kaiser, Bauer et al. 2009) or suffering from health concerns such as edema (Ahmed and Haboubi 2010).

1.4.5 Current recommendations for improving nutrition in AD

To date, there is a lack of efficacious treatment options available to treat nutritional deficits in AD. While many nutritional interventions have been proposed for the treatment of malnutrition in dementia, there are few that have been tested using RCTs and few that have demonstrated consistent results. As well, few studies have investigated the use of nutritional therapies in AD patients specifically. An intervention that has shown promise involves the use of ONS (Carver and Dobson 1995, Faxen-Irving, Andren-Olsson et al. 2002, Pivi, da Silva et al. 2011). Faxen-Irving et al. evaluated the use of ONS combined with staff education in comparison to controls who received regular daily care among a cohort of individuals with dementia. At their 6-month follow up, patients who received oral liquid supplements gained an average of 3.4 kg, in comparison to the unchanged weight of the control group (Faxen-Irving, Andren-Olsson et al. 2002). A prospective study by Pivi et al. found that AD patients receiving ONS twice daily had a significant improvement in weight and BMI after 6 months compared to controls and those randomized to nutrition education (Pivi, da Silva et al. 2011). However, both studies contained a small sample size without a placebo control group. As such, ONS may be a promising intervention for AD, but a placebo controlled RCT with a larger sample size is warranted.

Riviere et al. investigated the implementation of educational interventions in caregivers of outpatients with AD. Compared to controls, the intervention group had a significant increase
in weight and MNA score from baseline to 12-month follow up (Riviere, Gillette-Guyonnet et al. 2001). Conversely, a study evaluating the use of morning nutritional supplements in AD found that patients with lower BMI’s were more likely to compensate for this supplementation by reducing their food intake at lunchtime (Young, Greenwood et al. 2004). It has been found that greater AD severity increases one’s risk of being malnourished or at risk of malnutrition (Gillette-Guyonnet 2005, Spaccavento, Del Prete et al. 2009), thus increasing the need for effective interventions. Therefore, targeting patients with severe AD and lower BMIs likely requires an alternate approach. Additional interventions that have shown potential to increase food intake for dementia patients include the use of soothing music during meal times (Ragneskog, Brane et al. 1996) and a decentralized meal service, whereby meal portioning occurs on a resident’s floor, allowing for more specific food distribution per person (Shatenstein and Ferland 2000). Charras and Fremontier investigated the effects of shared meal times between staff and residents with dementia and reported an increase in weight compared to controls (Charras and Fremontier 2010).

Spaced retrieval and Montessori based activities have demonstrated positive effects in some dementia patients through increased BMI and MNA scores (Wu and Lin 2013), however results are inconclusive, as patients in other studies have not revealed these same improvements (Lin, Huang et al. 2010, Lin, Huang et al. 2011). Despite the potential in several of the above-mentioned treatments, the gold standard for efficacious nutritional interventions for AD patients remains unclear. As such, patients may greatly benefit from utilizing a novel pharmacologic approach.
1.4.6 The Endocannabinoid System

The endocannabinoid system (ECS) has emerged as a potential therapeutic target for various psychiatric and neurodegenerative disorders. The ECS is comprised of endogenous CBs arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG) as well as two primary CB receptors CB1 and CB2 (Lu and Mackie 2016). The ECS pathway begins with the synthesis of the endogenous CBs and acts through retrograde signalling (Pacher, Batkai et al. 2006). Following membrane depolarization, the binding of glutamate to postsynaptic glutamate receptors induces the opening of calcium channels, causing the accumulation of calcium. This results in the synthesis of endogenous CBs from the phospholipid bilayer of the post-synaptic membrane (Lu and Mackie 2016). The release of endogenous CBs from the cleavage of phospholipid molecules results in the diffusion of endogenous CBs across the synaptic cleft whereby they bind to CB receptors in the presynaptic membrane, reduce further calcium influx and cause a suppression of neurotransmitter firing. Anandamide and 2-AG are inactivated through reuptake and enzymatic degradation (Bisogno 2008). Anandamide is broken up by fatty acid amide hydrolase-1 and fatty acid amide hydrolase-2, while 2-AG is largely hydrolyzed by monoacylglycerol lipase (Di Marzo and De Petrocellis 2012). 2-AG has been shown to be present in the brain in abundantly higher amounts than anandamide (Stella, Schweitzer et al. 1997), and studies have revealed that it is a lower affinity ligand for the CB1 receptor compared to anandamide (Devane, Hanus et al. 1992, Sugiura, Kondo et al. 1995). Clinical work investigating 2-AG found that study participants who consumed palatable food had increased plasma levels of 2-AG and ghrelin compared to those who consumed nonpalatable food (Monteleone, Piscitelli et al. 2012), suggesting an inherent relationship between the rewarding properties of food intake and the ECS. Kirkham et al. evaluated endocannabinoid levels in rats
and found that during fasting, levels of 2-AG in the hypothalamus and limbic forebrain as well as anandamide in the limbic forebrain were higher compared to 2-AG levels in the hypothalamus upon feeding (Kirkham, Williams et al. 2002). This finding contributes to the literature suggesting the role of endocannabinoids in the regulation of appetite. Leptin, an appetite modulator associated with the suppression of food intake and weight loss has also been inversely correlated with levels of endogenous CBs (Monteleone and Maj 2013). Ghrelin and endogenous CBs, both orexigenic compounds, target the adenosine monophosphate-activated protein kinase pathway, which promotes gluconeogenesis and ultimately stimulates appetite (van Thuijl, Kola et al. 2008).

CB receptors are widely understood to be G-protein coupled receptors, which consist of seven transmembrane domains. CB1 and CB2 have both been characterized as inhibitory G protein receptors (Mackie 2008) and are located in abundant amounts in the central nervous system (CNS), particularly in the basal ganglia, hippocampus and cerebellum and within cells of the immune system, respectively (Aso and Ferrer 2014). CB1 is also located within liver and skeletal muscles, adipose tissue, and the digestive tract (Mackie 2008). A number of animal studies have revealed the association between CB receptors and food intake, particularly CB1. Wiley et al. demonstrated the effects of administering THC, a CB1 agonist, SR141716A, a CB1 antagonist and a CB2 receptor antagonist SR144528 to food-restricted mice. THC, a CB1/CB2 agonist, resulted in a significant increase in food intake. The CB1 antagonist SR141716A significantly decreased food intake, while the CB2 receptor antagonist did not alter food intake (Wiley, Burston et al. 2005). Similarly, Williams and Kirkham revealed that the appetite stimulant effects of THC were mediated by CB1 antagonist SR141716 but not by CB2 antagonist
SR144528 (Williams and Kirkham 2002). These results, demonstrated consistently through the literature, indicate the importance of CB1 in the modulation of food intake and appetite.

1.4.6.1 The ECS in healthy aging

Involved in various homeostatic mechanisms, the ECS aids in the regulation of a number of physiological functions throughout the body (Lu and Mackie 2016). A decline in ECS activity appears to accompany the aging process as indicated by a decrease in CB1 binding found in the basal ganglia (Romero, Berrendero et al. 1998), cerebellum and cerebral cortex (Berrendero, Romero et al. 1998) of aging rats. By genetically modifying CB1 in healthy mice, animal researchers revealed alterations to learning and memory associated with an age-related decline suggesting that a deficiency of CB1 likely contributes to the progression of aging (Bilkei-Gorzo, Racz et al. 2005). Conversely, Van Laere et al. found a sex dependent and region dependent increase in CB1 binding with aging using a high affinity radio ligand. Female participants revealed higher binding levels in the basal ganglia and hippocampal region of the limbic system while males had a greater degree of binding in other areas of the limbic system and the cortico-striato-thalamic-cortical circuit (Van Laere, Goffin et al. 2008).

1.4.6.2 The ECS in Alzheimer’s disease

The ECS has become a region of interest for the treatment of neurological disorders. In neurodegenerative disorders such as AD, ECS activity often becomes heightened during periods of CNS inflammation (Mulder, Zilberter et al. 2011). *In vitro* models have demonstrated that elevated levels of anandamide and synthetic CB agonists mediate the effects of inflammation by
limiting the production of pro-inflammatory markers (Ortega-Gutierrez, Molina-Holgado et al. 2005). Animal models with AD pathology have revealed elevated levels of 2-AG and CB2 (van der Stelt, Mazzola et al. 2006, Esposito, Iuvone et al. 2007) but decreased amounts of anandamide and CB1 (Esposito, Iuvone et al. 2007). Activation of CB1 and CB2 using a synthetic CB in rat models of AD prevented cognitive deterioration and amyloid beta induced microglia activation (Ramirez, Blazquez et al. 2005).

