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Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia

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Abstract *Rationale:* Nighttime agitation occurs frequently in patients with dementia and represents the number one burden on caregivers today. Current treatment options are few and limited due to substantial side effects. *Objectives:* The aim of the study was to measure the effect of the cannabinoid dronabinol on nocturnal motor activity. *Methods:* In an open-label pilot study, six consecutive patients in the late stages of dementia and suffering from circadian and behavioral disturbances—five patients with Alzheimer’s disease and one patient with vascular dementia—were treated with 2.5 mg dronabinol daily for 2 weeks. Motor activity was measured objectively using actigraphy. *Results:* Compared to baseline, dronabinol led to a reduction in nocturnal motor activity ($P=0.028$). These findings were corroborated by improvements in Neuropsychiatric Inventory total score ($P=0.027$) as well as in subscores for agitation, aberrant motor, and nighttime behaviors ($P<0.05$). No side effects were observed. *Conclusions:* The study suggests that dronabinol was able to reduce nocturnal motor activity and agitation in severely demented patients. Thus, it appears that dronabinol may be a safe new treatment option for behavioral and circadian disturbances in dementia.

Keywords Actigraphy · Behavioral disturbances · Dementia · Dronabinol · Nighttime agitation

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Introduction

Behavioral symptoms and day–night rhythm disturbances are frequent in patients with Alzheimer’s disease (AD). Indeed, 50% of AD patients suffer from agitation and 25% from aggressive behavior (Tariot 1999). Motor activity and agitation during the night are higher in AD patients than in healthy controls (Volicer et al. 2001), and approximately 50% of patients with severe AD develop day–night rhythm disturbances or agitated behavior during the evening hours (i.e., so-called sundowning; Hope et al. 1999). These symptoms can become a great burden to professional caregivers and family members. In fact, rhythm disturbances and sundowning are the number one cause of long-term hospitalization in AD patients (Hebert et al. 2001). Current treatment options include the use of benzodiazepines and neuroleptics. However, these drugs have a variety of adverse effects and often fail to reduce the behavioral disturbances in question (Ballard et al. 2004; Doody et al. 2001; Lee et al. 2004; Tariot et al. 2004).

Dronabinol (delta-9-tetrahydrocannabinol) is a CB₁ receptor agonist (Howlett et al. 2002). This receptor is expressed in many regions of the brain, including the hippocampus, neocortex, basal ganglia, and the cerebellum (Wilson and Nicoll 2002). CB₁ receptors mediate important brain functions, including nociception, cognition, motor activity, and mood (Breivogel and Childers 1998). Cannabinoids may even prevent AD pathology as CB₁ agonists have been shown to block microglial activation in vivo (Ramirez et al. 2005). Animal models suggest that CB₁ receptor agonists may have a positive effect on sleep architecture (Murillo-Rodriguez et al. 2003). CB₁ receptor agonists are currently used in the treatment of Tourette’s syndrome (Muller-Vahl et al. 2003a,b), multiple sclerosis (Svendsen et al. 2004), pain (Campbell et al. 2001), and nausea in patients receiving chemotherapy (Tramer et al. 2001). One preliminary study has indicated that dronabinol may be effective in alleviating anorexia and behavioral disturbances in AD patients (Volicer et al. 1997). To date, however, biometric instruments have not been used to corroborate such findings. Wrist actigraphy, a valuable and

objective means of obtaining data on motor activity and circadian rhythms, has been shown to be a valid method for measuring sleep–wake rhythms in patients with dementia (Ancoli-Israel et al. 1997; Mahlberg et al. 2004). The aim of our study was, thus, to apply this technique to obtain the first objective data on the effects of dronabinol on behavioral and day–night rhythm disturbances in dementia. We hypothesized that, by means of sleep induction and its effects on emotion, dronabinol would lead to less agitated behavior in AD patients at night.

