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Commentary

Targeting Neuroplasticity for the Management of Pain and Agitation in Alzheimer's Disease via Bergamot Nanotherapy

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Abstract

Alzheimer's disease (AD) accounts for 50–70% of cases of dementia worldwide and is a social burden to the affected population. Although several pathogenetic hypotheses have been proposed, evidence favoring the role of aberrant neuroplasticity in the development of the neuropsychiatric symptoms associated with dementia is increasing. Specifically, agitation is resistant to treatment and affects the quality of life, also because of the lack of safe and effective treatment for AD. Alterations in pain processing due to plastic modifications occur during aging and neurodegeneration. Up to 80% of AD patients have chronic pain due to age-related comorbidities that are misdiagnosed and remain unattended due to a lack of self-reporting because of communication hindrance, which also contributes to the development of agitation. Here, we reported a strategy to target altered neuroplasticity for treating pain and agitation by applying bergamot essential oil with evidence for in-vivo analgesic effects on

neuropathic and inflammatory pain preclinical models. Bergamot was engineered in a nanotechnology delivery system, NanoBEO, which provides the opportunity to investigate its efficacy in the NCT04321889 randomized, double-blind, placebo-controlled clinical trial BRAINAID. This trial can provide a rational basis for safe and effective treatment to alleviate agitation and pain, thus improving the quality of life of people suffering from AD.

Keywords
Neuroplasticity; Alzheimer's disease; dementia; agitation; neuropsychiatric symptoms; pain; bergamot essential oil; NanoBEO; BRAINAID

1. Mechanisms of Neurodegeneration in Dementia

Dementia is an umbrella term and includes neurological diseases characterized by memory loss and cognitive impairment. It mainly affects people over 65 years old. Alzheimer's disease (AD) accounts for 50–70% of cases of dementia worldwide among dementia with Lewy bodies, vascular dementia, frontotemporal dementia, and mixed dementia [1]. The prevalence of AD is increasing, with 55 million people affected and around 41 million people undiagnosed [2]. AD is estimated to affect 131 million patients globally by 2050 [3]. During the pandemic, the risk of death among AD patients increased, which further indicates its severity [4, 5]. Altered mitochondria can perform the activity of the inflammasome and the signaling of pro-interleukin (IL)-1β and pro-IL-18 [6]. The immune system is involved in the pathophysiology of AD [7], since AD is preceded by brain hypometabolism, oxidative stress, and accumulation of dysfunctional mitochondria from impaired mitophagy, causing aberrant inflammatory responses [6]. Moreover, aging is associated with brain inflammation and priming of microglia through IL-1β, tumor necrosis factor (TNF)-α, IL-4, IL-6, IL-9, IL-12, and IL-23, which also affect the levels of neurotrophins [8]. Proinflammatory cytokines are associated with cognitive decline in AD [9]. The risk factors that increase the susceptibility to the development of sporadic AD include age and mutations of apolipoprotein E4 (APOE4), along with mutations of other genes (e.g., apolipoprotein J and receptor 1 of complement component (3b/4b)), while amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) cause familial AD [6, 10-13]. The exact etiology of AD is not known. The available treatment methods are not effective, and better therapeutic options are necessary, although aducanumab was recently approved for treating AD [14].

2. Pain and Neuropsychiatric Symptoms in AD

Multifactorial neuropsychiatric symptoms are the most challenging symptoms associated with dementia [15]. They compromise the quality of life of the patients and are often related, at least partly, to misdiagnosed and underestimated pain, besides cognitive decline [16, 17]. These symptoms fluctuate and occur in 97% of AD cases. [18]. Patients develop at least one neuropsychiatric symptom, and up to 85% of them show the symptoms within five years of diagnosis [18]. Aberrant neuroplasticity is associated with chronic pain [19]. Cognitive functions and behavioral disturbances in dementia might improve after non-pharmacological treatment; non-pharmacological treatment is associated with modifications in brain activity and indicates the role

