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NAbiximols Clinical Translation To the treatment of Pain and Agitation In Severe Dementia (NACTOPAISD): Clinical trial protocol

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ABSTRACT

Up to 80 % nursing home residents with dementia experiences chronic pain. Contextually, 97 % presents fluctuant neuropsychiatric symptoms (NPS). Among the most challenging is agitation, connected with undertreated pain and managed through neuroleptics doubling death risk. Evidence is accumulating in favor of the involvement of the endocannabinoid system in nociception and NPS. This double-blind, placebo-controlled, randomized trial (NAbiximols Clinical Translation To the treatment of Pain and Agitation In Severe Dementia [NACTOPAISD]) aims at investigating efficacy and safety of oral spray nabiximols, containing Δ9-tetrahydrocannabinol and cannabidiol (Sativex®), for pain and agitation treatment in severe dementia patients (Mini-Mental State Examination $\leq$ 12) over 65. The coprimary endpoints are efficacy on pain and agitation, assessed through the recently validated Italian Mobilization–Observation–Behavior–Intensity–Dementia and the Cohen-Mansfield Agitation Inventory. The secondary endpoint is the evaluation of efficacy duration after wash-out and the assessment of quality of life through the DEMQOL. Any adverse events will be reported. The results undergo statistical analysis plan. NACTOPAISD might provide rationale for a translational safer pain and agitation treatment in severe dementia. It is approved by Calabria Region Ethics Committee and follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and the Consolidated Standards of Reporting Trials (CONSORT) statements.

1. Introduction

The issue raised by dementia is of key importance since some 75–90 % out of the 55 million people affected by Alzheimer's disease and related dementias (ADRD) all over the world do not receive diagnosis, even more during the current Coronavirus disease (COVID)-19

Abbreviations: AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; CBD, cannabidiol; CMAI, Cohen-Mansfield Agitation Inventory; CONSORT, Consolidated Standards of Reporting Trials; COVID-19, Coronavirus disease-19; DSM-5, statistical manual of mental disorders-5; EAS, Einstein Aging Study; ECS, endocannabinoid system; HRQL, health-related QoL; HIV, human immunodeficiency virus; I-MOBID2, Italian version of the Mobilization–Observation–Behavior–Intensity–Dementia; MMSE, Mini-Mental State Examination; MS, multiple sclerosis; NPS, neuropsychiatric symptoms; QoL, quality of life; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; THC, Δ-9-tetrahydrocannabinol.

