Clinical Evidence for Utilizing Cannabinoids in the Elderly

Itay Katz[1,2], Daphna Katz[1,2], Yehuda Shoenfeld MD FRCP MaACR[1,3] and Bat Sheva Porat-Katz MD[4]

[1]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
[2]Hadassah-Hebrew University Medical School, Jerusalem, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Smith Faculty of Agriculture, Food and Environment School of Nutritional Sciences, The Hebrew University of Jerusalem, Rehovot, Israel

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As history repeats itself, recent legalization changes have led cannabis back to our prescription pad. Tracing back to ~4000 BC, the medical merits of cannabis were utilized throughout history. Currently, medical cannabis is rapidly being introduced into the medicinal arsenal, prompting physicians to evaluate its medical and safety properties. Comprising a large part of the population and an even more prominent proportion of health care consumers, elderly patients constitute a substantial target group for treatment with medical cannabis. A recent Israeli study found that of 279 cancer patients receiving medical cannabis 50% were aged 60 or older [1]. Indeed, in light of the unique features of the geriatric population there is a need for a safe drug to address their complaints. Drugs such as antipsychotics or benzodiazepines are being used daily although they pose a high risk for the elderly's health and well-being. Since medicinal cannabis has shown promise for many conditions that trouble elderly patients, we set out to explore the current therapeutic potential of cannabis in this population.

CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM

The last three decades precipitated a giant leap forward in our knowledge of the endocannabinoid (eCB) system and cannabinoids, including the dramatic change in medical perception following the discovery of the eCB system's role in both physiological and pathological process [2]. As in most systems, the endocannabinoid system is comprised of cannabinoid receptors, endogenous ligands, and enzymes engaged in either synthesis or degradation.

- **Cannabinoid receptors**

To date there are two known cannabinoid receptor subtypes, CB1 and CB2, both classified as $G_{i/o}$ protein-coupled receptors. Yet the two receptors differ from each other not only in binding site but in distribution as well, with CB1 distribution being more prominent in the central nervous system, whereas CB2 is prominently distributed in the immune system. Although CB1 and CB2 are currently considered the main cannabinoid receptors, evidence suggests that cannabinoid compounds do not bind solely to CB receptors and may interact with other receptors, such as transient receptor potential cation channel subfamily V member 1 channels (TRPV1), peroxisome proliferator-activated receptors (PPARs), and others [3].

- **Endocannabinoid ligands**

The two main endogenous cannabinoid ligands are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). This pair of eCBs are derivatives of arachidonic acid and are synthesized locally in response to demand [3].

- **Endocannabinoids synthesis and degradation**

AEA is primarily synthesized by the action of N-acyltransferase (NAT) and N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD), and degraded predominantly by the activity of fatty acid amide hydrolase (FAAH). 2-AG is synthesized by the action of diacylglycerol lipase (DAGL), and degraded by monoacylglycerol lipase (MAGL). AEA and 2-AG share some oxidation pathways [3].

Different strains of *Cannabis sativa* encompass more than 545 different compounds, of which more than 100 are classified as phytocannabinoids and are unique to the *Cannabis sativa* plant. The two most prominent and researched phytocannabinoids are the dynamic duo Δ^9tetrahydrocannabinol (THC) and cannabidiol (CBD), each with its own merits and distinctive features. THC, considered the major psychoactive ingredient in *Cannabis sativa*, is a lipophilic molecule that exerts similar effects to AEA in animal models [2,4]. CBD is a major non-psychoactive constitute of *Cannabis sativa* and, like THC, is a lipophilic molecule. The pair share a biosynthesis pathway and differ only in the last stage of the process [2].

While cannabinoids can be consumed in their natural form, refined separately or as synthetic analogues, it seems that combined consumption exerts a superior beneficial effect. Surprisingly, and contrary to the "ideal" drug composition paradigm, the *Cannabis sativa* ensemble of ingredients seems to work syn-

ergistically, being more effective than the single ingredient. It appears that, indeed, the whole is greater than the sum of its parts, giving rise to the theory of "the entourage effect" [5].