of neuroplasticity in the effectiveness of this intervention [20]. Also, pain-induced neuroplasticity is related to the risk of AD (Figure 1) [21]. Around 20% of community patients [22, 23] and up to 60% of patients in nursing homes [23, 24] suffer from agitation, which is an extremely intractable neuropsychiatric symptom and is associated with unrelieved pain [25, 26]. The other common neuropsychiatric symptoms associated with AD, as assessed by the European Alzheimer's disease consortium (EADC), include apathy, depression, anxiety, irritability, hallucinations, aberrant motor behavior, delusions, disinhibition, elation, and appetite and sleep disturbances [27]. These symptoms are based on psychosis, psychomotor factors, mood liability factors, and instinctual factors, which can be grouped into different behavioral syndromes [27]. Agitation includes inappropriate verbal, vocal, or motor activity and might be aggressive, inappropriate in frequency, or related to the social context [28]. With age, AD patients are more likely to experience chronic pain due to musculoskeletal pain, which is the leading cause of disability among the elderly [29, 30], rheumatic conditions [31-33], neuropathies with up to 60% prevalence, such as diabetes [34] and shingles due to herpes Zoster infection [35] or spinal surgery [36], injury [37], and stroke [38]. Unfortunately, people suffering from AD who receive pharmacological treatment for pain are fewer than their peers with intact cognitive abilities in the general population of the elderly [39]. A one-year retrospective cross-sectional analysis showed that pain is highly prevalent in all types of dementia, and patients who experience pain develop more neuropsychiatric symptoms [40], confirming the finding that agitation is associated with pain and can be reduced by analgesia [15, 41, 42]. Our group found that the diagnosis and treatment of AD patients are poor; these patients also have limited access to the treatment of chronic pain, especially, neuropathic pain. They are often administered off-label antipsychotics and antidepressants for the management of neuropsychiatric symptoms [43-45]. This is partly due to communication hindrance and inefficient self-reporting of pain due to cognitive decline. This might spread the misconception that patients suffering from dementia feel less pain than their cognitively intact counterparts [25]. These patients might be administered unnecessary antipsychotics, antidepressants, and benzodiazepines, which might be harmful as these medications have cerebrocardiovascular side effects and anti-cholinergic properties, which might cause further cognitive decline.