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pandemic [1,2] in which they take the greatest risk of death [3]. Therefore, the amount of older people affected by dementia is noteworthy and, prodromically to the onset and during the clinical history of the disease, the 97 % of them develops fluctuant neuropsychiatric symptoms (NPS) [4]. This is crucial since the patients' quality of life (QoL) is remarkably affected by disorders of thought content [5], perception and mood [6,7] and behavior [8]. A safe and effective treatment for NPS is not available yet consisting in atypical antipsychotics doubling mortality risk [9], often used off-label for drug and therapy duration in the community context [10]. Moreover, neuropathological alterations are associated with behavioral disturbances. Agitation, occurring in some half patients [11], is one of the NPS most resistant to treatment that needs to be considered a form of help seeking in response to unrelieved pain. This observation is confirmed by the effective management of agitation through analgesia [12]. Patients suffering from dementia usually are aged over 65 years, thus presenting comorbidities responsible for chronic, inflammatory and neuropathic pain, often underdiagnosed because of the impaired and insufficient self-report skills [13]. Also, dementia and aging induce alterations of neuromodulation of pain perception and response to common painkillers [14–16]. The patients suffering from dementia [10,17,18] receive limited therapy for pain, mainly chronic and neuropathic due to conditions for which pharmacological studies in these patients are still lacking [19,20]. The severity of pain is linked to the occurrence of NPS and the use of antipsychotics [21]. Furthermore, pain interference is associated with a higher risk of developing dementia, as demonstrated on a sample of 1114 seniors aged $\geq$ 70 years belonging to the longitudinal cohort study of community-dwelling older adults Einstein Aging Study (EAS) [22]. Antipsychotics are endowed with serious side effects and poorly control NPS, therefore, their preferred treatment is non-pharmacological including three main categories: 1) sensory-oriented; 2) cognition-oriented; 3) movement-oriented [23]. In the category of the sensory-oriented non-pharmacological treatments it is possible to find the following therapies: music therapy; aromatherapy; light therapy; technology-assisted therapy; Snoezelen therapy; positive image therapy; animal-assisted therapy; clowning therapy [23]. The cognition-oriented treatments include: reminiscence therapy; simulated presence therapy; cognitive stimulation therapy; storytelling therapy. The exercise therapy and the outdoor therapy are movement-oriented therapies [23]. The non-pharmacological treatments prove efficacy and the principles supporting these interventions are in agreement with the following complementary models: 1) the "unmet needs" model; 2) a behavioral/learning model; 3) environmental vulnerability/reduced stress-threshold model [24]. Thus, the non-pharmacological therapy prevents or treats the underlying sensory unmet needs contributing to the development of the NPS, reducing restraints, treating pain appropriately, providing sufficient light and adequate toileting procedures [24]. In fact, a change of the reinforcement experienced by the patients is necessary to modify the NPS avoiding techniques risking to induce overreaction in patients with dementia that have lost their coping skills, presenting lowered stress threshold and environmental vulnerability [24]. Therefore, reality orientation, behavioral management, environmental modification, cognitive stimulation and increase of functional connectivity through music represent effective treatments [25]. Since it is demonstrated that efficacious pain therapy is the most effective option for the treatment of NPS [26], decreasing the need for the use of antipsychotics [27,28], novel effective analgesics are needed. The two cannabinoids including cannabidiol (CBD) and Δ-9-tetrahydrocannabinol (THC) are extensively investigated for their analgesic action through the endocannabinoid system (ECS). Particularly, the ECS was demonstrated to be target in multiple neuropathic pain models [29] and in chemotherapy-induced allodynia [30]. Preclinical data demonstrate the capability of CBD to modulate the co-occurrence of chronic neuropathic pain and depression- and anxiety-like behavior [31,32]. The cannabinoids approved for use in clinic are the following: dronabinol and nabilone for chemotherapy-associated nausea and vomiting and dronabinol also for human immunodeficiency virus (HIV)-associated anorexia, being used off-label in pain treatment [33]; CBD for add-on therapy to clobazam for Lennox-Gastaut or Dravet syndromes since 2 years of age [34]. In Italy, the oral spray formulation containing nabiximols, i.e. Sativex®, including THC and CBD and used in Canada, Germany, Spain and UK [35], is the sole approved for the treatment of spasticity associated to multiple sclerosis (MS). It demonstrated to be promising for MS induced central pain [36], but with controversial results [37]. Other magistral preparations are off-label [38]. Even though licensed for the sole spasticity in MS, a meta-analysis supports the efficacy of nabiximols in MS-associated neuropathic pain with the following results: pain reduction afforded by CBD/THC buccal spray is of 1.7 ± 0.7 points ($p = 0.018$), by CBD of 1.5 ± 0.7 ($p = 0.044$), by dronabinol of 1.5 ± 0.6 ($p = 0.013$) and by all these cannabinoids pooled together of 1.6 ± 0.4 ($p < 0.001$) [39]. Furthermore, a systematic and critical analysis of the specialized literature shows promising results in favor of cannabinoids for the treatment of NPS in moderate to severe dementia [40], in spite of debated findings [41,42]. The NACTOPAISD is the first clinical trial aimed at investigating the efficacy and safety of nabiximols in the treatment of pain and agitation in patients affected by severe dementia.