The neuroprotective effects of CBs in clinical research are becoming increasingly understood as CB1 has been found to reduce glutamate release (Hoffman, Laaris et al. 2010) and CB2 had been shown to promote decreased inflammation (Ashton and Glass 2007). A decrease in the quantity of CB1 has been found in brain tissue of AD patients, particularly in the hippocampus and basal ganglia (Westlake, Howlett et al. 1994) as well as in regions of microglial activation (Ramirez, Blazquez et al. 2005). Similarly, a decrease in levels of anandamide has been correlated with severity of cognitive impairment and amount of amyloid beta 42 (Jung, Astarita et al. 2012), a peptide highly abundant in AD pathology (Younkin 1998). In contrast, Benito et al. detected high amounts of fatty acid amide hydrolase and CB2 in plaques associated with astrocytes and microglia with no effect to CB1 (Benito, Nunez et al. 2003). In the post-mortem AD brain, CB2 has been identified in copious amounts and receptor levels have been correlated to the amount of beta amyloid deposition (Benito, Nunez et al. 2003).

THC, a CB1 and CB2 agonist has been shown to have anti-inflammatory, psychotropic and neuroprotective properties (Hampson, Grimaldi et al. 1998), and may also exhibit side effects such as somnolence and euphoria at higher concentrations (Karschner, Darwin et al. 2011). THC has also been shown to modulate opioid, serotonergic and glutamatergic receptors, indicating that there may be some clinical benefit for treating pain (Manzanares, Julian et al.
Synthetic analogs of THC, such as nabilone and dronabinol have been utilized to evaluate the potential for improving NPS (Walther, Mahlberg et al. 2006, Passmore 2008, Woodward, Harper et al. 2014) as well as symptoms of pain (Wissel, Haydn et al. 2006, Tsang and Giudice 2016), nausea (Dalzell, Bartlett et al. 1986) and weight loss (Gorter 1991, Struve, Kaempfer et al. 1993) in various clinical populations.

1.4.7 Nabilone

Nabilone, a synthetic CB with CB1 and CB2 partial agonist activity is currently approved by the Health Canada Therapeutic Products Directorate as an anti-emetic in chemotherapy (Dalzell, Bartlett et al. 1986). The half-life of nabilone and its metabolites are 2 and 35 hours, respectively (Ward and Holmes 1985). The onset of action occurs between 1 and 1.5 hours after oral administration with peak effects reached between 1 to 4 hours (Ward and Holmes 1985). Nabilone has a bioavailability of 20% after first pass metabolism and a distribution of 12.5 L/kg (Tsang and Giudice 2016).

Synthetic CBs such as nabilone are often associated with risk of euphoria, somnolence and dry mouth (Ward and Holmes 1985), but trials with AD patients have thus far demonstrated reasonably safe side effect profiles, suggesting that adverse events may be dose dependent. Ahmedzai et al. suggested the possibility that symptom severity resulting from nabilone treatment may decrease as the treatment progresses (Ahmedzai, Carlyle et al. 1983). Conservative doses ranging from 0.75 mg to 1.5 mg for oral THC (van den Elsen, Ahmed et al. 2015, van den Elsen, Ahmed et al. 2015), 2.5 mg to 7.0 mg of dronabinol (Volicer, Stelly et al. 1997, Walther, Mahlberg et al. 2006, Mahlberg and Walther 2007, Walther, Schupbach et al. 2006).
2011, Woodward, Harper et al. 2014) and 0.5 mg to 1.0 mg for nabilone (Passmore 2008) have been administered in various studies. To date, Passmore is one of few clinicians to evaluate nabilone for the treatment of clinically significant agitation in a single patient with AD. Administered at a dose of 0.5 mg daily, with an increase to 0.5 mg twice daily for 6 weeks, nabilone was well tolerated and the patient had a significant decrease in agitation (Passmore 2008). Carefully monitoring safety outcomes and adverse events that might result from nabilone is critical in an at-risk population, such as those with clinically significant agitation and moderate-to-severe AD.

1.4.7.1 Nabilone and Nutrition

Few studies have been designed with the intent of exploring the effects of a synthetic CB to improve nutritional status. Agonists with the ability to bind to CB1 have the potential to influence nutritional status as evidenced through previous clinical work using an alternate synthetic CB, dronabinol. In a 12-week placebo-controlled crossover trial, Volicer et al. found that AD patients receiving dronabinol during the first phase of the study had a significant weight gain of 7.0 kg while those who received study drug during the second phase had a significant weight gain of 2.3 kg compared to those receiving placebo. Evidently, those who received study drug during the first phase of the trial demonstrated greater weight gain than patients receiving placebo during the first phase of study, indicating the likelihood of carryover effects (Volicer, Stelly et al. 1997). A retrospective chart review investigating the use of dronabinol in patients with dementia found that although there were no significant changes in body weight, food intake per meal significantly increased (Woodward, Harper et al. 2014). Recently, a placebo-controlled trial using nabilone to treat cancer-induced anorexia found that patients receiving nabilone had a
significant increase in their caloric intake and carbohydrate consumption compared to patients receiving placebo (Turcott, Del Rocio Guillen Nunez et al. 2018).

In light of previous success using CB1/CB2 agonists to improve nutrition in various clinical populations, there is sufficient evidence to warrant an investigation into the use of nabilone in an AD population. In addition, the combined effect of targeting CB1 and CB2 may allow for both a direct improvement in nutritional status, as well as an indirect benefit, a result of targeting receptors with the potential to concomitantly reduce NPS. With the potential to reduce agitation, improvements in nutrition may also be identifiable as a byproduct of improved symptoms of agitation.
2 Methods

2.1 Study design

This study was a randomized, double blind, placebo-controlled crossover design (Figure I), to determine the safety and efficacy of nabilone with the potential for a larger phase 3, multicentre trial. Following a one-week placebo run-in, patients underwent two distinct phases of treatment during which they were randomized to receive either placebo or nabilone capsules (active treatment) for 6 weeks each with a one-week placebo washout between treatment phases.

Figure I. Treatment schedule. Blue boxes correspond to scheduled assessments and study visits.

2.2 Participant Selection

All participants for the current study were recruited from an RCT being conducted at Sunnybrook Health Sciences Centre. For the RCT, all patients were recruited from the Veterans Centre at Sunnybrook Hospital, outpatient psychiatry or neurology clinics affiliated with
Sunnybrook Health Sciences Centre. Patients who met the current DSM-5 criteria for dementia of the Alzheimer’s type, or mixed AD with vascular dementia were considered for inclusion. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre. All patients and/or their legal substitute decision makers provided written, informed consent prior to study enrolment.

### 2.3 Inclusion Criteria

Patients were enrolled in the study if they met the following criteria:

1. Male or female ≥ 55 years of age
2. DSM-5 criteria for Major Neurocognitive Disorder due to AD. Patients with Major Neurocognitive Disorder due to AD and Major Vascular Neurocognitive Disorder (i.e. mixed AD and cerebrovascular disease) were also considered
3. Standardized Mini Mental State Examination (sMMSE) (Molloy and Standish 1997) score ≤ 24
4. Presence of clinically significant agitation, assessed as a score ≥ 3 on the NPI agitation subscale
5. If treated with a cognitive enhancing medication such as ChEIs and/or memantine, dosage must have been stable for a minimum of 3 months. If ChEIs and/or memantine were discontinued, patient was deemed eligible to enroll following 1 month

### 2.4 Exclusion criteria

Patients were excluded from the study if they met any of the following:
1. Change in psychotropic medications less than 1 month prior to study randomization
2. Medical history with contraindications to nabilone
3. Significant cardiovascular disease including uncontrolled hypertension, clinically significant ischemic heart disease or arrhythmia and/or severe heart failure
4. History of other psychiatric or neurological conditions (i.e. psychotic disorders, schizophrenia, epilepsy) or previous abuse of/dependence on marijuana
5. Clinically significant delusions and/or hallucinations, assessed as a score ≥ 4 on the NPI delusions and hallucinations subscales

2.5 Study intervention and study schedule

Assessments were completed for the following weeks: screening/placebo run-in (week -1), baseline (week 0/beginning of treatment 1), week 2, 4, 6 (end of treatment 1), 8 (beginning of treatment 2), 10, 12 and 14 (end of treatment 2) as well as for week 15, a safety follow-up. Demographic data including age, gender, diagnosis date, concomitant medications, and height were collected during each patient’s screening visit. Measures of behaviour, nutrition, pain, vital signs, and adverse events were conducted at each study visit.