CANNABINOIDS AND PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative disorder mainly of dopaminergic neurons in the substantia nigra. While the etiology of PD is still unclear, the cellular mechanisms that underlie the complex interactions between genetics and environmental factors are gradually being unraveled. PD is known for its characteristic movement dysfunction and symptoms that commonly include tremor, bradykinesia, rigidity and gait abnormality, collectively known as Parkinsonism. PD may also involve non-motor clinically significant symptoms [6].

Despite the fact that CB1 is absent in the dopaminergic nigrostriatal neuron, the eCB system seems to play a major part in the modulation of dopaminergic transmission in the basal ganglia. Presumably the eCB system modulates GABA and glutamate inputs to the dopaminergic nigrostriatal neuron. Furthermore, evidence of the presence of CB2 and TRPV1 in the nigrostriatal neuron suggests an additional pathway of direct modulation [7]. Additionally, single nucleotide polymorphism within the *FAAH* gene has been associated with greater risk for PD-related pain [8].

The ability of the eCB to modulate the dopaminergic system holds promise for the future treatment of PD. Preclinical data suggest that selective pharmacological intervention in the eCB signaling pathway may have a beneficial effect in PD, both on motor and non-motor symptoms. An additional benefit may include neuroprotection [6]. Supporting this notion is the open-label observational study conducted by Lotan et al. [10] in 22 PD patients before and 30 minutes after consumption of *Cannabis sativa*. Following cannabis consumption the patients exhibited a significant improvement of 9.9 points in the mean score in the Unified Parkinson's Disease Rating Scale ($P < 0.001$). Furthermore, specific analysis revealed significant amelioration also in rigidity, tremor, bradykinesia, pain and sleeping problems with no significant adverse effect [9]. In another study, conducted as a randomized, double-blind, placebo-controlled, crossover trial, by Sieradzan et al. [11], PD patients reported a significant alleviation of total levodopa-induced dyskinesia following treatment with nabilone (THC analogue). Patients treated with nabilone achieved a 5 point reduction in the Rush Dyskinesia Disability Scale ($P = 0.05$, n=7) [10]. Notwithstanding both the preclinical data and the results reported by Lotan et al. [10] and Sieradzan et al. [11], other clinical studies aiming to explore the effects of cannabinoids in PD did not demonstrate a significant clinical change. Nonetheless, these studies [12,13] show the relative safety and toleration of cannabinoids in PD patients.

Overall, current preclinical and clinical data suggest a therapeutic potential for PD patients by targeting the eCB system. However, while we acknowledge the beneficial properties of cannabis that are already being utilized in the treatment of PD, it is not without reservation. It is our opinion that the ideal therapeutic effect in these patients is achievable only through specific compounds that target selective parts in the eCB signaling.

CANNABINOIDS AND DEMENTIA

Dementia is a clinical mental syndrome mainly affecting older adults, characterized by a progressive pathological impairment of memory, language, orientation, judgment, comprehension and overall cognition that affects the individual's ability to conduct everyday activities. These symptoms are predominantly accompanied by psychological and behavioral symptoms, i.e., motivation, emotional and social problems, as well as agitation and delusions. Dementia may result from several diseases and assaults, with Alzheimer's disease (AD) being the leading cause [13]. For the sake of convenience we will mainly address AD and refer to dementia as a syndrome rather than to the individual etiologies.

While the role of the eCB system in dementia has yet to be elucidated, the inherent changes of the eCB system in AD are fairly researched and characterized. These changes affect mainly two sites, the hippocampus and the cerebral cortex, which are also the two prominent sites affected by AD. The aforementioned changes are characterized by: (i) an increase in FAAH enzyme activity and levels in astrocytes associated with neuritic plaque; (ii) elevated 2-AG levels linked to β-amyloid hippocampal degradation, supposedly in an independent manner due to FAAH increase; (iii) CB2 up-regulation in microglial cells adjacent to β-amyloid plaques; and (iv) reduction in the number of CB1-positive neurons [14].