2. Materials and methods

2.1. Ethical approval

The present clinical trial follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [43,44] and the Consolidated Standards of Reporting Trials (CONSORT) [45] statements. This clinical trial was approved by Calabria Region Ethics Committee protocol (Protocol n. 118 of April, 21st 2022 to register the trial on ClinicalTrials.gov repository). This is a non-profit study, in which no form of remuneration is foreseen for study participants and for all the staff involved. The results of the trial will be published, without reference to the identity of the participants and ensuring confidentiality. A final report will be the subject of scientific publication and communications to scientific conferences. Auditing trial conduct will be independent from investigators and sponsors, since there is not a trial sponsor and the data monitoring committee members are independent experts who declare no competing interests.

2.2. Eligibility criteria

Consecutive patients, admitted to the service for neurodegenerative diseases managed by the Coordinator Centre S. Anna Institute, Crotone with diagnosis of dementia based on the diagnostic and statistical manual of mental disorders (DSM)-5 will be enrolled, accordingly with the following criteria:

Inclusion criteria:

- Age $\geq$ 65 years;
- Mini-Mental State Examination (MMSE) $\leq$ 12;
- Presence of clinically significant agitation [Cohen-Mansfield Agitation Inventory (CMAI) score $\geq$ 39 [46–48]];
- Informed consent by a legal representative;
- The assumption of needed authorized concurrent therapies for the treatment of agitation is allowed.

Exclusion criteria:

- Contraindications to nabiximols or history of hypersensitivity to any cannabinoid;
- Significant cardiovascular disease;
- Presence or history of other psychiatric disorders or neurological conditions;
- Abuse or history of abuse.

2.3. Outcomes and measures

The primary efficacy endpoint is mean ± standard error of the mean of agitation (CMAI) and pain score after 4 weeks of randomized treatment. Pain score will be measured through the recently validated Italian version of the Mobilization–Observation–Behaviour–Intensity–Dementia (I-MOBID2) [49]. The latter pain scale is peculiar being the sole to consider the frequent co-occurrence of musculoskeletal and visceral pain [50] consisting of two parts [51]: the first one assesses musculoskeletal pain via behavioral indicators, i.e. pain noises, facial expression of pain and defensive behaviors, during five guided movements of different body parts; the second part assesses pain from internal organs, head and skin, by pain behaviors and localization of pain on pain drawings. Agitation score will be measured through the weekly assessment of the CMAI score [46,47]. The secondary endpoint consists in the assessment of patients' health-related QoL (HRQL) through the 31-item interviewer -administered questionnaire proxy-reported by the caregiver DEMQOL [52]. The safety monitoring plan consists in weekly physician's assessment of severe adverse reactions and clinical worsening [measured through the Clinician's Global Impression of Change (CGI-C)], including possible increase of agitation (assessed through CMAI by assessors). Any increase $\geq$ 50 % of NPS as apathy, depression, hallucinations and delusions induced by nabiximols will be measured through the score of Neuropsychiatric Inventory - Nursing Home (NPI-NH) by assessors [53–55]. Mean ± standard error of the data will be analyzed according to the statistical analysis plan.

2.4. Treatment protocol

A baseline assessment (T0) will be performed before the administration of the intervention, consisting in an oromucosal spray containing THC and CBD in a 1:1 ratio (Sativex®). A volume of 100-μl of active medication deliver 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa through pump-action oromucosal spray. Placebo delivers the excipient plus colorants [37]. The dose will consist in one puff per day before bed time for 1 week, increasing to one puff twice a day in the morning and before bed time for the following two weeks [56], down titrating to one puff per day in the fourth week. The efficacy of the outcome measures will be weekly assessed. The duration of efficacy of the THC/CBD spray after withdrawal and the frequency and severity of withdrawal symptoms assessed will be weekly investigated during a 4-week washout period, considering that 2 weeks are suggested to be suitable for the active principles metabolism in older individuals [57,58]. In particular, to reduce the risk of potential withdrawal effects of active treatment, the dose obtained will be suspended in weeks 5–6 [56] administering one puff of placebo spray per day before bed time. Moreover, it was reported that older (over 50 years) people develop fewer undesirable cognitive, psychological and physiological effects [57]. Any other ongoing therapy will be maintained unchanged and the occurrence of need for rescue medications will be reported. No biological specimens will be stored for future use in ancillary studies. The participant timeline is reported in Table 1.