All eligible and consented patients began the trial with one week of placebo run-in (week -1). During week 0 (baseline), each patient received 1 capsule (0.25 mg) in the evening for 3 days, followed by 1 capsule (0.25 mg) twice a day (BID) for four days. During week 1, patients received 1 capsule (0.5 mg) each evening, followed by 1 capsule (0.5 mg) BID for week 2. During weeks 3 and 4, the study dose was increased to a maximum of 2 capsules BID (2mg/day total or placebo) or decreased based on tolerability. Following the first three days of week 6 where each patient was maintained at their dosage from the previous week, there was a taper-
down phase for the remaining four days (days four-five were reduced to 1 mg/day total and days six-seven were decreased to 0.5 mg/day total) to reduce the risk of potential withdrawal effects if the patient was receiving active treatment. This method of down-titration ensured that each participant would end his or her respective phase of treatment at the same dose.

2.6 Study Assessments

The MNA-SF was used to evaluate the nutritional status of all patients (Kaiser, Bauer et al. 2009), and the CMAI (Cohen-Mansfield, Marx et al. 1989) and Neuropsychiatric Inventory-Nursing Home (NPI-NH) version (Wood, Cummings et al. 2000) were used to assess behavioural measures. The sMMSE (Molloy and Standish 1997) was used as a screening tool for study inclusion as well as a measure of assessing cognition.

2.6.1 MNA-SF

The MNA-SF is a commonly used screening tool to assess nutritional status in clinical practice. The MNA-SF has been found to have high sensitivity and specificity relative to the MNA and is a realistic and efficient instrument for clinical use (Guigoz 2006, Kaiser, Bauer et al. 2009). It is comprised of a structured interview consisting of 6 items that ultimately categorize patients as malnourished, at risk of malnutrition or of normal nutritional status. Patients who receive a total scale score ranging from 0 to 7 are categorized as malnourished, those who attain a score of 8 to 11 are categorized as being at risk of malnutrition and those who have an overall score of 12 to 14 points are considered to be of normal nutritional status. The domains of the MNA-SF include (a) has food intake declined over the past 3 months due to loss
of appetite, chewing problems or swallowing difficulties (b) weight loss during the last 3 months, (c) mobility, (d) has the patient suffered psychological stress or acute disease in the past 3 months, (e) neuropsychological problems and (f) BMI. Each domain is scored from 0 to 2, or 0 to 3, with higher scores indicative of better nutritional status (Rubenstein, Harker et al. 2001). In a study by Kuzuya et al., established MNA-SF cut-offs predicted malnutrition defined by biochemical and anthropometric measures including BMI, serum albumin and cholesterol with 85.9% sensitivity and 84% specificity in frail elderly (Kuzuya, Kanda et al. 2005)

2.6.2 CMAI

The CMAI is a 29-point scale administered to primary caregivers or nurses that measures agitation in two dimensions, physical and verbal (Cohen-Mansfield 1989). The scale is comprised of 4 domains: physical/aggressive (i.e. how often does the patient hit?), physical non-aggressive (i.e. how often does the patient pace?), verbal/aggressive (i.e. how often does the patient scream?) and verbal/non-aggressive (i.e. how often does the patient ask repetitive questions?). Each domain has 11, 10, 3, and 5 questions, respectively and each question is scored based on the frequency of patient behaviour. The CMAI is frequently the scale of choice for assessing agitation in a population with dementia (Howard, Juszcak et al. 2007, Seitz, Adunuri et al. 2011). Cohen-Mansfield et al. revealed high inter-rater agreement among 3 nursing staff for the behaviours evaluated on the CMAI as well as internal consistency (Cohen-Mansfield, Marx et al. 1989).
2.6.3 NPI-NH

The NPI-NH is a widely used assessment of behavioural disturbances in dementia, administered to primary caregivers or nurses (Cummings, Mega et al. 1994, Wood, Cummings et al. 2000). The NPI-NH is a reliable scale and particularly applicable for nursing home residents with substantial behavioural symptoms (Wood, Cummings et al. 2000). The scale may be used to assess the following behaviours: (a) delusions, (b) hallucinations, (c) agitation, (d) depression, (e) anxiety, (f) euphoria, (g) apathy, (h) disinhibition, (i) irritability, (j) aberrant motor behaviour, (k) sleep and (l) appetite/eating disorders. Frequency and severity of these symptoms are judged on a 4-point and 3-point scale, respectively, and a 5-point scale is used to evaluate caregiver distress. Importantly, a significant correlation has been shown between the NPI-NH agitation subscale and the CMAI, providing evidence for its suitability in the assessment of agitation (Wood, Cummings et al. 2000).

2.6.4 sMMSE

The sMMSE is a measure of global cognition, utilized to assess the severity of an individual’s cognitive impairment (Molloy and Standish 1997). Scored out of 30, with lower scores indicative of poorer cognition, the sMMSE includes a range of cognitive domains such as orientation to time and place, recall, language, short and long-term memory. The sMMSE is an efficient scale that enables a comprehensive evaluation of cognition (Vertesi, Lever et al. 2001).
2.7 Randomization and masking

A block randomization code was computer generated by the Pharmacy department at Sunnybrook. All study personnel remained blind to the randomization code, block size and treatment allocation until the final patient had completed their follow-up check and the database was locked.

2.8 Statistical Analyses

All data analyses were performed using IBM SPSS Statistics version 24.0. Demographics and clinical characteristics were grouped by nutritional status into patients of normal nutritional status, at risk of malnutrition and malnourished, using analyses of variance (ANOVA) for continuous data and chi-square tests for categorical data. Continuous variables were reported as mean ± standard deviations. Categorical variables were reported as total number of people in addition to percentage of study population. A p-value of <0.05 was accepted as significant for all analyses conducted.
2.8.1 Primary Hypothesis

Compared to placebo, patients treated with nabilone will have improved nutritional status, as indicated by increased scores on the MNA-SF over time.

To evaluate the primary hypothesis, a mixed linear model, with time as the repeated measure was conducted. The MNA-SF scale score was included as the continuous dependent variable, while treatment type was included as an independent variable to compare the differences between nabilone and placebo. Fixed-effects variables included treatment type, time and treatment-by-time interaction. Main effects were analyzed to evaluate all variables in the model. Interaction effects between treatment and time were analyzed to evaluate the effect of nabilone over time. Additionally, an independent t-test and paired t-test were conducted to ensure there were no treatment order or carry-over effects, respectively.

2.8.2 Secondary Hypothesis

Compared to placebo, patients treated with nabilone will have improved BMI values over time.

To evaluate the secondary hypothesis, a mixed linear model, with time as the repeated measure was conducted. BMI values were included as the continuous dependent variable, while treatment type was included as an independent variable to compare the differences between nabilone and placebo. Fixed-effects variables included treatment type, time and treatment-by-
time interaction. Main effects were analyzed to evaluate all variables in the model. Interaction effects between treatment and time were analyzed to evaluate the effect of nabilone overtime.

2.8.3 Exploratory Hypothesis


A binary logistic regression was conducted to evaluate the exploratory analysis. The dependent variable, MNA-SF, was dichotomized into two groups based on patients who improved or had no change in MNA-SF score and those who worsened on the MNA-SF during nabilone treatment. Each model evaluated a categorical covariate such as whether or not a patient experienced a TEAE, a serious adverse event (SAE), early termination from the nabilone phase, or sedation.

2.9 Sample size calculation

The original sample size of the nabilone crossover RCT was predetermined to be 40 patients. For the purposes of the current study, an *a priori* calculation was conducted to ensure a sufficient sample size. For a mixed linear model with a medium to large effect size of 0.33, *α* of 0.05, and 3 predictors, a sample size of 38 patients was required for a study power of 0.80 (1-β).
3 Results

3.1 Participant Recruitment

Participants were obtained from the nabilone trial at Sunnybrook Health Sciences Centre (NCT02351882). In total, 104 patients were assessed for study eligibility; 65 patients were excluded from study participation for not meeting study criteria (n=14), declining to consent (n=32) and for various other medical reasons (n=19). There were 39 patients who met eligibility criteria and were randomized to participate in the study protocol. However, prior to the onset of phase 1, one patient was discovered to have clinically significant delusions and subsequently discontinued. As such, 38 patients were included in the study analysis (Figure II). There were 7 patients who experienced an adverse event leading to early discontinuation from the trial, and 4 participants who were terminated early from their nabilone phase, leading to an early crossover into their placebo phase.