Though lacking sufficient data, current data on cannabinoids treatment in both Parkinson's disease and dementia suggest cannabinoids treatment as beneficial, mainly for motor dysfunction in PD and neuropsychiatric complaints in dementia

Although preclinical data suggest the potential role of cannabinoids in disease progression and possible prevention, clinical data supporting that notion have yet to be determined. Nonetheless, a substantial amount of clinical data supports the beneficial therapeutic effect of cannabinoids on behavioral symptoms in patients with dementia. In a placebo-controlled crossover-designed study, Volicer et al. [16] were the first to demonstrate an amelioration in behavioral disturbance in AD patients following treatment with dronabinol (THC analogue) (n=15, P value unclear) [15]. Later on, a Cochrane systematic review from 2009 found the Volicer trial to be the only study that met the inclusion criteria. However, due to a lack of quantitative data in the Volicer study, the Cochrane authors concluded that the result could not be adequately validated [16]. In a retrospective systematic chart review, Woodward and co-authors [18] demonstrated a significant reduction in agitation among demen-

tia patients associated with dronabinol intervention (n=40, $P < 0.0001$) [17]. A similar beneficial effect of dronabinol on nocturnal agitation was reported in an open-label pilot study (n=6, $P < 0.05$) by Walther et al. [18]. A new prospective cannabinoid treatment for dementia is illustrated by a recent case report suggesting cannabinoids for the treatment of sexual disinhibition. A 71 year old dementia patient suffering from sexual disinhibition who was non-responsive to conventional psychiatric intervention was treated with nabilone. The outcome was a subsequent reduction in disinhibition in sexual behavior, thus illuminating a new trait that might be beneficial in patients with dementia [19]. Contrary to the results mentioned above, a recent randomized, double-blind, placebo-controlled study failed to achieve significant change in patients' Neuropsychiatric Inventory (NPI) score following THC treatment. Possibly, the lack of positive results in this study can be attributed to the low THC dosage [20].

Both preclinical and clinical data suggest a therapeutic beneficial potential of cannabinoid for demented patients, although the clinical data support cannabinoid treatment mainly for behavioral, agitation and other neuropsychiatric symptoms. Based on all the current data it seems that cannabinoids is an efficient and safe therapy to manage behavioral disturbances in dementia patients.

CANNABINOIDS AND SLEEP DISTURBANCES IN THE ELDERLY

Changes in sleep patterns and quality of sleep are considered a natural part of aging. Poor sleep quality is often associated with impairment in quality of life, yet its effect on the elderly's health is much greater. Difficulty maintaining sleep has been found to correspond with a more pronounced cognitive decline in elderly patients with normal cognition [21]. Moreover, in a 12 year follow-up in the general population, short sleepers with poor quality of sleep were found to have a 63% higher risk of cardiovascular disease [22]. Current treatment options include benzodiazepines, non-benzodiazepines and melatonin, which may subject patients to various adverse effects, some endangering their health.

Studies examining cannabinoids treatment for sleep disturbances and weight loss in the elderly are scarce and insufficient for recommending treatment

Research exploring the influence of cannabis on sleep suffers from low grade evidence and conflicting data. Based on these data a recent meta-analysis concluded that non-medicinal use of cannabis may cause reduced slow-wave sleep and resultant increased phase 2 time. In contrast, the medicinal use of cannabis appears to reduce sleep disturbances and improve sleep quality without affecting sleep duration [23]. Specific indications of sleeping problems include:

- REM sleep behavior disorder (RBD): CBD appears to be a prospective line of treatment in patients suffering from both Parkinson's disease and RBD. In a case series of four patients suffering from Parkinson's disease and RBD, CBD treatment led to a remarkable reduction in frequency of symptoms [24].
- Night-time agitation: a small study of six patients suffering from severe dementia (five with AD and one with vascular dementia) and exhibiting night-time agitation showed that THC led to a significant reduction in nocturnal motor activity as well as an improvement in the Neuropsychiatric Inventory Total Score following treatment [18].