Methods

Patients

Six consecutive inpatients at our geriatric psychiatry unit who had been diagnosed with dementia accompanied by nighttime agitation, day–night rhythm disturbances, or sundowning were included in this open-label trial. Patients' guardians provided informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Charité Universitätsmedizin Berlin. The four women and two men had a mean age of 81.5 years ($SD=6.1$). The severity of disease was rated using the Functional Assessment Staging Tool (FAST) (Sclan and Reisberg 1992) and the Mini Mental State Examination (MMSE) (Folstein et al. 1975). The mean FAST and MMSE scores were 5.67 ($SD=0.52$) and 10.33 ($SD=6.28$), respectively.

To be included in the study, patients had to meet diagnostic criteria for dementia according to DSM-IV (American Psychiatric Association 1994) and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al. 1984). Five patients were diagnosed with probable dementia of the Alzheimer's type and one with probable vascular dementia. To participate in the trial, patients also had to be in stable medical condition. All prestudy medication for medical or psychiatric illnesses was kept unchanged for at least 1 week prior to the trial, as well as during the trial itself. Prestudy medication included allopurinol, aspirin, angiotensin-converting enzyme inhibitors, diuretics, statins, thyroxine, H₂ blockers, insulin, digitoxine, or isosorbide dinitrate (ISDN). Four patients had been taking psychiatric drugs before the trial and continued to do so for the length of the study; these included risperidone, carbamazepine, donepezil, galantamine, mirtazapine, or chloral hydrate. As additional medication, patients were allowed to take lorazepam 1 mg, clomethiazole 250 mg, or pipamperone 40 mg up to three times per day. Each dose was counted as one unit of additional medication.

Measurements

Continuous recording of motor activity was initiated immediately after hospital admission using a wrist

actometer (Actiwatch, Cambridge Neurotechnology Co., UK) worn on the patient's nondominant arm. Patients wore the same actometer for the length of the study. The actometer uses an accelerometer which produces voltage when the device is moved. Inside the sensor, the degree and force of the movements are converted into activity counts, which are then recorded. Movement counts were performed every minute for the entire length of the trial. Motor activity counts were calculated for three time periods: the nocturnal period (9 PM–6 AM), the diurnal period (6 AM–9 PM), and the evening period (3 PM–9 PM). Before entering the trial, baseline scores were assessed using the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994). At the end of the treatment, the NPI assessment was repeated. All ratings were made by one investigator (SW).

Procedure

After 2 days of baseline assessments, patients received 2.5 mg dronabinol (MARINOL capsules, UNIMED Pharmaceuticals, Inc., USA) every night at 7 PM for 2 weeks. The time of administration was set at 7 PM because oral dronabinol has been shown to exert its initial effects 30–90 min after ingestion, with maximum plasma levels being reached after 2–3 h; the effects of the medication can last as long as 12 h, depending on the dose administered (Grotenhermen 2003).

Analysis

The primary outcome measure was the reduction in nocturnal motor activity during the last five nights of the treatment period compared to the two nights at baseline, as measured by actigraphy. The secondary outcome measures were NPI total score and NPI subscores for nighttime behaviors, delusions, and hallucinations. For further comparison, relative changes in nocturnal activity were calculated by dividing the activity at the end of the treatment period by the activity at baseline. Significant differences were explored within paired groups using the Wilcoxon signed rank test. The level of two-tailed significance was set at $P<0.05$.

Results

No adverse events occurred during the study. The average number of additional medications per day during the trial was 0.93 units ($SD=0.86$). Three patients received less units per day during treatment compared to baseline, while three patients had a slight increase in additional medication. Thus, the amount and frequency of additional medication did not change significantly between baseline ($M=1.04$ units per day, $SD=0.66$) and treatment with dronabinol ($M=0.92$ units per day, $SD=0.77$, $z=-0.946$, $P=0.406$). Motor activity is shown in the Table 1. After 14 days of dronabinol treatment, nocturnal motor activity

Table 1 Motor activity data at baseline and end of 14 days of treatment with 2.5 mg dronabinol