Figure II: Patient inclusion process for the nabilone study.
3.2 Participant characteristics

Demographics and clinical characteristics of patients enrolled in the nabilone trial at baseline are presented below (Table 1). To analyze demographics and baseline characteristics, patients were grouped into categories based on their nutritional status scores as defined by the MNA-SF. Groupings include patients who were of normal nutritional status (n=5), those who were at risk of being malnourished (n=22), and patients who were malnourished (n=11). The majority of patients in the current study were at risk of malnutrition. There were a significantly greater number of inpatients within the malnourished subgroup as well as those at risk of malnutrition, compared to individuals of normal nutritional status. BMI was significantly different between the three groups of varying nutritional status. Individuals who had normal nutritional status had the highest BMI values, followed by those at risk of malnutrition, and those who were malnourished. There was a trend towards poorer cognition in patients with greater malnourishment. There were no significant differences between baseline medications, age or gender. CMAI verbal non-aggressive scores were significantly higher for patients with normal nutritional status, but patients did not significantly differ on CMAI total score or any other CMAI subdomain. Malnourished patients had the greatest NPI appetite score, and the poorest MNA-SF total score. Data are presented as means and standard deviations for continuous variables or total number of individuals and percentage of study population for categorical variables. Figure III and figure IV represent the distribution of MNA-SF scores and BMI values at baseline for all patients in the nabilone trial.
Table 1: Demographic and baseline clinical characteristics of patients enrolled in the nabilone study.

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=5)</th>
<th>At risk (n=22)</th>
<th>Malnourished (n=11)</th>
<th>p-value (significance at p&lt;0.05)*</th>
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<td>Total patients analyzed (n=38)</td>
<td>Mean ± SD or n (%)</td>
<td>Mean ± SD or n (%)</td>
<td>Mean ± SD or n (%)</td>
<td></td>
</tr>
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<td>Sociodemographics</td>
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<tr>
<td>Age (years)</td>
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<td>87.7 ± 9.3</td>
<td>89.5 ± 11.1</td>
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<tr>
<td>Number of inpatients</td>
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<td>16 (73)</td>
<td>10 (91)</td>
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<td>Gender (# of males)</td>
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<td>18 (82)</td>
<td>9 (82)</td>
<td>0.122</td>
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<tr>
<td>Nutrition</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>28.6 ± 4.4</td>
<td>24.5 ± 3.3</td>
<td>22.7 ± 3.7</td>
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<tr>
<td>MNA-SF</td>
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<td>9.5 ± 2.2</td>
<td>5.7 ± 1.8</td>
<td>0.000*</td>
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<td>Medications</td>
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<tr>
<td>Number of concomitants</td>
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<td>12.5 ± 5.1</td>
<td>11.9 ± 5.9</td>
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<td>10 (45)</td>
<td>7 (64)</td>
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<td>7 (32)</td>
<td>3 (27)</td>
<td>0.862</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1 (20)</td>
<td>11 (50)</td>
<td>5 (45)</td>
<td>0.476</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>5 (100)</td>
<td>20 (91)</td>
<td>8 (73)</td>
<td>0.224</td>
</tr>
<tr>
<td>Cognitive Performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>11.3 ± 9.7</td>
<td>7.3 ± 7.0</td>
<td>3.0 ± 2.8</td>
<td>0.080</td>
</tr>
<tr>
<td>SIB</td>
<td>70.5 ± 10.6</td>
<td>35.9 ± 29.5</td>
<td>30.0 ± 31.3</td>
<td>0.233</td>
</tr>
<tr>
<td>Total patients analyzed (n=38)</td>
<td>Normal (n=5) Mean ± SD or n (%)</td>
<td>At risk (n=22) Mean ± SD or n (%)</td>
<td>Malnourished (n=11) Mean ± SD or n (%)</td>
<td>p-value (significance at p&lt;0.05)*</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Behavioural Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAI Physical/Aggressive</td>
<td>18.8 ± 9.5</td>
<td>19.4 ± 9.5</td>
<td>27.6 ± 13.4</td>
<td>0.109</td>
</tr>
<tr>
<td>CMAI Physical/Non-Aggressive</td>
<td>27.4 ± 7.6</td>
<td>22.9 ± 7.5</td>
<td>25.1 ± 9.5</td>
<td>0.480</td>
</tr>
<tr>
<td>CMAI Verbal/Aggressive</td>
<td>7.6 ± 3.6</td>
<td>7.4 ± 4.0</td>
<td>9.0 ± 3.2</td>
<td>0.510</td>
</tr>
<tr>
<td>CMAI Verbal/Non-Aggressive</td>
<td>22.6 ± 3.6</td>
<td>13.6 ± 6.0</td>
<td>11.6 ± 7.1</td>
<td>0.007*</td>
</tr>
<tr>
<td>CMAI Total Score</td>
<td>76.4 ± 11.2</td>
<td>63.3 ± 13.4</td>
<td>73.4 ± 24.5</td>
<td>0.153</td>
</tr>
<tr>
<td>NPI Total Score</td>
<td>44.4 ± 13.1</td>
<td>30.7 ± 15.5</td>
<td>36.8 ± 16.2</td>
<td>0.181</td>
</tr>
<tr>
<td>NPI Agitation</td>
<td>7.4 ± 3.3</td>
<td>6.9 ± 3.4</td>
<td>7.9 ± 2.6</td>
<td>0.699</td>
</tr>
<tr>
<td>NPI appetite</td>
<td>2.4 ± 5.4</td>
<td>1.5 ± 2.2</td>
<td>5.7 ± 4.5</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

a) The SIB was only conducted in a subgroup of the sample (normal: n=2, at risk of malnutrition: n=17, malnourished: n=9)

b) Normal MNA-SF score = 12-14, At Risk MNA-SF score = 8-11, Malnourished MNA-SF score = 0-7
Figure III. Baseline MNA-SF scores for all patients in the nabilone trial.

Figure IV. Baseline BMI values for all patients in the nabilone trial.
3.3 Analyses to Test Hypotheses

3.3.1 Primary Hypothesis

As shown in table 2, the treatment x time interaction term suggested that there were no differences in change in MNA-SF between treatment groups over time ($b = -0.020$ (95%CI -0.27 to 0.23), $p=0.87$) (see Figure V). In addition, MNA-SF scores did not significantly change over time ($b = -0.026$ (95%CI -0.21 to 0.15), $p=0.77$). There were no carry-over ($t(32)=1.03$, $p=0.31$) or treatment order ($t(37)=0.53$, $p=0.60$) effects.

### Table 2: Results from a mixed linear model evaluating effects of nabilone versus placebo on MNA-SF total score. All results are measured against the placebo reference group.

<table>
<thead>
<tr>
<th>Dependent variable: MNA-SF Score</th>
<th>$b$</th>
<th>Std. Error</th>
<th>t (df)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>-0.026</td>
<td>0.089</td>
<td>-0.29 (53.52)</td>
<td>-0.21 to 0.15</td>
<td>0.77</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.444</td>
<td>0.507</td>
<td>0.89 (30.76)</td>
<td>-0.60 to 1.48</td>
<td>0.39</td>
</tr>
<tr>
<td>Treatment by time</td>
<td>-0.020</td>
<td>0.121</td>
<td>-0.17 (39.09)</td>
<td>-0.27 to 0.23</td>
<td>0.87</td>
</tr>
</tbody>
</table>
3.3.2 Secondary Hypothesis

The treatment x time interaction term suggested that there were no differences in change in BMI between treatment groups over time \( (b=0.020 \text{ (95\% CI } -0.13 \text{ to } 0.17), \ p=0.79) \) (see Table 3; Figure VI). There was a decrease in 62 grams over the duration of the study but BMI did not significantly change over time.

Table 3: Results from a mixed linear model evaluating effects of nabilone versus placebo on BMI. All results are measured against the placebo reference group.

