Essential oils for the control of the neuropsychiatric symptoms of dementia. A pharmacotechnological appraisal

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Abstract. The neuropsychiatric symptoms (NPS) of dementia represent one of the most challenging disorders characterizing this neurodegenerative disease. A safe and effective treatment of NPS is still lacking and analgesia has proven efficacy. Here, we propose the path followed by the essential oil of bergamot (BEO) as prototype for rigorous research to overcome the bias of aromatherapy in dementia. In this way, the rational basis for translation of essential oils in the management of pain contributing to NPS may be provided.

Keywords: dementia, neuropsychiatric symptoms, agitation, pain, essential oils, NanoBEO.

Alzheimer's disease and related dementias (ADRD) have a noteworthy social burden, even more in view of the fact that up to 80% of long-term care facilities guests suffers from ADRD and around 75-90% people is not diagnosed (1). These patients are affected by cognitive deterioration, but before the onset and over the course of the disease 97% develops neuropsychiatric symptoms (NPS) (2), remarkably reducing their quality of life. Whether or not an effective and safe therapy exists for NPS is yet argument of debate. Among drugs against cognitive decline, the low affinity non-competitive N-methyl-D-aspartate (NMDA)-receptor antagonist memantine shows some effectiveness only on the delay of mild AD agitation (3), the most challenging NPS. The treatment of agitation consists in the use of the atypical antipsychotic risperidone for longer than 6-12 week, to avoid the increase of risk of serious cerebrovascular adverse events (CVAEs). Evidence for safe and effective management of agitation has been actively searched for over the last thirty years; drugs with the most different mechanisms of action have been investigated without a sound rationale (4). As a result of the above deduction, inconsistency within single study and among studies hampered the quality of the body of evidence gathered with high doses of antipsychotics and citalopram that had resulted effective in some trials (5). Likewise, *Melissa officinalis* and *Lavandula officinalis* exert some efficacy on agitation (6), but the quality of the latter evidence is downgraded due to methodological biases with essential oils, e.g. lack of exact dosing and titration of active components and of double-masking because of the scent (7). Some 80% of patients affected by dementia in nursing homes suffers from pain, due to age-related comorbidities, often inadequately relieved even in the community due to lack of self-reporting making diagnosis and assessment difficult (8). Incidentally, aging affects pain processing (9) and no accurate information about efficacy and safety of analgesic treatments for these patients is available. In fact, they are often excluded from clinical trials (10), even more in migraine (11-13) because it occurs usually before 50 years of age, but it can convert to late medication overuse headache (MOH) in the 38% of cases (14) affecting also the elderly. Accurate analgesic treatment is demonstrated to significantly reduce agitation. Therefore, it is conceivable that management with essential oils endowed with pharmacological action on

chronic, inflammatory and neuropathic pain (15), can turn out the best treatment for the latter resistant NPS. The efficacy of essential oils in NPS needs to be investigated conducting clinical trials addressing the criteria to provide high strength recommendations. To this aim several aspects deserve consideration: 1) the essential oil needs to have demonstrated analgesic effect; 2) preclinical research corroborating its antinociceptive efficacy has to comply with allocation, masking and design criteria for the conduction of good quality *in vivo* research; 3) the experimental pain model exploited for preclinical research needs to reflect as completely as possible the clinical condition of interest, that in this case is chronic pain due to central sensitization; 4) the administration of the natural products must occur in a pharmaceutical form pledging to deliver active components in exact amount, in order to guarantee reproducibility of the observed effect; 5) finally, clinical translation must be carried out via adequately designed and powered, double-blinded, randomized trials. For instance, trials evaluating pain in the elderly in general and even more in cognitive impairment and stroke are underpowered and do not use assessment tools developed for the outcome planned to be measured (10, 16). With all the above in mind, here we describe the rigorous research process that now allows clinical translation of the essential oil of bergamot (BEO), providing a safe control of agitation. BEO is proven to exert anti-nociceptive and anti-allodynic effects in pain models resembling chronic and neuropathic pain (17), often undertreated in clinic. The latter essential oil is also endowed with anxiolytic effects, involving serotonergic mechanisms important in agitation and devoid of sedation and of benzodiazepine-like action known to worsen cognitive decline (18). To prevent phototoxicity, BEO has been defurocoumarinized (European Medicine Agency [EMA], 13 September 2011 EMA/HMPC/56155/2011 Committee on Herbal Medicinal Products [HMPC]). To overcome the whole set of issues encountered by essential oils in clinical trials, BEO has undergone a technological process described as follows: 1) encapsulated in a nanotechnology delivery system based on solid lipid nanoparticles (SLN) with anti-oxidant components devised in an odorless cream indistinguishable from placebo (19); 2) subjected to patent (EP 4003294). This engineered system, named NanoBEO, allows stability and titration of the active components, affording reproducibility of data and possibility to perform double-blind clinical trials. In particular, it is under clinical investigation in the randomized, double-blind, placebo-controlled BRAINAID trial (NCT04321889) (20). The latter is designed to assess the efficacy and safety of NanoBEO on agitation and pain in non communicative patients affected by severe AD. Sample size is calculated to give reliable outcome measures; in the case of pain, to obtain a reliable measure a developed tool has been recently validated in the trial setting (21), to obtain assessment without self-report. Further research needs to evaluate herbal-drug pharmacokinetic interactions (22). Also, promising preclinical evidence exists underscoring cannabinoids modulation of concurrent chronic neuropathic pain and depression- and anxiety-like behavior (23, 24). Therefore, nabiximols, consisting of cannabidiol (CBD) and Δ-9-tetrahydrocannabinol (THC) and engineered in oral spray formulation could exert beneficial effect on agitation (NAbiximols Clinical Translation To the treatment of Pain and Agitation In Severe Dementia [NACTOPAISD]).

In conclusion, the management of NPS and particularly agitation is a hard challenge for the clinician. Drugs with the most disparate mechanisms of action without a sound rational basis have undergone clinical investigation and this is reflected in the lack of successful candidates. Therefore, due to tight link between agitation and unrelieved pain in non communicative patients suffering from dementia, it is anticipated that novel pharmacological treatments directed towards pain management may achieve control of agitation. NanoBEO offers the paradigmatic prototype of an essential oil engineered for clinical translation and this now provides the rational basis for safe and effective control of agitation in the fragile population of patients suffering from severe dementia.

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