2.5. Consent to participation and publication

This trial was approved by the Calabria Region Ethics Committee (Protocol n. 118 of April, 21st 2022). According to the D. lgs 196/2003, the Helsinki agreements and subsequent amendments, the Good Clinical Practice and current legislation, the Guidelines for the treatment of personal data in clinical trials of 24 July 2008 and in accordance with European data protection legislation, each participant or his/her legal representative will be required to sign a consent form as acceptance of all aspects of the study contained in the patient information sheet and as a consequent expression of his willingness to participate in the study. The information sheet will be duly illustrated to the subjects or legal representatives. A legal representative of the patient will be informed about the study and provided a consent form to be properly signed and dated by all the parties and collected by the healthcare operators before any procedure foreseen by the protocol is carried out. This manuscript and the manuscript containing the randomized clinical trial results will not include data from any individual person. Model consent for publication of data in anonymized form will be provided to each participant or his/her legal representative.

2.6. Allocation, masking and data management

Healthcare personnel, patients, outcome assessors (trained nurses) and data analysts will be blinded after assignment to interventions and also about the nature of the interventions. The randomization codes of allocation will be generated using Random Number selection Microsoft Office Excel 2010 (Microsoft, Milan, Italy). No member of the trial who will administer intervention and placebo or analyze data will have access to the codes up to the end of the trial. Data analysts will be blinded about the assignment to interventions. Participants' allocated intervention will never be revealed during the trial. To guarantee security and data quality, double data entry will be performed by two independent researchers. The sole responsible secretariat of the clinical center will collect and maintain personal information about patients, in order to protect confidentiality before, during and after the trial.

2.7. Sample size and statistical analysis

Due to the lack of studies assessing the efficacy of nabiximols in pain or agitation during dementia, the most similar study with agitation in dementia assessed through CMAI as primary outcome is the NCT02351882 double-blind, randomized cross-over study [55], whose sample size calculation based on paired t-test with a total of 30 subjects and an alpha of 0.05 is powered (0.89) to detect medium to large effect sizes for CMAI change scores between treatment and placebo, retrieves a total of $n = 40$ patients (10 drop-outs = 25 % attrition). In order to prevent bias, also due to the small sample size of the first study investigating the efficacy of nabiximols on the specified outcomes, no blocking, e.g. incomplete randomization, will be performed. Analyses will be performed according to intention-to-treat procedures. The obtained results will undergo statistical analysis according to their distribution, considering $p < 0.05$ significant. According to the statistical analysis plan, for the comparison of the characteristics between the two groups, $\chi 2$ and Mann-Whitney U tests will be used. Differences in the primary and secondary outcome measures will be evaluated through $\chi 2$, Wilcoxon and Mann–Whitney U tests. Differences in mean and standard error of the mean of the outcome measures will be analyzed using Student's t-test. Analyses will be carried out using IBM SPSS-27 statistics software (Chicago, IL, USA).

3. Discussion

Pain and NPS remarkably reduce the patients' HRQL and contribute to increase their risk of mortality due to inappropriate pharmacological treatments, therefore safer and more effective therapies are needed. Already in 1997 a placebo-controlled crossover trial on 11 patients with a diagnosis of probable Alzheimer's disease showed the efficacy of dronabinol on disturbed behavior [59]. Another randomized, double-blind, crossover trial investigated the effect of nabilone in comparison to placebo (6 weeks each treatment over a 14-week duration) with a 1-week washout between phases on agitation and NPS in 39 AD patients proving its efficacy [60]. Some data concerned with safety, pharmacodynamics and pharmacokinetics of THC (orally administered in tablet form, Namisol®, twice daily at 10 a.m. and 4 p.m. for 3 days, separated by a 4-day washout period; weeks 1–6, 0.75 mg; weeks 7–12, 1.5 mg) on 10 patients suffering from dementia were obtained in a randomized, double-blind, placebo-controlled, crossover trial [61]. The results of this study illustrate a $t_{1/2} \sim 5$ h reaching 7–8 for 11-OH-THC, a

Table 1
Schedule of enrollment, interventions and assessments.

