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SYNTHETIC CANNABINOIDS IN DEMENTIA WITH AGITATION: CASE STUDIES AND LITERATURE REVIEW

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Abstract

Objective: The management of agitation in dementia is a growing problem and conventional modes of intervention have limited efficacy. Synthetic Cannabinoids have been studied in other conditions like pain and multiple sclerosis. There is limited data available on their role in dementia. The authors aim to review the available literature and report on the efficacy of treatment with synthetic cannabinoids in two cases of dementia.

Method: Two cases of patients with severe dementia were reported on for the off label use of Nabilone for their symptoms of psychomotor agitation and aggression. Informed consent was obtained from the patients' substitute decision makers. The Kensington Standardized Behavioural Assessment (KSBA) tool and family observations were used to evaluate the patients' response to Nabilone treatment. The current literature was reviewed for the use of synthetic cannabinoids in the treatment of aggression in severe dementia.

Results: In the cases there was little improvement in the combined KSBA score after initiation of Nabilone, however there were improvements in the areas of aggressive and emotional behaviour . Families reported improvements in the patients after administration of Nabilone.

Conclusions: Nabilone improved psychomotor agitation, aggression and communication. There were no bedsores in any of the patients on Nabilone. This was an incidental finding.

Key words: synthetic cannabinoids, Nabilone, agitation, dementia, Kensington Standardized Behavioural Assessment, aggression

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1.1.1 Introduction

Synthetic cannabinoids have been studied and utilized in the management of pain,

nausea and multiple sclerosis (Elikottil et al. 2009, Tramer et al. 2001, Davis et al. 2008, Thaera et al. 2009). Clinical research with cannabinoids in the field of psychiatry has been isolated to small trials in the treatment of dementia related behavioural disturbances (Volicer et al. 1997, Walther et al 2006). This is despite the growing body of scientific evidence supporting the potential positive effects of synthetic cannabinoids on Alzheimer's disease (AD) processes. A Cochrane review of cannabinoids for the treatment of dementia reported that more double blind placebo controlled trials are required to determine efficacy in this population (Krishnan et al. 2009). There is also a paucity of case reports in the literature describing use of these agents in clinical practice. One case report outlines a positive result with the cannabinoid receptor agonist Nabilone in a patient with Alzheimer's type dementia related agitation (Passmore 2008).

1.1.2 AIMS

1. Describe two cases in which the use of synthetic cannabinoids resulted in significant improvements on the KSBA scale
2. Review literature on the use of synthetic cannabinoids in dementia with agitation.

1.1.3 Methods

The Kingston Standardized Behavioural Assessment (KSBA) screening tool (Hopkins et al. 2006) was utilized as a standardized measure at baseline and

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weekly after administration of a synthetic cannabinoid. The questionnaire was administered by a coauthor familiar with the KSBA. The KSBA was identified as being user friendly and one that could be used on a regular basis by staff.

Qualitative behavioral data was also collected from hospital staff and family members following drug initiation as it became clear that improvements noted by family and staff were not reflected in the scale used.

The substitute decision makers were informed of the off label use of the medications and potential side effects and benefits. They were also told about the current levels of evidence available on its use. Informed consent was obtained from the substitute decision makers.

The families were told that no personal identifying information was being used.

1.1.4 Literature review

A literature search of the Cochrane, Medline, PsychInfo and CINHAL databases was performed using keywords Alzheimer's disease or dementia or neurodegenerative disease and cannabinoid or endocannabinoid or marijuana. Limits were set to human data only. Articles were also hand selected. Authors of pertinent articles were contacted to obtain unpublished data.

1.1.5 Case 1

A-79-year old Caucasian male diagnosed with Alzheimer's disease (AD) in 2002 was admitted to the dementia unit of a nursing home in May 2007 due to increasing agitation and caregiver burden. On admission donepezil 10mg daily and increasing doses of tryptophan were added to the patient's treatment regimen of Memantine 20mg twice daily, Citalopram 20mg daily and Risperidol 2mg twice daily. Despite these adjustments in therapy aggressive behaviors that had been present intermittently at home began to escalate, including pushing and pulling at staff and residents necessitating treatment with increasing doses of Haloperidol and Quetiapine. The patient developed delirium following the addition of these medications resulting in admission to the local psychiatric hospital for assessment and management.