Patient	Activity counts (10^3)					
	Diurnal (6 AM–9 PM)		Evening (3 PM–9 PM)		Nocturnal (9 PM–6 AM)	
	Baseline	End	Baseline	End	Baseline	End
1	80.11	35.63	40.50	16.77	24.29	3.76
2	92.30	113.51	36.04	63.28	37.72	32.89
3	99.14	26.97	47.78	14.80	53.99	10.16
4	57.19	50.74	27.61	21.72	19.90	9.52
5	185.88	228.18	100.24	122.99	80.92	31.07
6	116.56	78.12	83.81	32.65	30.80	11.42
Median	95.72	64.42	44.14	27.19	34.26	10.79
SE ^a	18.05	30.69	11.89	17.15	9.31	5.03
Z ^b	−0.943		−0.943		−2.201	
P (2-tailed)	0.345		0.345		0.028*	

* $P < 0.05$ ^aStandard error^bWilcoxon signed rank test (two-tailed) of actimetric activity. Two days of baseline compared to last 5 days of treatment

had decreased from baseline in all subjects ($P=0.028$; see also Fig. 1); the average relative reduction in nocturnal motor activity was 59% from baseline (range 13–85%). This reduction was already evident during the first 2 days of treatment (see Fig. 2). There were no significant changes in any of the other actigraphic parameters (see Table 1 and Fig. 2).

Not only was the NPI total score lower at the end of the dronabinol treatment period ($z=-2.207$, $P=0.027$), but the NPI subscores also revealed significant reductions in aberrant motor behavior ($z=-2.032$, $P=0.042$), agitation ($z=-2.032$, $P=0.042$), and nighttime behaviors ($z=-2.032$, $P=0.042$). Exploratory testing showed that appetite dis-

turbances ($z=-2.060$, $P=0.039$) and irritability ($z=-2.023$, $P=0.043$) were reduced as well. In addition, a trend towards a reduction in anxiety was observed. The subscore for delusions, apathy, and hallucinations did not change during dronabinol treatment.

Discussion

For the first time, objective measures have been used to show that the short-term administration of dronabinol may be an effective treatment option in patients with severe dementia who are suffering from behavioral and day–night

Fig. 1 Effects of 14 days of dronabinol treatment (2.5 mg at 7 PM) on nocturnal motor activity in patients with agitation in severe dementia. *Wilcoxon signed rank test

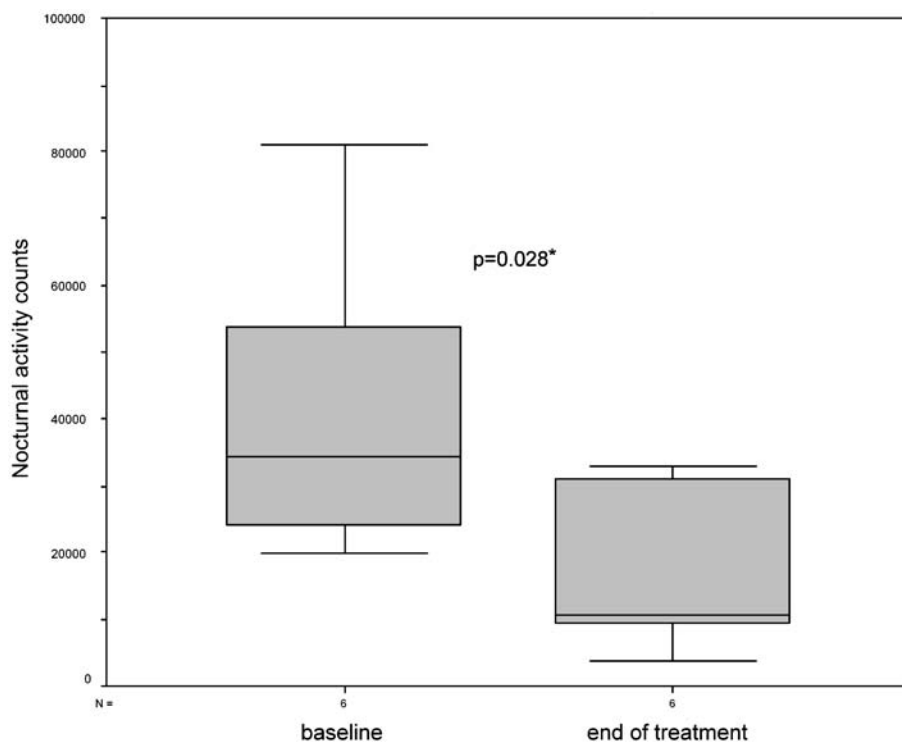
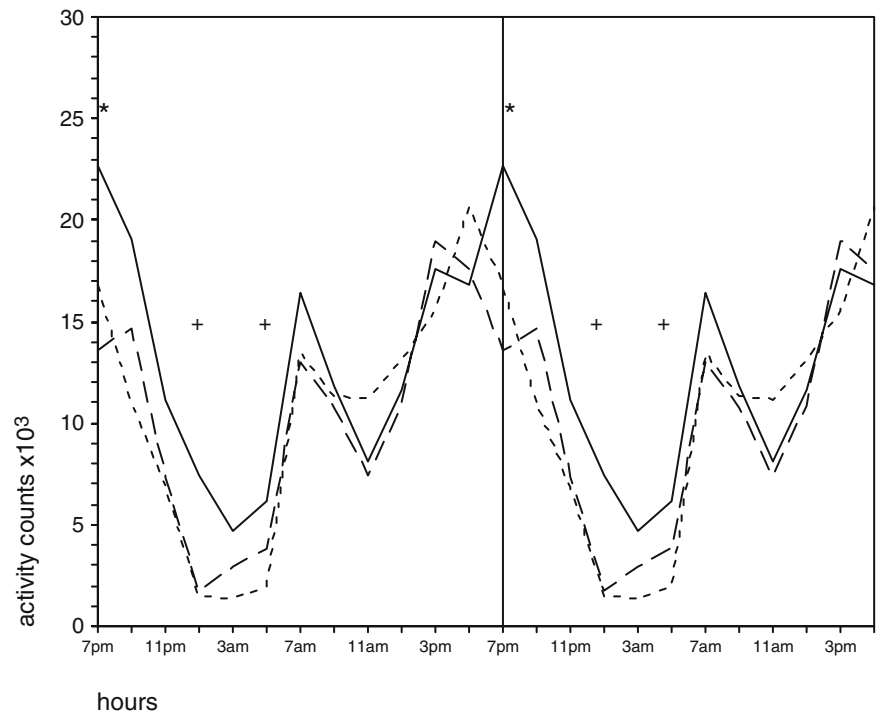