<table>
<thead>
<tr>
<th>Dependent variable: BMI</th>
<th>( b )</th>
<th>Std. Error</th>
<th>t (df)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>-0.062</td>
<td>0.045</td>
<td>-1.38 (55.33)</td>
<td>-0.15 to 0.03</td>
<td>0.17</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.340</td>
<td>0.405</td>
<td>0.84 (34.91)</td>
<td>-0.48 to 1.16</td>
<td>0.41</td>
</tr>
<tr>
<td>Treatment by time</td>
<td>0.020</td>
<td>0.076</td>
<td>0.27 (33.75)</td>
<td>-0.13 to 0.17</td>
<td>0.79</td>
</tr>
</tbody>
</table>
3.3.3 Exploratory Hypothesis

As shown in figure VII, there were a total of 23 patients who improved or had no change in scores on the MNA-SF and 13 patients who worsened on the MNA-SF during nabilone treatment. During nabilone treatment, there were no significant differences in the proportion of patients who experienced a TEAE (OR=1.731 (95%CI 0.41 to 7.29), p=0.46), SAE (OR=0.300 (95%CI 0.03 to 2.90), p=0.41), early termination (OR=1.607 (95%CI 0.40 to 6.44), p=0.50) or sedation (OR=2.489 (95%CI 0.62 to 10.06), p=0.20) between patients in whom nutritional status worsened compared to those in whom nutritional status improved or remained stable, as assessed by the MNA-SF (Table 4).
Figure VII. Number of patients who improved/had no change or worsened on MNA-SF total score and MNA-SF subdomains during nabilone and placebo.

Table 4: Binary logistic regressions evaluating patients in whom nutritional status worsened compared to those in whom nutritional status improved or remained stable, as assessed by the MNA-SF during nabilone treatment.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>MNA-SF improved/no change (n=23)</th>
<th>MNA-SF worsened (n=13)</th>
<th>Odds Ratio (OR)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>13 (57)</td>
<td>9 (69)</td>
<td>1.731</td>
<td>0.41 to 7.29</td>
<td>0.46</td>
</tr>
<tr>
<td>SAE</td>
<td>5 (22)</td>
<td>1 (8)</td>
<td>0.300</td>
<td>0.03 to 2.90</td>
<td>0.30</td>
</tr>
<tr>
<td>Covariates</td>
<td>MNA-SF improved/no change (n=23)</td>
<td>MNA-SF worsened (n=13)</td>
<td>Odds Ratio (OR)</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Early termination of nabilone phase</td>
<td>8 (35)</td>
<td>6 (46)</td>
<td>1.607</td>
<td>0.40 to 6.44</td>
<td>0.50</td>
</tr>
<tr>
<td>Sedation</td>
<td>9 (39)</td>
<td>8 (62)</td>
<td>2.489</td>
<td>0.62 to 10.06</td>
<td>0.20</td>
</tr>
</tbody>
</table>
4 Discussion

4.1 Baseline Characteristics of Study Population

The present study investigated the effects of nabilone for the treatment of poor nutrition in a moderate to severe AD patient population with clinically significant agitation. A significantly greater number of inpatients were found to be at risk of malnutrition or malnourished, compared to outpatients. It may be that patients in long-term care do not have access to the same quantity or quality of food as the outpatients who participated in the current study. Supporting this, literature has indicated that patients residing in long-term care are often at greater risk of malnutrition and have worse nutritional status compared to those still residing in community settings (Suominen, Muurinen et al. 2005, Tombini, Sicari et al. 2016). Patients of normal nutritional status had significantly higher verbal non-aggression than patients at risk of malnutrition and those who were malnourished. The verbal non-aggression category of the CMAI includes several questions, a few of which inquire about a patient’s behaviour as it pertains to repetitive sentences, complaining and unwarranted requests for attention or help. A possible explanation may be that because patients of normal nutrition were trending towards better cognition compared to those of worse nutritional status, higher cognition may be contributing towards patient’s abilities to express themselves in a non-aggressive verbal manner in contrast to a verbal aggressive manner (Zahodne, Ornstein et al. 2015). Malnourished patients had the highest NPI appetite scores, suggesting the greatest presence of disturbing eating behaviours such as a loss of appetite as well as weight loss.
4.2 Study Findings and Interpretation of Results

4.2.1 Primary and Secondary Hypotheses

The primary hypothesis of this study investigated the effects of nabilone on the nutritional status of patients with AD over time. The MNA-SF was used as a measure of nutritional status, as it encompasses many facets of nutrition and has been well validated within the literature for a geriatric patient population (Kaiser, Bauer et al. 2009). The MNA-SF is also one of the most commonly used subjective measures of nutritional status (Kaiser, Bauer et al. 2009). Based on previous studies in diverse clinical populations (Gorter 1991, Volicer, Stelly et al. 1997, Woodward, Harper et al. 2014, Turcott, Del Rocio Guillen Nunez et al. 2018), synthetic CBs have shown promising effects for the treatment of various components of nutrition including food intake and weight gain. Contrary to what was hypothesized, MNA-SF scores did not significantly differ between patients treated with nabilone compared to those on placebo over time. Patients treated with nabilone did not have a statistically significant improvement in nutritional status compared to those on placebo and there were no significant changes in MNA-SF over time irrespective of treatment. No significant treatment order effects were detected, indicating that patients who received nabilone during phase 1 of the study did not significantly differ from patients receiving nabilone during phase 2 with respect to their nutritional status. Likewise, no carryover effects were detected, demonstrating that the washout period between phase 1 and 2 was sufficient to ensure that patients randomized to receive nabilone during the first phase of treatment did not continue to experience effects of study drug during phase 2.

The secondary study hypothesis evaluated the effects of nabilone on patient’s nutrition by investigating an objective measure of nutritional status, BMI. Although accurate measures of BMI can often be difficult to obtain in a severe AD population (Ahmed and Haboubi 2010,
Sherrod, Dew et al. 2017), BMI has been shown to be a reliable measure of nutritional status in some studies (Ferro-Luzzi, Sette et al. 1992). Contrary to the secondary study hypothesis, there was no statistically significant improvement of BMI over time for nabilone treatment compared to placebo. Additionally, there was no significant change in BMI over the duration of the study or between treatment groups.

4.2.2 Interpretation of Primary and Secondary Hypotheses

In contrast with the stated primary hypothesis, nabilone treatment did not have a significant impact on nutrition compared to placebo over the course of the study. These results indicate that for the selected trial duration, the dosage utilized did not significantly impact patient’s nutritional status, assessed using a subjective scale, the MNA-SF. Numerous subcomponents of nutrition are addressed within the MNA-SF. On the MNA-SF, subdomain (A) inquires about food intake over the past 3 months. It is possible that by asking the question in reference to a previous 3-month interval, a caregiver may be more inclined to report a patient’s former decline in food intake, rather than accurately reporting more recent changes in appetite, should one exist. This would ultimately impact a patient’s overall score on the MNA-SF, with the potential to account for a lack of change.

In line with the current findings, a placebo controlled clinical trial by Volicer et al. did not detect a significant difference in caloric intake between dronabinol treatment and placebo (Volicer, Stelly et al. 1997). Although Volicer et al. detected a significant change in body weight during their 12-week trial, subsequent trials examining the use of THC and synthetic THC have failed to yield significant results for nutrition with respect to weight or BMI. Factors most likely
to be influenced by nabilone and contribute to promoting a change in nutritional status on the MNA-SF include food intake and BMI. Both subdomains are assessed categorically and therefore, may not be as sensitive as necessary to detect a change in a short period of time. As a synthetic CB, nabilone has been implicated as an appetite stimulant, a result of being a CB1 partial agonist (Pertwee 1999). Although possible that nabilone promoted an increase in appetite, it can be difficult to increase food intake in institutionalized patients where meals are provided in standardized portions and there is a relative lack of availability of extra snacks. Increasing intake in nutritionally compromised patients with dementia can also be challenging because dysphagia is particularly common in this population (Easterling and Robbins 2008). The orexigenic effects of synthetic CBs in various populations remains inconclusive as Wilson et al. found that dronabinol administration resulted in weight gain for 53% of elderly patients, but not in 40% of patients residing in long term care (Wilson, Philpot et al. 2007). A RCT by Turcott et al. in cancer patients found that 8-weeks of nabilone treatment was not sufficient to significantly increase appetite or weight compared to placebo, but that patients receiving nabilone had a significantly higher carbohydrate intake compared to those receiving placebo. Similarly, a retrospective chart review in dementia patients found a significant increase in food consumption but no significant change in weight from baseline to an average follow up period of 17 days. It may be that for pharmacological interventions such as nabilone, a minimum duration of time is required to enhance caloric and nutrient intake to the point of observing significant increases in appetite and/or weight. One of the benefits of utilizing a crossover design for the current research is the implication that each patient serves as their own control. Patients that safely completed phase 1 of the trial, regardless of randomization to placebo or nabilone, then completed phase 2 with the alternate treatment. Having each patient act as their own control removes patient
variation and allows for a greater degree of accuracy in analysis with fewer subjects (Li, Yu et al. 2015).