On admission all psychotropic medications were discontinued leading to resolution of the delirium. The patient was diagnosed with advanced dementia and was noted to have a duration of illness of 5 years. While in hospital the aggressive behaviour continued to be difficult to manage. It required 3 to 4 staff members to do daily cares and pad changes due to combative behaviours. The patient regularly pulled the arms off of his wheelchair and lashed out at staff members. His substitute decision maker was reluctant to introduce any new medications but agreed to the administration of Lorazepam.

Over the course of the next two years the patient remained in hospital and several medications from different groups were used to manage his aggression. An initial trial of olanzapine was not tolerated as it appeared to cause akathesia. Valproic acid resulted in petechiae and easy bruising. Gabapentin 900mg daily was initiated and Memantine was reintroduced and titrated to 10mg twice daily. Following reintroduction of Memantine the patient appeared to become more irritable and had decreased comprehension. The addition of these medications to his treatment regimen did not make an appreciable improvement in the patient's behaviour. Medical staff reported he became increasingly irritable and displayed a decline in comprehension. Despite significant effort on part of the hospital staff, difficult behaviour persisted especially during personal care. The patient was reported to have rocked continuously in his wheelchair throughout the day and began to yell and call out throughout the night. Skin breakdown became a problem as the patient spent more time in bed or in his wheelchair.

Nabilone 0.5mg once daily was initiated and increased one week later to 0.5mg twice daily. Following one week of Nabilone administration staff reported decreased agitation with daily personal care and a calmer affect and demeanor. One month after initiation of Nabilone staff reported decreased psychomotor agitation including cessation of pulling at wheelchair arms, decreased sun downing and staffing was decreased to 1-2 during personal care. Staff noted resolution in skin breakdown. At times the patient had been reported by nursing staff to speak clearly and appropriately using short sentences. He displayed improved eye contact as well as improved responses to verbal command. He even smiled more frequently. The patient's family members also commented on significant improvement in behaviour after the initiation of Nabilone. The KSBA was used to quantify the patient's behaviour before and after initiation of Nabilone. There was little improvement in the patient's combined KSBA score after initiation of Nabilone, however the KSBA did show consistent improvement in the areas of aggressive and emotional behaviour (**table 1**).

1.1.6 Case 2

60-year-old Caucasian male diagnosed with Frontotemporal dementia at age 53 was admitted 07/01/2010 to a psychiatric hospital from a long-term care facility for evaluation and management of a 6-month history of escalating aggressive behaviour. Staff reported the patient had been throwing juice at his nurses and swinging out at staff. On admission to hospital the patient required 3-4 staff to provide daily care, two of which were required to be male.

The patient's medication regimen on admission included Memantine 10mg twice daily, Citalopram 40mg daily, Quetiapine 150mg three times daily and Valproic acid 250mg twice daily. Two weeks after admission the aggressive behavior continued prompting a trial of Nabilone 0.5 mg daily. After initiation of Nabilone staff documented that the patient demonstrated some improvement in agitation, however began rising throughout the night and would become upset if redirected. Five days later Nabilone was increased to 0.5mg twice daily and Zopiclone was added at bedtime. After these adjustments in treatment nursing staff noted a substantial decrease in aggressive behaviour. One staff member was sufficient for personal care as opposed to the 3-4 that were previously required. The patient also began to express himself in single words and brief phrases.

The patient was discharged on Nabilone 0.5mg twice daily. He returned to his long-term care facility where staff reported he exhibited a return to aggressive behaviours. These behaviours included hitting other patients, swinging at staff during cares and toileting, turning violent without warning and pushing residents and staff. They also noted labile mood and a regression in speech. These recurrent difficulties with the patient

resulted in an emergency department visit one day after discharge and his return to the local psychiatric hospital 6 weeks after discharge. Upon readmission to hospital the patient was initially restless and displayed some combativeness. Three days into this hospital admission the patient's Nabilone dose was increased to 0.5mg three times daily. Quetiapine was also increased to 75mg twice daily and 150mg at bedtime. This was added primarily to help with sleep (Quetiapine had been tried previously on higher doses with poor results for reduction in agitation. He did not respond well to any other medication for sleep). After several days in the psychiatric unit he became less agitated, easier to redirect and was more cooperative with personal care. He was also found to be smiling frequently and speaking in one word answers and short sentences. Fewer staff members were also needed for personal cares and no skin breakdown was noted after initiation of Nabilone. The patient was finally discharged 13/02/2012.