Fig. 2 Motor activity counts of six severely demented inpatients prior to, during the first 2 days of, and during the last 2 days of a 14-day treatment period with 2.5 mg dronabinol administered at 7 PM. Data are given as means for 2-h intervals in a double plot. Baseline (*solid line*), dronabinol start (*dashed line*), dronabinol end (*dotted line*). $N=6$. Wilcoxon signed rank test: * $P<0.05$ baseline vs dronabinol start; + $P<0.05$ baseline vs dronabinol end



rhythm disturbances. The reduction in nighttime motor activity was already apparent after the first dose of dronabinol. It remains to be seen whether these effects are due to sleep induction via the CB₁ receptor (Murillo-Rodriguez et al. 2003).

Naturally, the results of the present study are preliminary. We chose, for example, to test a low dose of dronabinol because of the general differences in pharmacokinetics between younger and older individuals. In addition, although our patients were in stable medical condition at the time of the trial, some of them had substantial comorbidities, such as moderate heart or kidney disease. Earlier trials of oral dronabinol have reported dose-dependent side effects, including drowsiness, dizziness, dysphoria, hypotension, hallucinations, headaches, and palpitations (Campbell et al. 2001; Svendsen et al. 2004; Tramer et al. 2001; Volicer et al. 1997). It is reassuring to note that we were unable to observe any side effects due to dronabinol or any aggravation of heart or kidney disease in our patients. As a result, it is possible that higher doses of dronabinol may be safe and lead to even better results. Finally, for ethical reasons, we chose not to conduct the study in a double-blinded, controlled fashion at this time. NPI ratings were performed by the same rater and may thus be biased by subjective perception. The actimetric data, however, were obtained objectively.