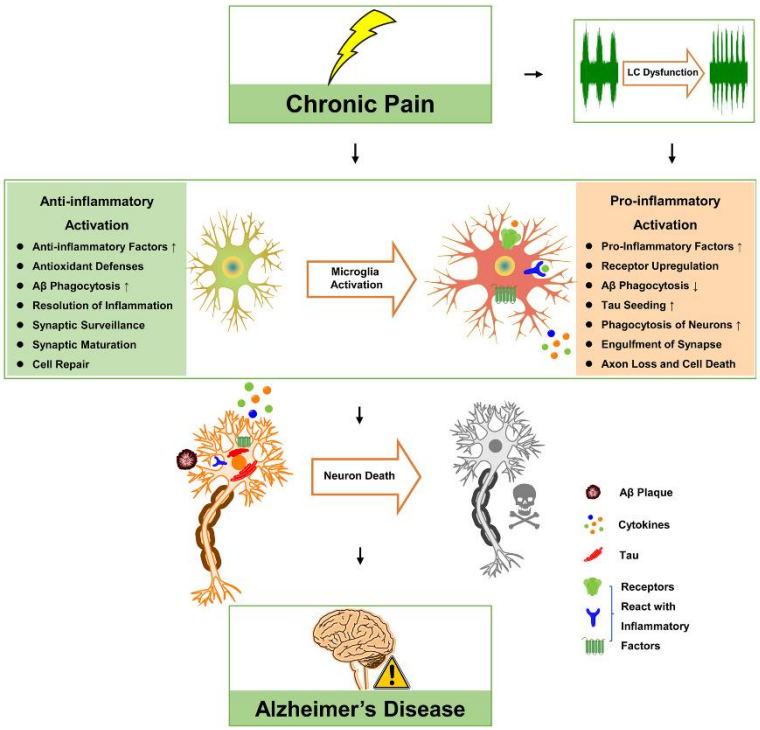

Figure 1 A possible mechanism of chronic pain induced in Alzheimer's disease pathogenesis by the dysfunction of the locus coeruleus (LC)-noradrenaline (NE) system and microglial neuroinflammation. Chronic pain induces pathological activation of the LC-NE system and increases NE release in brain areas, such as the prefrontal cortex and hippocampus, which might be a mechanism of chronic pain-induced microglial proinflammatory activation. Proinflammatory activation might exacerbate AD pathogenesis by decreasing Aβ phagocytosis, increasing tau seeding, and promoting the loss of synaptic function and cytokine-induced neuron death in these brain regions. Reproduced with permission from [21].

3. Management of Pain and Neuropsychiatric Symptoms Through Neuroplasticity

The pharmacological treatment of neuropsychiatric symptoms includes the use of atypical antipsychotics, such as quetiapine and aripiprazole. Among these drugs, risperidone is only approved for up to 6–12 weeks of administration because it increases the risk of death due to cerebrovascular accidents [46]. Several pathological alterations occur in neurodegeneration, affecting the cholinergic nucleus basalis [47] and the areas involved in pain modulation, such as the periaqueductal gray [48] and the locus coeruleus [47], associated with the descending inhibitory pain pathway. The level of expression of 5-HT2A receptors was also lower in the frontal and temporal cortices of the post-mortem brain in severe AD [49]. The T102C polymorphism of the 5-HT2A receptor gene is a possible risk factor for the development of neuropsychiatric symptoms [50, 51]. Neurodegeneration and aging not only alter pain processing [52] but also enhance neuronal vulnerability and aberrant responsiveness to stress pathways [53, 54] because of abnormal neuronal and synaptic plasticity that occur in depression and AD through inflammaging [55]. Aging and neurodegeneration induce primed microglia to produce proinflammatory cytokines [56, 57] and decrease the levels of brain-derived neurotrophic factor (BDNF) responsible for neurogenesis [58]. Primed glia alters glutamatergic neurotransmission [59], which is fundamental in pain and dementia,

through perisynaptic excitatory amino acid transporters (EAATs) [60, 61]. A study on rats that were subjected to arthritic pain showed that the presynaptic group III metabotropic glutamate receptors (mGluRs) are involved in the synaptic plasticity of the amygdala [62]. The central nucleus of the amygdala (CeA) is known as the nociceptive amygdala since it receives nociceptive inputs from the spinal cord, brainstem, thalamus, and cortex. The CeA integrates the cognitive and conscious perception of painful stimuli in these areas [63]. Altered neuroplasticity is affected by the mechanism of action of the glutamatergic modulator ketamine, which has fast antidepressant effects [64]. A single administration of the N-methyl-D-aspartate (NMDA) antagonist ketamine (and its S-enantiomer approved by the FDA for resistant depression) can induce fast-onset antidepressant action that lasts two weeks, and the mechanism might involve the synthesis of BDNF [65-67]. Therefore, targeting glutamatergic neurotransmission can modulate neuroplasticity, which affects pain processing and neuropsychiatric symptoms, such as depression.