To further evaluate nutritional status in this population, our secondary hypothesis examined BMI, an objective measure of nutrition. Contrary to the hypothesized, there was no significant difference between nabilone treatment and placebo for BMI over time. Barring any health complications, each patient received incrementally increasing doses of nabilone for a 6-week duration. It may be that for the dosage prescribed, the required length of time for observing a noticeable change in weight, and therefore BMI, is greater than the allotted period that patients were receiving study drug. According to Cook et al., one explanation as to why BMI is a controversial measure for assessing nutrition in an elderly cohort is that the optimal reference range of 20-25 kg/m² is not appropriate for geriatric patients, and more appropriate cut-offs have not be clearly defined (Cook, Kirk et al. 2005). Additionally, variability in equipment and staffing can lead to inaccurate measures of height, and therefore BMI (Cook, Kirk et al. 2005). Clinicians must also be careful about the use of BMI as a measure of nutrition in the elderly as it is a poor marker of percent body fat and is unable to distinguish between fat mass and fat free mass (Nuttall 2015). Assessing body composition is particularly important to become aware of possible metabolic changes or the onset of various age-related diseases (Camina Martin, de Mateo Silleras et al. 2014). Despite clinical studies that have had significant findings with respect to the improvement of appetite or weight loss from a synthetic CB in dementia (Volicer, Stelly et al. 1997, Woodward, Harper et al. 2014), cancer (Sallan, Cronin et al. 1980, Turcott, Del Rocio Guillen Nunez et al. 2018) and AIDS populations (Gorter 1991, Beal, Olson et al. 1995), the literature remains inconclusive. Many studies that have utilized CBs in an AD population have not resulted in a significant weight change for patients; have been unable to
detect a measurable difference in food consumption (van den Elsen, Ahmed et al. 2015), or have failed to investigate nutritional components altogether (Walther, Mahlberg et al. 2006, Passmore 2008, Walther, Schupbach et al. 2011).

**4.2.3 Exploratory Hypothesis**

The exploratory hypothesis of the present study investigated the impact of safety outcomes on nutritional worsening in patients receiving nabilone treatment. Nabilone has been associated with side effects of moderate severity (Ward and Holmes 1985) but the literature remains inconclusive in regards to the safety profile of CBs such as nabilone for a moderate to severe AD population. In the present study, there were no significant differences in the risk of serious safety events between patients who experienced an improvement or no change in nutritional status and those who worsened in nutritional status during nabilone treatment. In addition, the likelihood of TEAEs, SAEs, early termination during the nabilone phase, and sedation did not differ between patients who worsened on nutritional status and those who improved or remained stable in nutrition, as assessed by the MNA-SF.

**4.2.4 Interpretation of Exploratory Hypothesis**

By dichotomizing patients who received nabilone into those who improved or had no change on the MNA-SF compared to those who worsened, it was possible to observe if changes in nutritional status were impacted by safety outcomes. Patients in the nabilone trial were closely monitored by nursing staff, caregivers and study staff for the presence of significant adverse events. All TEAEs and SAEs were determined by the qualified investigator (QI) of the study and
TEAEs were noted by the QI as possibly or probably related to study drug. One of the most common TEAE occurrences in the current study was lethargy. Lethargic behaviour may be the result of increased sedation resulting from treatment with nabilone. Previous studies using nabilone have reported TEAEs such as dizziness, dry mouth, lethargy and sedation (Ware, Fitzcharles et al. 2010, Tsang and Giudice 2016). Increased levels of sedation may negatively impact nutrition if sedative effects result in a decline in food intake (Jager and Witkamp 2014). However, in the current study, there were no significant differences in the likelihood of sedation between patients that worsened in nutritional status compared to those with no change or improved nutritional status. Although not significant, patients who worsened in nutritional status were approximately 2.5 times more likely to be sedated. Therefore, sedative effects of nabilone should be further explored in future studies.

A RCT by van den Elsen et al. administered 4.5 mg of oral THC to dementia patients (van den Elsen, Ahmed et al. 2015) with no significant treatment effects for NPS or weight. Van den Elsen also assessed safety outcomes and found that the number of patients experiencing adverse events did not significantly differ between THC and placebo. These findings in combination with the current results suggest the necessity of additional research into the optimal timeline and dosage required to observe positive significant effects with CBs. When treating a vulnerable population with a pharmacological intervention, it is imperative that safety is of the highest priority. Although nabilone did not have a significantly positive effect on nutrition in the present study, the results of the exploratory analysis suggest that the treatment regimen utilized did not pose a safety concern for the cohort in the nabilone trial with respect to nutrition. This suggests that future work should investigate whether nabilone has the potential to positively
modify nutrition at a more efficacious dosage, while maintaining the safety profile suggested by the nabilone trial.

4.3 Limitations and Recommendations for Future Studies

One of the limitations of the current study is the sample size. Although an *a priori* sample size calculation was conducted to ensure that 38 patients would be sufficient for the intended analyses, having a small sample size restricts the number of covariates that may be included in each model. By having a larger sample size, it would be possible to evaluate the longitudinal relationship between nutrition, nabilone and factors that may contribute to a more comprehensive understanding of the diverse relationships present in AD patients. Specifically, future work should be conducted to look into the relationship between changes in nabilone, nutrition and agitation, a NPS highly prevalent in AD patients. Subsequently, if a significant relationship were detected, a larger sample would also allow for a mediation analysis to assess possible mediators between nabilone and nutrition such as the interaction between treatment group and change in agitation on a potential change in nutritional status. Few mediation analyses are conducted with less than 100 patients (Fritz and Mackinnon 2007) and as such, by running a larger clinical trial with a greater number of participants, the study would be sufficiently powered to detect a mediation effect if one exists.

Demographics such as age and gender and baseline clinical characteristics may also have a significant impact on the way in which AD patients prescribed nabilone respond to treatment. In the present study, there was a discrepant ratio of male to female participants as we had a greater number of males than females. Previous literature has found that females often have
poorer nutritional status compared to males (Agarwalla, Saikia et al. 2015, Sanders, Behrens et al. 2016), and as such, future work should investigate if a treatment effect is possible with a larger number of female participants in the sample population. It is also of interest to evaluate whether baseline weight or BMI may impact nutritional response to nabilone as studies in various populations have revealed that baseline nutritional status may influence treatment response (Di Fiore, Lecleire et al. 2007, Jia, Kindracki et al. 2018). Investigating relevant baseline demographics is an important step in managing treatment options and trial design for participants with varying nutritional status. The current trial did not have sufficient power to conduct analyses to investigate the predictive effects of baseline characteristics. If it can be determined whether baseline factors significantly impact treatment response, it may be possible to stratify future patients based on their likelihood to respond positively or experience adverse events, resulting from nabilone treatment. Therefore, investigation is warranted to assess if a larger cohort of patients, selected based on predictors that may contribute towards nutritional improvement may result in a positive treatment effect in response to nabilone.

Another possible limitation of our study is the use of caregiver rated scales such as the MNA-SF. Although components of the scale are quantitative in nature, they are in large part observational measures, leaving margin for error and individual interpretation. To mitigate this concern as best as possible, caregivers and nursing staff providing responses were kept as consistent as possible. In the current study, conservative dosages of nabilone were prescribed to ensure safety and minimize the frequency of adverse events associated with the study drug. Several studies utilizing dronabinol have prescribed 2.5 to 7.0 mg per day (Volicer, Stelly et al. 1997, Walther, Mahlberg et al. 2006, Mahlberg and Walther 2007, Walther, Schupbach et al. 2011, Woodward, Harper et al. 2014), for 2 to 6 weeks. A case study using nabilone
administered 0.5 to 1.0 mg per day (Passmore 2008) for 6 weeks and successfully improved symptoms of agitation, without any reported effects on nutrition (Passmore 2008). Studies utilizing various types of nutritional interventions have resulted in increased percentage of food and protein intake, BMI or weight over the course of 10-weeks, 12-weeks or 6-months, respectively (Shatenstein and Ferland 2000, Wong, Burford et al. 2008, Charras and Fremontier 2010). Therefore, it may be that higher doses of nabilone for a longer duration of time are required in order to observe significant improvements to various components of nutrition.

