Long-Term Care Updates

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Dronabinol for Dementia?

An evidence-based review

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Introduction

Dementia involves the loss of cognitive functioning severe enough to interfere with daily life, and these changes in cognitive functioning can also affect behavior, emotions, and relationships. While dementia is more common in older adults, it is not a normal part of aging. It is caused by damage to brain cells, impairing the cells' ability to communicate with one another. Different types of dementia relate to damage of brain cells in different regions of the brain. The most common type of dementia is Alzheimer's disease – others include frontotemporal dementia, vascular dementia, Lewy body dementia, and mixed dementia.[1,2]

Because there are no approved therapies available to cure or reverse the effects of dementia, treatment typically involves managing symptoms that arise with the disease. This includes medications for memory loss, agitation, behavioral changes, and sleep disturbances.[2] However, many of these agents can present problems of their own. For instance, atypical and typical antipsychotics are not recommended in patients with dementia and have a boxed warning regarding the increased risk of death and cerebrovascular accident in patients with dementia.[3] Selective serotonin receptor inhibitors (SSRIs) have been shown to improve symptoms related to behavior and agitation in patients with dementia; however, SSRIs also have the potential to increase the QTc interval and may not be an option for all patients with dementia; thus, alternative options are needed.

Dronabinol is a synthetic delta-9-tetrahydrocannabinol (THC) that activates the cannabinoid, CB1 and CB2, receptors. Agonists at the CB1 receptor in the brain have been shown to inhibit glutamatergic, dopaminergic, and other neurotransmitter release - mediating the effects of improved anxiety and depression commonly seen with THC. Agonists at the CB2 receptor have an anti-inflammatory effect, decreasing central and peripheral inflammation that can contribute to the behavioral effects of agitation and aggression often seen in dementia patients. Dronabinol has been approved for anorexia in patients with acquired immunodeficiency syndrome (AIDS), as well as in patients with chemotherapy-induced nausea and vomiting. While there is interest in using dronabinol in patients with dementia, it is not FDA-approved for this purpose.[5,6]

This newsletter will address the safety and efficacy of dronabinol on agitation in patients with dementia.

Clinical Research

Several meta-analyses addressing the safety and efficacy of cannabinoids, including dronabinol, for the management of agitation and neuropsychiatric symptoms (NPS) associated with dementia have been published. These analyses have generally found that, when pooling results from studies on various cannabinoids, these interventions are potentially efficacious in treating NPS and agitation associated with dementia; however, heterogeneity, small sample sizes, and other potential biases limit the validity and generalizability of these findings. Additionally, none of the analyses provided subgroup analyses on studies specifically evaluating dronabinol.[6-9]

Because pooled results are not available from research specifically addressing dronabinol use in patients with dementia, a closer look at prospective and retrospective research in this area is warranted.

Walther et al. conducted a very small (n=2) randomized, placebo-controlled, double blind crossover trial to assess the efficacy of dronabinol for nighttime agitation in patients with dementia. The study period was four weeks, and the patients were given 2.5 mg of dronabinol or placebo for the first two weeks, then crossed over to the other therapy for another two weeks. The medications were given at 7pm, and information bias was controlled by packaging dronabinol and the placebo in identical capsules. Patients were included in the study if they were diagnosed with Alzheimer dementia or mixed dementia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA). Patients were excluded from the study if they had a history of seizures, substance dependence other than nicotine, and took psychotropic medications within the last four weeks. Behavior disturbances were assessed weekly using the Neuropsychiatric Inventory (NPI), and agitation was assessed nightly between 9pm to 6am using continuous wrist actigraphy with a device like a wristwatch on the nondominant arm. Patient A, who received dronabinol for the first two weeks, had a decline in nocturnal motor activity until the third week of the trial when she/he was switched to placebo. Levels returned to baseline during the fourth week of the trial (second week of the placebo arm). Patient B, who received placebo first, had nocturnal motor activity decline the greatest during the first week of dronabinol treatment, but this activity increased to baseline during the second week of active treatment. The NPI scores decreased throughout the trial; however, the authors stated that only slight behavioral changes across all NPI items were seen during the trial period. Researchers concluded that CB1 agonists, such as dronabinol, may improve behavior and psychological symptoms associated with dementia. Limitations of this study include small sample size, inability to perform statistics, and agitation only being measured at night. These limitations impede the ability to make clear conclusions regarding the efficacy of dronabinol on agitation from this study.[10]

Volicer et al. conducted a small (n=15) randomized, double-blind, placebo-controlled, crossover trial assessing the effects of dronabinol on disturbed behavior in patients with dementia. The study period was twelve weeks, and the patients were given dronabinol 2.5 mg or placebo twice daily (morning and noon) for the first six weeks, and then switched to the other treatment option for the remaining six weeks. The extent of disturbed behavior was calculated each week by interviewing primary caregivers and determining a rating scale using the Cohen-Mansfield Agitation Inventory (CMAI). One patient died of a myocardial infarction two weeks before the end of the study. He was on the placebo treatment arm and was included in the analysis. Three patients were terminated due to seizure and infection; however, no other serious adverse reactions to dronabinol occurred. Tiredness, somnolence, and euphoria occurred more during the dronabinol treatment than placebo period. Twelve patients were included in the final analysis, of which six were randomized to receive dronabinol first and six were randomized to receive placebo first. All patients were male, except one. Disturbed behavior decreased during both treatment periods, and the decrease in this behavior continued during the placebo period for the group that received dronabinol first. Disturbed behavior decreased significantly more in the dronabinol first treatment group when CMAI scores were expressed as a percentage of the baseline ($p=0.05$). The researchers concluded that dronabinol was effective in decreasing agitation in patients with dementia, but a larger study is needed. The main limitation of this study was small sample size. This study demonstrated that dronabinol may have some effect in decreasing agitation, and these effects may be apparent for weeks after treatment concludes.[11]

