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Dazed and Confused – Medical Cannabis in Alzheimer’s Disease

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Neuropsychiatric symptoms in Alzheimer's disease (AD) are associated with adverse outcomes for patients and their caregivers. Agitation, one of the most distressing neuropsychiatric symptoms, involves emotional distress, excessive psychomotor activity, aggressive behaviors, disruptive irritability and disinhibition [1]; adequate options for alleviating these neuropsychiatric symptoms are lacking. While nonpharmacological interventions are suggested as first-line treatment, they aren't effective in managing symptoms for every patient, resulting in pharmacological interventions for some patients. Traditionally, these interventions include off-label use of antipsychotics, sedative/hypnotics, anxiolytics, acetylcholinesterase inhibitors, memantine and antidepressants; where the efficacy doesn't necessarily outweigh the associated risks [2]. Unfortunately, given a modest efficacy offset by relatively poor adherence, safety and tolerability, these treatments have limited utility. Finding more effective and better-tolerated interventions for neuropsychiatric symptoms is a major challenge for investigators and clinicians and must become an urgent priority. While research has been limited regarding the use of cannabinoids as alternative pharmacological therapy for agitation related to Alzheimer's disease, this condition is listed as a qualifying indication for medical marijuana in some states where it has been legalized.

In this issue of AJGP, in a thought provoking brief report, Maust and colleagues explore which states allow dementia or "agitation of Alzheimer's Disease" as a specific indication for medical marijuana and the proportion of licenses granted for this indication in the most recent year for which data was available. Over 40% of states/localities that allow medical marijuana permit this indication but very few licenses are currently granted. The authors expect an increase with time.

Several neurobiological effects of cannabinoids might be relevant in the treatment of dementia. These compounds are the active components derived from the cannabis plant (*Cannabis sativa*). An endogenous cannabinoid system has been identified where these compounds exert their effect by acting at two specific cannabinoid receptors, CB1 and CB2. CB1 receptors are found throughout the CNS, particularly in the hippocampus, basal ganglia and cerebellum, whereas CB2 receptors are mostly expressed in peripheral tissues. Delta-9-tetrahydrocannabinol (THC), the most biologically active isomer of (-)-trans-D9-tetrahydrocannabinol ((6aR,10aR)-delta-9-tetrahydrocannabinol), is a psychoactive compound that activates cannabinoid receptors (mainly type 1), which represses neurotransmitter release in the brain and regulates synaptic transmission. Pre-clinical studies show evidence suggesting neuroprotective effects of cannabinoids. The exact mechanism of action is not known, but could involve reduced excitotoxicity through regulation of glutamate and reduced neuroinflammation [3]. The cannabinoid receptor agonist, dronabinol, is reported to improve anorexia, agitation and nocturnal disturbances in patients with dementia, however most studies to date have been small and results are not consistently positive. A retrospective study of 40 inpatients with dementia who received dronabinol for behavioral and appetite disturbances found a significant decrease in all domains of the Pittsburgh Agitation Scale, in addition to improvement in Clinical Global Impression (CGI) scores, sleep duration and meal consumption, with good tolerability [4]. Also supportive was an open label study of 11 patients with Alzheimer's disease and associated behavioral and psychological symptoms of dementia that were treated with medical cannabis oil over 4 weeks. This was associated with significant reduction in CGI severity score, caregiver distress, and NPI domains including delusions, agitation/aggression, irritability, apathy, and sleep, while also maintaining a good safety and tolerability profile [5]. Conversely, a 3-week

randomized controlled trial of THC in tablet form to treat behavioral disturbances and pain in patients with dementia showed no benefit over placebo, however it was well tolerated. The authors suggested that the target dose used was too low as no psychomimetic effects were observed [6].

We struggle with multiple issues surrounding this interface. The legalization of medical marijuana has stirred up politicians, healthcare providers, and the American public, however, clarity on the evidence behind risks and benefits of broader use of medical marijuana is lacking. Furthermore, the discrepancy between state and federal laws confounds the picture. Most publications focus on the legal issues rather than scientific evidence. Inconsistent laws make it hard for healthcare providers to determine whether and how to recommend using medical marijuana. With increasing use of medical marijuana and relative lack of research, medical experts including the American Medical Association and American College of Physicians have requested the re-classification of marijuana to a Schedule II controlled substance, which would remove barriers to researching it as a potential medical therapy.

The quality and potency of the drug, as well as delivery method, are also in question. How will we assure patients and ourselves that the medical marijuana they are consuming contains the same amount of medication within each dose? Patients are allowed to grow their own plants at home in some states, which means that the plants may be variably tended to, thus affecting their potency. Delivery methods and varying metabolic rates and volumes of distribution can alter the onset of action, the degree and duration of effect and the time to be excreted from the body. Careful standardization of THC concentration and quality assurance of manufacturing is imperative and no less important here than in the manufacturing of other medications. Given the evolving landscape surrounding medical marijuana legislation, the

Federation of State Medical Boards recently issued a position statement to guide licensed physicians who choose to recommend marijuana in patient care. In addition to cautioning physicians to abstain from using marijuana while practicing medicine, the Board suggests certain expectations to follow when recommending marijuana to patients. These include establishing a patient-physician relationship; documenting an in-person medical evaluation; informed and shared decision making; document a written treatment agreement; recommending use guided by current standards of practice and in compliance with state laws, rules, and regulations; ongoing monitoring; seeking appropriate consultations as indicated; maintaining a comprehensive medical record; and avoiding conflict of interest with a marijuana dispensary or cultivation center [7]. In addition to following these guidelines in clinical practice, we need to support scientific research on this age-old remedy that has found new purpose in our society, to ensure that our medical marijuana certifications are in the best interest of our patients and that our practice is evidence-based.

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