4.4 Conclusions

Identifying a way to improve nutrition in an already vulnerable population has the potential to reduce morbidity and mortality (Magri, Borza et al. 2003), caregiver burden, and improve quality of life for patients (Volkert, Chourdakis et al. 2015). The results of this clinical trial found that nabilone did not have a significant positive impact on nutritional status in patients with moderate to severe AD over time. Although no significant treatment effect was detected by the MNA-SF, a subjective measure of nutrition or BMI, an objective measure of nutrition, further research is warranted to assess nabilone for the treatment of nutritional status for a longer duration of time. An inverse relationship has been identified between BMI and NPS such as agitation and aggression (White, McConnell et al. 2004) as well as malnutrition and an increase in NPS (Gillette-Guyonnet, Nourhashemi et al. 2003, Greenwood, Tam et al. 2005, Spaccavento, Del Prete et al. 2009). With a sufficient sample size, exploration should be conducted into the underlying mechanism between malnourishment and agitation in patients with severe AD. From a safety perspective, the risk of experiencing a significant adverse event was not significantly different between those who experienced an improvement or no change in nutritional status and
those who worsened in nutritional status during nabilone treatment. With additional research into the effects of nabilone on nutrition, both from an objective and subjective approach, as well as the relationship between nutrition and clinical characteristics in AD, it may be determined that with modifications to the current treatment regimen, nabilone has the potential to make a significant clinical impact on nutritional status.
References


Appendices

Appendix A – Research Ethics Board Approval
The Renewal Form is an application for continuing ethics approval and must be submitted for review and approval prior to the study’s expiry date. Ethics approval expires each subsequent year from the day REB approval was initially granted unless otherwise indicated by the Sunnybrook REB. Failure to submit this form prior to the expiry date signifies that the study does not have REB approval and all research activities must be suspended. Conducting research without REB approval may result in a notice of non-compliance involving corrective action, up to and including, termination of the research study.

Principal Investigator (PI): [Redacted]

REB Project Identification Number (PIN): 319-2013

Full Study Title: Safety and efficacy of nabilone for agitation in patients with moderate-to-severe Alzheimer's disease: a pilot study

1. Date of initial Sunnybrook REB approval (dd/mmm/yyyy).
   
   02/Apr/2014

2. Type of REB review requested. (Final decision rests with the REB Chair.)

   □ Delegated Review □ Full Board Review

3. Is this an Industry-Sponsored/Supported study?

   □ YES (If YES, complete the table below.) □ NO (If NO, proceed to question 4.)

   Invoicing Information for Industry-Sponsored/Supported Studies
   A fee of $500 Cdn is invoiced for all Industry-Sponsored/Supported Studies applying for continuing ethics approval.

   Invoice to the Following Company:

   Contact Name:
   Telephone:
   Street Address:
   City:
   Country:
   E-mail:
   Suite:
   Province/State:
   Postal/Zip Code:
4. Was there a lapse in approval? ☐ YES ☒ NO

If YES:
   a. Was there a need to continue research related medical treatment of current research participants for their safety and well-being? ☐ YES ☐ NO

   b. Provide the reason for the lapse and identify the steps taken to prevent future lapses:

5. Is this study open for enrollment at Sunnybrook? ☐ YES ☒ NO

If YES, attach a copy of the current Informed Consent Form(s).

If NO, provide reasoning:

| We have closed recruitment for this study after enrolling 39 patients, as drug supply was no longer available. A request to update our trial on clinicaltrials.gov has been submitted and has been approved. |

6. How many participants at Sunnybrook:

<table>
<thead>
<tr>
<th></th>
<th>Were planned for enrollment</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Were consented</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>Were enrolled</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>Are currently receiving study treatment/intervention</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Completed study treatment/intervention &amp; are currently on follow-up</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Completed study treatment/intervention &amp; follow-up</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>Withdraw consent</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Were planned for inclusion in a chart review (retrospective or prospective)</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Were included in a chart review (retrospective or prospective)</td>
<td>0</td>
</tr>
</tbody>
</table>

Provide clarification if rows 4-7 do not add up to equal row 3 OR if rows have been left blank:

| N/A |

7. Have all reportable Serious Adverse Events (SAEs) experienced by a Sunnybrook participant been reported to the REB?

☒ YES ☐ NO, will submit immediately ☐ NO reportable SAEs have occurred

8. In the opinion of the PI, is there a concern or trend in the SAEs that have occurred with Sunnybrook participants?

☐ YES ☒ NO ☐ NO SAEs have occurred

If YES, provide details and action taken.
9. Have all significant protocol deviations/violations been reported to the REB?
   ☐ YES ☐ NO, will submit immediately ☒ NO significant deviations/violations to report

10. Since the last REB approval, is there any new ethical or scientific information outside of a protocol amendment that would be relevant to the continuing review of this study?
   ☐ YES ☒ NO
   If YES, provide details.

11. Since the last REB approval, is there any change in the conflict of interest information provided to the REB for any of the investigators, study staff or members of their immediate family? ☐ YES ☒ NO
   If YES, provide details.

12. Person completing this form.
    Title: ☐ First Name: ☐ Last Name: ☐
    Dept/Div: Psychiatry Institution: Sunnybrook Research Institute
    Full Address: 2075 Bayview Avenue ☒ Room Number: ☐
    Telephone: ☐ Extension: ☐ E-mail: ☐

13. Statement of Principal Investigator (PI).
    I assume full responsibility for the scientific and ethical conduct of this study and agree to conduct this study in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Human Subjects (TCPS), Personal Health Information Protection Act (PHIPA) and any other relevant regulations or guidelines. I certify that all researchers and personnel involved in this study at this institution are appropriately qualified and trained to fulfill their role in this study.

[Signature]
19 Mar 2018

Signature of Principal Investigator Date (dd.mmm.yyyy)
Research Ethics Office Use Only

The Sunnybrook REB has reviewed the information provided and confirms that this study has obtained ethics approval by way of:

☒ Delegated Review → Date of review: **MAR 22, 2018**

☐ Full Board Review → Date of Full Board meeting: ____________

This study is **only approved for the following period:**

**APR 2, 2018** to **APR 2, 2019**

Chair/Vice-Chair, Research Ethics Board
Appendix B – Informed Consent Form
INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Safety and efficacy of nabilone in patients with Alzheimer’s disease: a pilot study

Investigators:
K.L. Lanctôt, PhD Sunnybrook Health Sciences Centre
N. Herrmann, MD Sunnybrook Health Sciences Centre

You are being asked to consent on behalf of your loved one to participate in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood.

This form explains the purpose of this research study, provides information about the study, the tests and procedures involved, possible risks and benefits, and the rights of participants.

Please read this form carefully and ask any questions you may have. Please ask the study staff or one of the investigators to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

INTRODUCTION

As the patient’s Substitute Decision Maker, you are being asked to provide Informed Consent as he/she is unable to provide consent for him/herself. If the patient regains capacity to consent for him/himself, your consent for them will end. Throughout this form, “you” means the patient you are representing.
You are being asked to consider your participation in this study because you suffer from Alzheimer’s disease (AD) or a related dementia and are also experiencing agitation. Agitation, which is a common AD symptom, is known to correlate with physical health problems (falls and weight loss), AD progression and caregiver burden. As a result, treating these behavioural symptoms is important in improving the quality of life of AD patients and their caregivers.

A group of drugs called atypical antipsychotics (example: olanzapine, quetiapine and risperidone) are commonly used to treat agitation and aggression in AD. However, not everyone benefits, and concerns about safety have increased. Common side effects associated with antipsychotics include increased Parkinsonian symptoms. They have also, but rarely, been associated with severe side-effects like stroke and reduced life span.

The goal of this study is to determine whether nabilone is an effective treatment option for dementia patients with aggression and agitation.

**WHAT IS THE USUAL TREATMENT?**

Currently, dementia patients with agitation and/or aggression may be prescribed antipsychotics (example: olanzapine, quetiapine and risperidone).