Walther et al. conducted an open-label pilot study (n=6) to measure the effect of dronabinol on nighttime agitation. Patients were included if they had been diagnosed with dementia according to DSM and NINCDS-ADRDA criteria with nighttime agitation, day-night rhythm disturbances, or sundowning. All concomitant medications were kept stable one week prior to the study and throughout the study period. The trial period was two weeks, and patients received 2.5 mg of dronabinol every evening at 7pm. The primary outcome, decrease in nighttime motor activity during the last five nights of the treatment period compared to the first two nights at baseline, was assessed continuously using a wristwatch actometer on the patient's nondominant arm. Motor activity was measured during three different time periods: nocturnal (9pm-6am), diurnal (6am-9pm), and evening (3pm-9pm). The secondary outcome, NPI score, was assessed at baseline and at the end of the trial. Motor activity decreased significantly only during the nocturnal time period ($p < 0.05$), and was calculated to be decreased 59% from baseline. The total NPI score was significantly decreased from baseline ($p<0.05$), and so were the aberrant motor behavior, agitation, and nighttime behavior subscores of the NPI scale. The numeric decrease in NPI score was not given in the study. The author's concluded that dronabinol may have an effect for decreasing behavioral and agitation disturbances in patients with dementia. The limitations of this study include a small study size and threats the internal validity (open-label, nonrandomized, uncontrolled).[12]

Woodward et al. conducted a retrospective cohort study (n=40) to assess the efficacy and safety of dronabinol as an adjunctive treatment for agitation and aggression associated with dementia. The primary outcome was changes in behavior disturbances. These changes were scored at baseline and after seven days of dronabinol treatment using the Pittsburgh Agitation Scale (PAS), Clinical Global Impression (CGI), and Global Assessment of Functioning (GAF). The mean duration of dronabinol treatment was 17 days, and the mean dose was 7 mg/day. Thirty-seven patients were prescribed an antipsychotic medication, but no difference was found in the number prescribed before and after treatment ($p=0.875$). Cholinesterase inhibitors, memantine, antidepressants, and anticonvulsants were frequently used, as well. The total PAS score decreased significantly during treatment ($p <0.0001$), and so did aberrant vocalization, motor agitation, aggressiveness, and resisting care domain portions of the PAS assessment. The CGI score significantly decreased as well ($p<0.0001$); however, the GAF score did not significantly decrease ($p=0.0969$). None of the patients had to discontinue treatment due to intolerance, but 26 adverse events were reported. Of the adverse events reported, sedation, delirium, urinary tract infection, and confusion were the most frequent; however, because of the design of this study it is unclear if these adverse effects are related to dronabinol or other concomitant comorbidities or medications. The researcher's conclusions are that this cohort study shows the potential benefit of dronabinol for agitation and aggression associated with dementia; however, this study has a few threats to internal validity (open-label, nonrandomized, uncontrolled, inability to adjust for confounders).[13]

Future Research

A phase two pilot interventional clinic trial addressing dronabinol adjunctive treatment of agitation in patients with dementia is currently ongoing. The estimated enrollment is much larger than previous trials (n=160), and the study expected to be completed by May 2023. The study period is three weeks, and participants will receive either dronabinol 2.5 mg twice daily for one week and increase to 5 mg twice daily for weeks two and three or placebo twice daily. The primary outcome is agitation measured by the Pittsburgh Agitation Scale and NPI. Patients can be included in the trial if they are diagnosed with dementia due to Alzheimer's disease, presence of agitation defined by the International Psychogeriatric Association, severe agitation defined by NPI-C Agitation or NPI-C Aggression >4, informed consent, 60-95 years old, and admitted to an associated clinical site. Patients will be excluded if they have a serious or unstable medical illness (cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, hematologic), seizure disorder, baseline delirium determined by the Confusion Assessment Method (CAM) and DSM, current use of lithium, and inability to swallow a pill. This study will be able to better assess the effect of dronabinol on agitation associated with dementia due to a larger sample size and rigorous primary outcome measures that directly assess agitation.[14]

Conclusion

While there are a few studies assessing the efficacy of dronabinol use for agitation associated with dementia, they all have significant limitations that affect their validity. However, despite the small sample sizes, open-label design, and/or retrospective outlook in the previous studies, each provided similar conclusions - dronabinol has the potential to decrease agitation associated with dementia. Still, higher-quality clinical research addressing this question is warranted. On the horizon is a larger randomized controlled trial expected to be completed in May 2023. This study will be able to produce a more conclusive recommendation regarding dronabinol use for agitation in patients with dementia. Overall, evidence to support the use of dronabinol for agitation associated with dementia is limited to poorly designed clinical trials and observational research; thus, the decision to use dronabinol in patients with dementia should be guided by clinical judgment and patient preference, and limited to patients with agitation not controlled with conventional agents.

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