	STUDY PERIOD									
	Enrolment	**Allocation**	**Post-allocation:Interventions**				**Follow-up**			
TIMEPOINT	*-within 1 week*	*Baseline and 1 week1 titration*	*week1*	*week2*	*week3*	*week4*	*week5 down-titration*	*week6 down-titration*	*week7*	*week8*
ENROLLMENT:	X									
Eligibility screen	X									
Informed consent	X									
Routine clinical assessment, physical examination, CGI-C and NPI-NH	X									
Allocation		X								
INTERVENTIONS:										
Sativex®			←	—	—	→				
Placebo			←	—	—	→				
ASSESSMENTS:										
CMAI and I-MOBID2		X	X	X	X	X	X	X	X	X
DEMQOL		X	X	X	X	X	X	X	X	X
Routine clinical assessment, physical examination, CGI-C and NPI-NH		X				X				X

median Tmax = 1–2 h, with linear PK at increasing dose, wide interindividual variability, and a mean Cmax (ng/mL) after the first dose (0–6 h) of 0.41 (0.18–0.90) for the 0.75-mg dose and of 1.01 (0.53–1.92) for the 1.5-mg dose; after the second dose (6–24 h), Cmax = 0.50 (0.27–0.92) and = 0.98 (0.46–2.06) for the two doses, respectively [61]. Moreover, the effect of drugs can be different according to the NPS considered [53]. However, medical cannabis containing THC, dronabinol and oral CBD/THC oil show efficacy on a wide spectrum of NPS [62–64]. Therefore, any effect of Sativex® on NPS other than agitation up to increase ≥ 50 % of NPS as apathy, depression, hallucinations and delusions is going to be assessed during this trial. Based on the studies supporting the efficacy of the synthetic cannabinoids dronabinol and nabilone on NPS in dementia [59,65–68], the effects of nabilone on the improvement of agitation, NPS and cognition in patients with moderate-to-severe AD are under investigation in the NCT02351882 double-blind, randomized cross-over study [55]. The EudraCT2020-001056-17 STAND (Sativex® for the Treatment of AgitatioN in Dementia) study is meant to explore the feasibility of a multicentre, randomized, controlled trial in residential nursing home settings investigating the effect of Sativex® for the treatment of agitation and aggression in AD. The protocol of the ACTRN12619000474156 study aims at assessing the safety of 3:2 THC:CBD purified oil on behavior symptoms, quality of life and discomfort caused by pain in communicative aged 65 years or older patients suffering from mild dementia [58]. In this complex frame the present placebo control, randomized, clinical trial aims at shedding light for the first time on the efficacy of the oromucosal spray Sativex® delivering nabiximols in the treatment of pain and agitation in non communicative demented patients. The trial NACTOPAISD follows the way paved by the randomized, double-blind, placebo-controlled trial (NCT04321889) [69] to assess the efficacy of NanoBEO [70], the engineered essential oil of bergamot endowed with strong preclinically proven analgesic [71,72] and anxiolytic [73] properties, in the control of agitation and pain in patients suffering from severe dementia. In fact, the common purpose of the latter two clinical trials is to provide novel treatments to reduce the use of off-label antipsychotics harmful for this fragile population excluded by several trials, e.g. migraine, and in which most pharmacological advances are not tested [74–76]. The results of the trial NACTOPAISD can form the rational basis for a safer and effective therapy of NPS and pain in severe dementia.

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CRediT authorship contribution statement

Conceptualization: D.S., L.L., S.M., P.T., P.N., G.B., M.T.C.; Data curation and Methodology: D.S., F.G., S.B. All authors have read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability

No data was used for the research described in the article.

Acknowledgments

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Institutional Review Board Statement

The study will be conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Calabria Region (Protocol n. 118 of April, 21st 2022).

Informed Consent Statement

Informed consent will be obtained from all subjects or legal representatives involved in the study.

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