Our trial has several important limitations. First, the sample size of this pilot study was very small. Second, although any prestudy psychotropic drugs were kept unchanged for at least 1 week prior to the trial, as well as during the trial itself, it is conceivable that they contributed to the reduction we observed in psychomotor activity. Third, we did not measure the effects of dronabinol on cognition or function in this trial. In a recent study on the

use of dronabinol in patients with Tourette's syndrome, no influence on neuropsychological function was observed (Muller-Vahl et al. 2003a). In very elderly patients with severe illnesses, however, dronabinol might potentially lead to a deterioration in cognition and function. Clinically, we were unable to observe this effect in our patients. However, because we did not measure the effects on cognition or function over the course of treatment, such side effects cannot be ruled out.

Others have suggested that dronabinol may have a favorable impact on anorexia and disturbed behavior in patients with Alzheimer's disease (Volicer et al. 1997). The biometric data obtained in the present study corroborate these findings. We suspect that controlled clinical trials will reveal dronabinol to have beneficial effects in severely demented patients. Indeed, dronabinol may prove to be a new treatment option for these individuals and help prevent costly long-term hospitalizations.

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References

- American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Press, Washington, DC
- Ancoli-Israel S, Clopton P, Klauber MR, Fell R, Mason W (1997) Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. *Sleep* 20:24–27

- Ballard CG, Thomas A, Fossey J, Lee L, Jacoby R, Lana MM, Bannister C, McShane R, Swann A, Juszczak E, O'Brien JT (2004) A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. *J Clin Psychiatry* 65:114–119
- Breivogel CS, Childers SR (1998) The functional neuroanatomy of brain cannabinoid receptors. *Neurobiol Dis* 5:417–431
- Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ (2001) Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 323:13–16
- Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44:2308–2314
- Doody R, Stevens J, Beck C, Dubinsky R, Kaye J, Gwyther L, Mohs R, Thal LJ, Whitehouse P, DeKosky ST, Cummings JL (2001) Practice parameter: management of dementia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 56:1154–1166
- Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198
- Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 42:327–360
- Hebert R, Dubois MF, Wolfson C, Chambers L, Cohen C (2001) Factors associated with long-term institutionalization of older people with dementia: data from the Canadian Study of Health and Aging. *J Gerontol A Biol Sci Med Sci* 56:M693–M699
- Hope T, Keene J, Fairburn CG, Jacoby R, McShane R (1999) Natural history of behavioural changes and psychiatric symptoms in Alzheimer's disease. A longitudinal study. *Br J Psychiatry* 174:39–44
- Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG (2002) International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* 54:161–202
- Lee PE, Gill SS, Freedman M, Bronskill SE, Hillmer MP, Rochon PA (2004) Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. *BMJ* 329:75–79
- Mahlberg R, Kunz D, Sutej I, Kuhl KP, Hellweg R (2004) Melatonin treatment of day–night rhythm disturbances and sundowning in Alzheimer disease: an open-label pilot study using actigraphy. *J Clin Psychopharmacol* 24:456–459
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34:939–944
- Muller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U (2003a) Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. *Neuropsychopharmacology* 28:384–388
- Muller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, Emrich HM (2003b) Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry* 64:459–465
- Murillo-Rodriguez E, Blanco-Centurion C, Sanchez C, Piomelli D, Shiromani PJ (2003) Anandamide enhances extracellular levels of adenosine and induces sleep: an in vivo microdialysis study. *Sleep* 26:943–947
- Ramirez BG, Blazquez C, Gomez dP, Guzman M, de Ceballos ML (2005) Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. *J Neurosci* 23:1904–1913
- Sclan SG, Reisberg B (1992) Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality. *Int Psychogeriatr* 4(Suppl 1):55–69
- Svensden KB, Jensen TS, Bach FW (2004) Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 329:253
- Tariot PN (1999) Treatment of agitation in dementia. *J Clin Psychiatry* 60(Suppl 8):11–20
- Tariot PN, Profenno LA, Ismail MS (2004) Efficacy of atypical antipsychotics in elderly patients with dementia. *J Clin Psychiatry* 65(Suppl 11):11–15
- Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ (2001) Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 323:16–21
- Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ (1997) Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 12:913–919
- Volicer L, Harper DG, Manning BC, Goldstein R, Satlin A (2001) Sundowning and circadian rhythms in Alzheimer's disease. *Am J Psychiatry* 158:704–711
- Wilson RI, Nicoll RA (2002) Endocannabinoid signaling in the brain. *Science* 296:678–682