1.1.7 **Table 1**

Behaviors	Case One				Case Two			
	0	Day 11	Day 36	Day 78	0	Day 14	Day 46	Day 63
Daily Activities	10	9	10	9	11	7	11	8
Attention/Concentration/ Memory	3	3	2	4	3	4	4	4
Emotional Behavior	3	3	2	2	3	0	4	1
Aggressive Behavior	4	4	3	2	3	1	4	2
Misperceptions/ Misidentifications	3	3	3	3	2	0	4	3
Paranoid Behavior	1	1	1	1	0	0	2	0
Judgement/Insight	4	5	5	5	3	3	5	3
Perseveration	4	3	4	5	2	1	2	2
Motor Restlessness	1	1	1	1	4	2	4	4
Sleep/Activity/ Sundowning	3	3	3	2	3	1	2	2
Motor/Spatial Problems	3	3	3	4	1	2	3	3
Language Difficulties	5	6	5	5	4	5	5	5
Total Score	44	44	42	43	39	26	51	37

Table 1. Kingston Standardized Behavioural Assessment (KSBA) tool was used to measure changes in 2 dementia patient's behaviour after the addition of Nabilone to their treatment regimens. The KSBA was performed prior to Nabilone administration (time 0) followed by 3 additional assessments thereafter.

*In Case two, the assessments for days 0, 14 and 63 were performed while the patient was in the hospital, whereas the day 48 assessment was performed while the patient was at a nursing care facility.

KSBA- 1.1.8

A Brief outline and drawbacks we experienced

The KSBA very effectively organizes common behaviours seen in individuals suffering from dementia into twelve categories that group behaviour into psychological or psychiatric symptoms. The KSBA is a goal directed tool that allows for the opportunity to highlight challenging behaviours and track changes (Hopkins et al. 2006) in behaviour providing important information for care plan development. The most significant changes in the two case studies occurred in the domains of emotional behaviour, aggressive behaviour, and sleep/sun downing behaviour. The improvements in these domains resulted in a decrease in the number of caregivers needed to complete personal cares safely. The reduction of symptoms in these domains has enabled social interactions not previously possible such as the participation in-group activities, which has undoubtedly improved their quality of life. Drawbacks of using the KSBA to quantify behaviours in these patients are that the tool does not track the frequency of behaviours or the number of staff required to perform an intervention on the patient. This information is important when working with patients with such high needs as it has placement implications. Other behavioural scales include the Cohen-Mansfield Agitation Inventory, Neuropsychiatric Inventory, Behave-Ad, and CERAD (Consortium to establish a registry for Alzheimer's disease rating scale) are alternative assessment tools that can be used in this patient population. As previously stated the KSBA was chosen for its ease of administration, but it did not capture the reports of family members in its scores, which show only minimal reductions.

1.1.9 Report from families

Family members reported "feeling a burden lifted". Specifically, they report a decrease in feeling "overwhelmed", "anxious", "preoccupied", "stressed" or "upset" that their loved one had changed so much from "his/her former self". They also reported more "satisfaction" in their visits. They noticed that their loved one appeared to be "calmer" and "relaxed" with an "increased ability to follow simple conversation".

Very noteworthy was one family's observation that their loved one was able to "participate in patterned family interactions by completing phrases and simple sentences". The family had "assumed" that their loved ones capacity to do this had been "lost to the disease".

Families noticed that their loved one "smiled more" and they noticed a "decrease in psychomotor activity". Family members felt that their loved ones behaviour was "more predictable" and there was a decrease in aggression during the visits. Family members also describe the "essence" of their family member "re-emerging". These changes contributed to a decrease in family burden and an increase in overall family wellbeing.

1.2.0 Current understanding of the role of synthetic cannabinoid

The incidence of Alzheimer's Disease (AD) has sky rocketed with the rate of disease estimated to quadruple by 2050 worldwide (Dhawan et al. 2008). During the course of dementia greater than 90 percent of patients will exhibit behavioral and psychological symptoms of dementia such as depressive state, hallucinations, delusions, agitation, anxiety, dysphoria, irritability, disinhibition and aberrant motor function (Steinberg et al. 2008). Agitation in AD has been estimated to occur in 60% of patients and appears to be associated with disease severity (Senanarong et al. 2004). Aggressive behaviour in AD manifests as excessive motor and/or verbal activity, irritability, uncooperativeness, vocal outbursts or abuse, threatening gestures or language, physical destruction or assault (Sachs 2006). Agitation and aggression can pose significant challenges to caregivers within the home and may necessitate nursing home placement. Behavioural symptoms were found to predict institutionalization in over half of the studies reviewed in one analysis (Gaugler et al. 2007). It has been proposed that dementia with mixed aggression and depression account for the greatest use of high cost medical services among those required for dementia patients (Sachs 2006). Effective strategies to manage dementia-related aggression are therefore imperative for caregivers in an effort to maintain ability to care for patients in their homes as well as to decrease strain on the healthcare system. Appropriate management is also important in community care facilitates to maintain a safe working environment both for patients and staff.