4. Novel Therapeutic Approaches for Pain and Neuropsychiatric Symptoms

The treatments administered currently, such as the use of acetylcholinesterase inhibitors (AChEI) and memantine, are not proven to effectively treat neuropsychiatric symptoms [68]. Specifically, memantine might only delay the onset of agitation [69]. The clinical trials in which psychotropic drugs were administered to treat agitation failed to offer an effective and safe strategy for treating the spectrum of neuropsychiatric symptoms. Complementary therapies are efficacious in the management of these symptoms, but strong evidence in clinical trials is lacking due to methodological biases [70, 71]. Various novel non-pharmacological treatment strategies might be used, including music therapy, light therapy, technology-assisted therapy, exercise-based therapy, Snoezelen therapy, positive image therapy, and animal-assisted therapy [72]. These interventions might satisfy unmet needs, reduce overreactions, and increase functional connectivity. Here, we targeted altered neuroplasticity for pain and agitation treatment in AD by administering bergamot essential oil (BEO), which has strong analgesic effects *in vivo* on neuropathic and inflammatory pain preclinical models [73] and probably does not interact with other drugs [74]. Microdialysis experiments and studies on synaptosomes have highlighted its capability to induce glutamate release through exocytosis or *via* a Ca^{2+}-independent carrier-mediated process depending on its concentration [75]. This is fundamental since aberrant glutamatergic neurotransmission has been experimentally shown to influence pain and related behavioral symptoms [76, 77]. Moreover, BEO does not have sedative actions [78, 79], and this is fundamental for AD patients. Finally, BEO and its fractions can be effectively administered through inhalation and the transdermal route [80, 81]. The only reported toxicity of BEO consists of phototoxicity caused by furocoumarins [82]. The nonvolatile residue of BEO contains about 0.2% bergapten, which is responsible for the phototoxicity of BEO. Therefore, a bergapten-free extract of the essence (BEO-BF) was encapsulated in a nanotechnology delivery system called NanoBEO [83]. NanoBEO was added to a cream formulation for transdermal administration. The cream consists of solid lipid nanoparticles enriched with α-tococopherylstearate to confer anti-oxidant properties, in which BEO-BF was encapsulated. This nanotechnology delivery system is able to prevent the methodological biases of the clinical trials conducted in aromatherapy up to now. NanoBEO can entrap the smell allowing masking in clinical trials, prevent components from degrading, permit titration of the dose, and can be applied through an airless dispenser affording feasibility of administration [84]. NanoBEO (recently patented

(EP 4003294)) retains the antinociceptive and anti-allodynic actions of BEO, to which it adds efficacy to scratching behavior, which is a typical neuropsychiatric symptom [83]. Its efficacy and safety in treating agitation and pain in over 65 patients affected by severe AD will be investigated in the NCT04321889 randomized, double-blind, placebo-controlled clinical trial BRAINAID [85]. The primary endpoint is represented by the reduction of agitation assessed through the Cohen-Mansfield agitation inventory (CMAI), according to the clinical trials for reduction of agitation in AD [86]. Adequate pain assessment in non-communicative AD patients often prevents the administration of appropriate treatment. In the NCT04321889 trial, pain assessment will be performed using the recently translated, adapted, and validated scale in the Italian setting, Italian Mobilization-Observation-Behavior-Intensity-Dementia (I-MOBID2), for non-verbal patients with severe dementia [87]. This method elucidates even concealed musculoskeletal and visceral pain [88]. This study can provide valuable insights into this population which is usually excluded from clinical trials [89]. Patients suffering from AD are often excluded from clinical trials that assess the efficacy of therapy for painful conditions, such as migraine [90-92]. This prevents researchers from determining the best therapeutic options [93], which also occurs in the case of polypharmacy [94].

5. Conclusions

The development of neuropsychiatric syndromes, in general, and agitation, in particular, is challenging for patients suffering from AD. An effective and safe treatment is unavailable. Misdiagnosed and inappropriately treated pain related to the development of neuropsychiatric symptoms need to be targeted for managing these resistant symptoms. The glutamatergic transmission is closely associated with neuroplasticity of pain processing and with the mechanism of action of pharmacological and non-pharmacological treatments, which affect neuropsychiatric symptoms. Therefore, an essential oil with analgesic activity and the ability to modulate glutamatergic neurotransmission might be used for treating AD. Here, we highlighted BEO as it has antinociceptive and anti-allodynic properties related to glutamate modulation. After removing furocoumarins to avoid phototoxicity, BEO was engineered in a nanotechnology delivery system to prevent the methodological biases of clinical trials that use aromatherapy. The efficacy and safety of the nanotechnology delivery system NanoBEO in the treatment of agitation and pain were is object of investigation of the NCT04321889 randomized, double-blind, placebo-controlled clinical trial BRAINAID.

Author Contributions

Conceptualization: D.S., P.T., M.T.C., G.B. All Authors have read and agreed to the final version of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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