CANNABINOIDS AND MALNUTRITION IN THE ELDERLY

Malnutrition and weight loss impose a great risk on the elderly's health. The pernicious effect of weight loss and malnutrition affects numerous aspects of the elderly's well-being. The relation between weight loss and mortality emphasizes the significant role of the nutritional state in patients' prognosis. Moreover, weight loss was also associated with frailty, functional decline, and both severity and rate of disease progression in dementia [25].

Although in popular culture cannabis is known for giving one the "munchies" – a sensation of increased hunger following cannabis consumption – clinical trials exploring cannabis' beneficial effect on the elderly suffering from cachexia are scarce. In light of the insufficient data, both the Cochrane Review (2009) and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition for patients with dementia (2015) concluded that current data do not support cannabis treatment for cachectic demented patients [16,25]. Nonetheless, preliminary results indicate a potential weight-gaining effect of cannabis. A small scale placebo-controlled crossover study conducted in 15 AD patients showed a significant increase in patients' body weight and triceps skinfold thickness following treatment with dronabinol (CB1 receptor agonist) [15]. Another small trial examined the effect of dronabinol in patients with involuntary weight loss while residing in long-term care. Twenty-eight patients were followed over a 12 month period while receiving dronabinol for at least 12 weeks. The study's results diverged, with 53% of patients gaining weight while 39% lost weight [26]. More promising results were accomplished in a recent retrospective study. The charts of 40 patients treated with dronabinol were examined, with mean duration of 16.88 days of dronabinol treatment. Although body weight did not significantly change, a significant change in the amount of food consumed was found. Owing to the limitation in the study's design, it can be presumed that a longer duration of dronabinol treatment might elicit a change in body weight [17].

ADDITIONAL INDICATIONS FOR CANNABINOID TREATMENT

Cannabinoids are currently being utilized for a vast range of medical conditions, and although these conditions are not specific to elderly patients a potential efficacy for patients with these diseases can be presumed. Among others, these include chronic pain conditions [27], various cancer morbidities [28,29], epilepsy

[30], systemic sclerosis [31], inflammatory bowel disease [32], dysautonomic syndrome [33] and many more [34].

SAFETY, ADVERSE EFFECTS AND DRUG INTERACTION OF CANNABINOIDS IN THE ELDERLY

- **Adverse effects**

The medical literature is abundant with reports of various adverse events, the largest number of adverse events reported to be about 8000, following cannabinoids consumption in their different forms. Among these adverse effects, tachycardia (37%–77%), agitation (16%–41%) and nausea (13%–94%) were the top rated complaints in numerous studies [3]. Since most of these studies were conducted in a general population further elaboration will not be provided.

- **Safety concerns**

As with most drugs, cannabinoids lack targeted studies focusing on adverse reactions in the elderly. A recent systematic review set out to explore the safety of cannabinoids in elderly patients. Based on six different studies comprising a total of 260 patients, van den Elsen et al. [35] concluded that sedation/drowsiness was the most frequent complaint among patients. Importantly, no severe adverse effects were reported, apart from two patients with chronic obstructive pulmonary disease (COPD) who developed cardiac arrhythmias and one patient with grand mal seizure who died 2 months later from causes not related to cannabis. Two randomized, double-blind, placebo-controlled, crossover trials examined the safety of Namisol® (a form of oral THC, Echo Pharmaceuticals, The Netherlands) given to healthy older subjects or demented patients. Among the healthy subjects drowsiness (27% of adverse events) was the most prevalent adverse effect, followed by dry mouth (11%) [36]. Patients suffering from dementia received either Namisol or placebo for a 6 week period (each) separated by a 4 day washout. Namisol treatment resulted in a significant increase in heart rate, VAS (Visual Analogue Scale) internal perception scores, and body sway with eyes closed, while systolic pressure decreased. Contrary to these results, VAS scores for "feeling high" (euphoric) and external perception, body sway with eyes open and diastolic pressure did not differ [37].