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to determine the effects of nabilone on dementia patients with symptoms of agitation and/or aggression. In addition, the results of this study will be used to assess the feasibility of future clinical trials.

**WHAT WILL HAPPEN DURING THIS STUDY?**

If you decide to consent to this study, you will be asked to undergo an initial assessment which will involve a medical evaluation and a brief test of memory and behavioural
symptoms. We will also be collecting their demographic information, medical history and current medications.

Once it has been determined that you are eligible to participate in the study, the primary physician or consulting psychiatrist will be contacted to provide consent for the patient. You will then be randomly assigned into one of two groups. One group will receive nabilone and then placebo. The other group will receive placebo and then nabilone. All participants receive both nabilone and placebo, but the order is randomized. The placebo will look the same as the nabilone. Neither you, your caregiver, your nurse, your primary physician, nor the investigators will know which study group you will be in.

During this study, you will be monitored and assessed by trained study personnel. There will be 10 assessment dates in total:

- Screening visit
- Baseline visit (start of treatment 1)
- Week 2 (treatment 1)
- Week 4 (treatment 1)
- Week 6 (end of treatment 1)
- Week 8 (start of treatment 2)
- Week 10 (treatment 2)
- Week 12 (treatment 2)
- Week 14 (end of treatment 2)
- Week 15 (safety follow-up)

Assessments will include a physical examination, an adverse event review and a questionnaire about their memory. We will also be speaking with their nurse regarding their mood, behaviours and activities of daily living. At screening, baseline, week 6, 8 and 14, approximately 2½ tablespoons of blood will be drawn. At screening, the study physician may also order an ECG based on your past medical history, or the results of your physical exam. The electrocardiogram will make sure that your heart is in stable condition before you enter the study. If the results from the interview, blood sample or electrocardiogram (ECG) show clinical abnormalities, with your permission, we will contact your primary physician.

In case of an emergency, you may be removed from the study for your safety. Information on which study group you were randomized to can be provided to your physician if needed.
HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that 40 people will participate in this study, all from Sunnybrook Health Sciences Centre. The entire study should take about 3 years to complete and the results should be known in 3 ½ years.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

You may experience side effects from participating in this study. Some side effects are known and listed below, but there may be side effects that are not expected. If you decide to participate in this study, you should contact Myuri Ruthirakuhan, Eleenor Abraham, and Chelsea Sherman at 416-XXX-XXXX ext XXXX about any side effects or study-related injuries that they experience.

If you are in a group that receives nabilone, side effects may, or may not include the following (look at the table below).

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency</th>
<th>Severity</th>
<th>Long Term Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expected</td>
<td>Likely</td>
<td>Rare</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dizziness</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychological High</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Depression</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Involuntary Muscle Movements</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sensation Disturbance</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anorexia</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical Weakness</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Headache</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Low Blood Pressure</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Euphoria</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rapid Heart Rate</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Shakiness (Tremors)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fainting</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nightmares</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Distortion of understanding of time | X | X | X
Confusion | X | X | X
Seizures | X | X | X

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Nabilone is approved in Canada and is used in the management of severe nausea and vomiting. It is a medication based on one substance in marijuana.

You may or may not benefit directly from participating in this study. Your participation may or may not help other people facing agitation with Alzheimer’s disease.

CAN PARTICIPATION IN THIS STUDY END EARLY?

The investigators may decide to remove you from this study without your consent for any of the following reasons:
- The investigators decide that continuing in this study may be harmful to you
- They are unable or unwilling to follow the study procedures

If you are removed from the study, the investigators will discuss the reason(s) with you.

You can also choose to end your participation at any time. If you withdraw voluntarily from the study, you are encouraged to contact The Department of Psychiatry, Sunnybrook Health Sciences Centre immediately. The information that was collected before you left the study will still be used. No new information will be collected without your permission.

WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?

You will not incur any costs as a result of participation in this study.

WHAT HAPPENS IF I HAVE RESEARCH RELATED INJURY?

In the case of a research related injury your physician will be immediately notified. A decision will be made in the best interest of the patient, of whether to continue or to be withdrawn from the study.
ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?
You will not be compensated for your participation in this study. However, you will be reimbursed for parking and travel expenses for each study visit.

HOW WILL MY INFORMATION BE KEPT CONFIDENTIAL?
All personal and medical information will be coded. This will ensure that there is no medical information that can be connected to you. The study investigators and coordinator will have access to your medical information as it is important to maintaining safety throughout the course of the study.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?
If you decide to participate in this study you can expect the following:

There will be 10 assessments in total. The first one will be a screening visit, followed by a visit at baseline. The remaining assessments will be conducted at 2, 4, 6, 8, 10, 12 and 14 weeks after the baseline visit. A final safety follow-up visit at week 15 will be conducted. The screening, baseline and weeks 6, 8 and 14 will take approximately 1-2 hours. All other visits will last approximately 30 minutes.

DO THE INVESTIGATORS HAVE ANY CONFLICTS OF INTEREST?
There are no conflicts of interest to declare related to this study.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?
All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish translated into your preferred language.

2. Participating in this study is your choice (voluntary). You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, it will not have any effect on your future medical treatment or health care. Should you choose to withdraw from the study you are encouraged to contact Sunnybrook Health Sciences Centre at immediately.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the
right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the person in charge of this study (Principal Investigator). If you have any questions about your rights as a research participant, you may call the Chair of the Sunnybrook Research Ethics Board.

4. By signing this consent form, you do not give up any of your legal rights.

5. You have the right to receive a copy of this signed and dated informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. If you become sick or injured as a direct result of your participation in this study, your medical care will be provided.

8. Any of your personal information (information about you and your health that identifies you as an individual) collected or obtained, whether you choose to participate or not, will be kept confidential and protected to the fullest extent of the law. All personal information collected will be kept in a secure location. The study staff, the Sunnybrook Research Ethics Board, and the regulatory authority (ies) (Health Canada and/or FDA) will have access to your personal information for purposes associated with the study, but will only be allowed to access your records under the supervision of the Principal Investigator and will be obligated to protect your privacy and not disclose your personal information. None of your personal information will be given to anyone without your permission unless required by law. When the results of this study are published, your identity will not be disclosed. The data for this study will be retained for 25 years.

9. If, as a result of your participation in this study, any new clinically important medical information about your health is obtained, you will be given the opportunity to decide whether you wish to be made aware of that information.

10. You have the right to access, review and request changes to your personal information (i.e. address, date of birth).

11. You have the right to be informed of the results of this study once the entire study is complete.
DOCUMENTATION OF INFORMED CONSENT

You will be given a copy of this informed consent form after it has been signed and dated by you and the study staff.

Full Study Title: Safety and efficacy of nabilone in patients with Alzheimer's disease: a pilot study

Name of Participant: __________________________________________

Participant/Substitute decision-maker

By signing this form, I confirm that:

- This research study has been fully explained to me and all of my questions answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study
- I have been informed of the rights of research participants
- I have read each page of this form
- I authorize access to my personal health information, medical record and research study data as explained in this form
- I have agreed, or agree to allow the person I am responsible for, to participate in this research study
- I understand that my family doctor may be informed of my participation in this research study
- This informed consent document may be placed in my medical records

________________________________  ____________________________  ___________________
Name of participant/Substitute decision-maker (print)  Signature  Date
ASSISTANCE DECLARATION

Was the participant assisted during the consent process? □ Yes □ No

☐ The consent form was read to the participant/substitute decision-maker, and the person signing below attests that the study was accurately explained to, and apparently understood by, the participant/substitute decision-maker.

☐ The person signing below acted as a translator for the participant/substitute decision-maker during the consent process. He/she attests that they have accurately translated the information for the participant/substitute decision-maker, and believe that that participant/substitute decision-maker has understood the information translated.

____________________________      ____________________________   _____________________
Name of Person Assisting (Print)  Signature          Date

Person obtaining consent

By signing this form, I confirm that:

• This study and its purpose has been explained to the participant named above
• All questions asked by the participant have been answered
• I will give a copy of this signed and dated document to the participant

____________________________      ____________________________   _____________________
Name of Person obtaining            Signature          Date
consent (print)

Statement of Investigator

I acknowledge my responsibility for the care and well being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research.

____________________________      ____________________________   _____________________
Name of Investigator (print)         Signature          Date