The first fore mentioned case study is an example of an Alzheimer's type dementia patient whose aggressive behaviour was greatly impeding his care. The current standard of care was not improving the patient's agitation and care giver burden was high. The addition of Nabilone to this patient's therapy resulted in qualitative improvements in both patient behaviour and caregiver burden as described by the nursing staff. Passmore et al. (2008) also noted a marked reduction in patient response aggression during personal care in his case report. It was concluded in a study by Volicer et al. (1997) that the synthetic Cannabionid Dronabinol decreased agitation in AD patients.

In the second case report, the patient was diagnosed with frontotemporal dementia. Although this patient's aggressive behaviour decreased with initiation of Nabilone, he displayed a recurrence of aggressive behaviours upon return to the long-term care facility. When the patient was readmitted to psychiatric hospital the patient's aggressive behaviour again decreased suggesting an environmental component to behaviour. It appears Nabilone had some part in decreasing the patient's aggressive behaviour as demonstrated by improved behaviour on return to the psychiatric unit, but was unable to significantly modify behaviour when the patient was in a stressful environment. Thus, Nabilone was able to ameliorate aggressive behaviours in this patient but not eradicate them. It could be, however, that Nabilone is not as effective in frontotemporal dementia as it is in AD. The strong positive result of Nabilone treatment in AD in our case report and others warrants further discussion on the proposed mechanism by which cannabinoid derivatives like Nabilone can impact AD.

Considerable research has been devoted to the study of this devastating disease resulting in the discovery of pathological processes believed to contribute to the formation and progression of AD. Disease processes that have been identified include: the deposition of β amyloid, plaque formation, Tau neurofibrillary tangles, inflammation, oxidative stress, acetylcholine disruption in the brain and neurodegeneration (Klein and Newton 2007, Dhawan et al. 2008, Campbell and Gowran 2007, Iuvone et al. 2009, Campillo and Páez 2009). These components of AD pathology hold promise as targets for the modification of the disease by pharmacological means.

Synthetic cannabinoids, including Nabilone, are under investigation for their potential ability to disrupt various AD processes. Such investigations were in part instigated by the identification of cannabinoid receptors (CBR) in the human brain. Two CBRs of interest have been described, CB1-R and CB2-R. CB1-R has been found to be primarily located in the brain and spinal cord. CB2-R is principally located in cells of the immune system namely B cells, T cells and notably microglial cells (Onaivi 2009, Klein and Newton 2007, Ramirez et al. 2005). Nabilone acts on both CB1 and CB2 receptors (Campillo and Páez 2009). In the interest of this discussion we will focus only on the known effects of cannabinoids that have the potential to disrupt AD pathology.

Both CB1-R and CB2-R have neuroprotective effects via decreased glutamate release and anti-inflammatory effects respectively (Campbell and Gowran 2007). CB1 and CB2 receptors are demonstrated to be co localized in senile plaques (Ramirez et al. 2005). CB1-R are inhibitors of Aβ-toxicity in vitro (Campillo and Páez), and neurons lacking CB1-R are found to be more vulnerable to damage (Campbell and Gowran 2007). CB1-R action has also been implicated in the enhancement of neurogenesis (Campbell and Gowran 2007) and CB2-R is indicated to be pro-neurogenic as well (Campillo and Páez). An increase in CB2-R in certain brain regions after pathological neuroinflammation has been identified (Tolón et al. 2009, Campillo and Páez). In AD, activated microglial cells surround senile plaques and contribute to local inflammatory responses (Ehrhart et. 2009, Dhawan et al. 2008, Ramirez et al. 2005). It is thought that initially microglial cells act to remove β-amyloid deposits but later become overwhelmed, remaining in the area releasing harmful pro-inflammatory mediators which generate more Aβ fragments (Campbell and Gowran 2007) and cause tau hyperphosphorylation (Dhawan et al. 2008). This data alone suggests the inhibition of inflammation may play a substantial role in disrupting AD processes. There is some evidence that specific NSAIDs may slow cognitive decline in AD and even lower likelihood of disease onset (Dhawan et al. 2008) but whether this is purely a result of their anti-inflammatory action has yet to be defined. CB2-R agonists have been shown to cause microglial cells to decrease inflammatory mediators (Ehrhart et. 2009). Studies have also found CB2-R agonists can promote microglial phagocytic function thus increasing their ability to remove β-amyloid deposits (Ehrhart et. 2009, Tolón et al. 2009). Ramirez et al. (2005) have