Since drowsiness is frequently the most common complaint among the elderly consuming cannabinoid, a recent study set out to examine the effect of THC on balance and gait. In a randomized, placebo-controlled, crossover trial, demented patients were treated with THC for 3 days and measured for balance and gait performance 2 hours after treatment. THC exposure increased stride length and trunk sway during patients' preferred speed walking and increased sway while standing with eyes closed. No effects were observed during dual-task walking or while standing with eyes open. Furthermore, there were no cases of falls during the study period [38].

Cannabinoids present a relatively safe profile of action in elderly patients. Hence, cannabinoid treatment should be considered more readily when other options fail, even in cases of scarce data

Table 1. Common drugs, which interact with cannabinoids, used by the elderly

Drug	Reference
Warfarin	[40]
SSRI	[40]
TCA	[40]
Barbiturates	[40]
Fluoxetine	[40]
Chlorpromazine	[39]
Lithium	[40]
Indinavir	[40]
Nelfinavir	[40]
Sildenafil	[40]
Theophylline	[39,40]
Ethanol	[40]
Anticholinergics	[40]

- **Drug interactions**

Elderly patients typically consume a large number of prescription drugs. Thus, drug interactions are a major concern for physicians treating elderly patients. Although cannabis is usually regarded as a safe alternative, it should be remembered that no drug is innocent, and the fact that its origin is "natural" does not ensure safety, as seen with digitalis and digoxin. Hence, prescribing medical cannabis should be under advisement with regard to possible interactions. Current data suggest that cannabis or some of its properties are metabolized by CYP3A4, CYP2C9 and CYP2C19, while possibly inducing CYP1A2. These enzymes affect some common drugs used by the elderly such as warfarin and sildenafil. For a more elaborate list see Table 1 [39,40].

CONCLUSIONS

In the last decade *Cannabis sativa* has rebranded itself from a common illicit drug to a new valid medical treatment for various conditions. In light of this new reality, physicians are confronted with a dilemma: the public demand for cannabis versus the lack of medical training regarding cannabis treatment. The dilemma is intensified in geriatric patients, considered to be a unique population due to frailty and over-medication. Thus, knowledge on the safety and therapeutic potential of cannabinoids is crucial when treating an elderly patient. Due to a paucity of research, cannabinoid treatment is predominantly an additive/replacement therapy, regarded as the last resort when conventional therapy protocol

fails. As such, in the natural course of Parkinson's disease, cannabinoids can be utilized as a third-line or supplementary treatment, with evidence indicating their efficacy in reducing tremor, dyskinesia, rigidity and pain, and improving sleep. As in Parkinson's disease, physicians treating patients with dementia often cannot offer effective treatment for the neuropsychiatric symptoms, and the result is treatment with possible deleterious effects. The use of medical cannabis in dementia appears to be a safe option for behavioral problems although clinical data are still inadequate. Other conditions for which evidence is scarce and preclude recommendations are sleep disturbances and weight loss; additional data are sorely needed. Lastly, the medical literature suggests that cannabinoids have a relatively safe profile for use in geriatrics, with drowsiness being the most common complaint. This safety profile is the core of cannabinoid treatment, making it a possible key player in elderly medical care.

Correspondence
I. Katz
33 Rupin Street, Rehovot 7634538, Israel
Phone: (972-8) 946-1888, **email:** itay.katz1@mail.huji.ac.il

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