reported that microglial activation induced in vivo by β-amyloid was completely prevented by cannabinoid administration, and that cannabinoids also prevented the cognitive deficits occurring in β-amyloid treated rats. Despite the positive initial evidence for the use of cannabinoids in AD, some have indicated that CB2-R may not always play a protective role against the Aβ peptide induced inflammatory state. Instead this effect may be dependant in part on the phase of the disorder (Bisogno and Marzo 2008). For example, early CB2-R activation could be deleterious as it may block the early repair process mediated by microglial cells (Bisogno and Marzo 2008). Evidence points to cannabinoids having a greater efficacy in diseases with chronic neuroinflammation like AD (Klein and Newton 2007), in part explaining why Nabilone had a lesser effect on our patient with Frontotemporal dementia.

CBR independent actions of cannabinoids have been identified which reduce neuronal oxidative injury by means of scavenging reactive oxygen species, reducing lipid peroxidation and reversing Tau hyperphosphorylation (Campillo and Páez, Campbell and Gowran 2007). Cannabinoids have been shown to competitively inhibit acetylcholine esterase leading to increased acetylcholine availability, as well as reducing amyloidogenesis and subsequent neurotoxicity (Campbell and Gowran 2007, Klein and Newton 2007, Bisogno and Marzo 2008). It is apparent that cannabinoids have multiple mechanisms by which they could impact AD progression.

Currently the majority of evidence for pharmacologic management of dementia-related agitation exists for atypical antipsychotics, cholinesterase inhibitors and selective serotonin reuptake inhibitors (Passmore 2008). In 2002 evidence of increased strokes in patients with AD treated with Risperidone prompted Health Canada to release an advisory to clinicians (Wooltorton 2002). By 2005 a public health advisory, based on a meta-analysis of four atypical antipsychotics in AD, was released advising of increased mortality (4.5% with atypical antipsychotics vs 2.6% with placebo) in patients with dementia-related agitation (Public health advisory 2005). Given the adverse effects of the current standard of care; the development of safe, effective alternative treatments is a pressing matter.

The case reports as described earlier along with the report by Passmore (2008) and our current understanding of the actions of cannabinoids, indicates there may be a role for Nabilone in the treatment of AD with aggression. Nabilone and similar cannabinoid derivatives are particularly attractive as potential pharmacological interventions because of their comparatively mild side effect profile. Some common side effects of synthetic cannabinoids are increased appetite, vasodilation, hypotension, bradycardia, decreased intraocular pressure, drowsiness, anxiety, decreased concentration and possibly acute psychosis (Klein and Newton 2007, Williamson and Evans 2000). This being said, what remains to be elucidated regarding the cannabinoid class of drugs is their clinical efficacy.

In conclusion, synthetic cannabinoids hold great promise for the treatment of Alzheimer's type dementia with aggression. This case report and others have demonstrated positive effects of the use of synthetic cannabinoids in this patient population. Given the limited clinical evidence supporting their use, large scale clinical trials are necessary to determine the clinical efficacy of synthetic cannabinoids in AD patients.

1.2.1 Conclusions and findings during this study

Synthetic cannabinoid play a positive role in the treatment options for agitation in both Alzheimer's and Frontotemporal dementia. Key points were,

1. Twice daily dosing is not as effective as four times a day.
2. Families noted improved speech after the initiation of treatment. This was in output and sentence structure. The improvement was not sustained.
3. Tolerance seems to develop every 6-8weeks in the early stages of treatment with a need to increase the dose by 0.5mg. Each patient could have a maximum effective dose depending on the other medications being used concomitantly.
4. There was no adverse effect noted and an improved appetite was consistently seen. There were no seizures or drug interaction of note. It was well tolerated in the study group.
5. Nabilone on its own may not be sufficient to control agitation but it seems to reduce the total dose of antipsychotics needed. Serving well to augment existing treatment.

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