RESEARCH ARTICLE

Evidence for accuracy of pain assessment and painkillers utilization in neuropsychiatric symptoms of dementia in Calabria region, Italy

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Abstract
During the clinical course of dementia, beside cognitive impairment and memory loss, a very complex challenge is posed by the neuropsychiatric symptoms (NPSs). Accurate evaluation and treatment of pain impacts positively the agitation of demented patients aged ≥ 65 years. To gather information on the utilization of pain killers in demented patients a preliminary survey has been conducted in collaboration with the Calabrian Pharmacovigilance Territorial Service of the health district of Catanzaro (Italy). The study has taken into consideration the prescriptions of acetylcholinesterase inhibitors and memantine during the period ranging from July 2015 to June 2016 and the percentage of patients treated against pain with non steroidal antinflammatory drugs, opioids, and anticonvulsants have been monitored. The latter have been evaluated statistically for difference between the treatment before (pre) and after (post) the settlement of acetylcholinesterase inhibitors (AChEI) or memantine therapy. The results do support accuracy in painkillers utilization in the course of dementia in the regional population of Calabria (Italy).

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Introduction
Dementia has a remarkable social burden since it accounts for over 46 million patients, with more than 131.5 million expected by 2050 [see Onyango (2018)]. Beside cognitive impairment and memory loss, a very complex challenge is posed by the neuropsychiatric symptoms (NPSs) of dementia, responsible for a severe reduction of the patients' quality of life. 97% of the demented patients present these symptoms during the clinical course of the disease (Steinberg et al., 2008) and, sometimes, even before the onset (Jost and Grossberg, 1996; Donovan et al., 2014). The definition of NPSs is very complex, due to their overlapping and superimposability to some symptoms belonging to different neuropsychiatric conditions. Nevertheless, the occurrence of NPSs is characterised by three main phases, detectable as: 1) irritability and depression; 2) agitation and anxiety; 3) psychotic symptoms, such as hallucinations, and motor alterations (Masters et al., 2015). Because of the lack of effectiveness of disease-modifying drugs in dementia, the pharmacological treatment of the latter symptoms consists in administering atypical antipsychotics (risperidone, olanzapine, aripiprazole, and quetiapine). Risperidone, the only one approved for this use, is the safest atypical antipsychotic and indicated in short-term use for no longer than 6–12 weeks, because of the increased risk of death and for cerebrovascular accidents associated with this drug [see Ballard et al. (2018)]. Agitation, according to the definition of the International Psychogeriatric Association, consists in excessive motor activity or verbal or physical aggression (Cummings et al., 2015), and is one of the symptoms most resistant to the treatment. Moreover, it is noteworthy that agitation can be caused by underdiagnosed and unrelieved pain (Husebo et al., 2011; Sampson et al., 2015), often affecting the population of the elderly subjected to osteoarthritis, trauma, cancer, post-herpetic neuralgia and diabetic neuropathy among others. The involvement of pain is also supported by the neuropathological changes reported in pain system structures including the periaqueductal gray (Parvizi et al., 2000). A multicenter cluster randomised controlled trial (ClinicalTrials.gov NCT01021696 and Norwegian Medicines Agency EudraCTnr 2008-007490-20) has investigated how the assessment and pharmacological treatment of pain impacts the agitation of patients aged ≥ 65 years. The intervention group was subjected to a standardized stepwise protocol of sequentially administered analgesic drugs (oral paracetamol, oral morphine, buprenorphine transdermal patch, or oral pregabalin) (Husebo et al., 2011). A significant average reduction in agitation in the 17% of the intervention group, reverted at the withdrawal of the analgesics, was highlighted confirming the need for accurate evaluation and treatment of pain

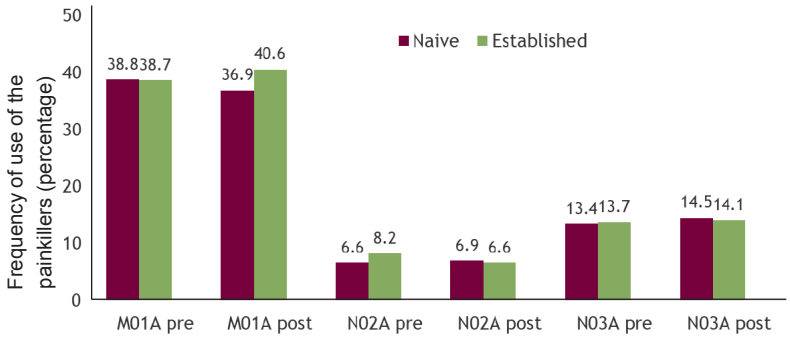

Figure 1 Percentage of demented patients treated with steroidal antinflammatory drugs (FANS), opioids and anticonvulsants against pain.
The most used drugs are FANS (M01A), followed by anticonvulsants (N03A) and opioids (N02A), less employed. There is no statistically significant difference between the treatment before (pre) and after (post) the settlement of AChEI or memantine therapy. Established: Patients already treated for dementia before the beginning of the study; Naïve: patients whose treatment with drugs against dementia started during the study.

for the management of agitation (Husebo et al., 2011). Here we now report original data supporting accuracy in painkillers utilization in neuropsychiatric symptoms of dementia in the regional population of Calabria.

Materials and Methods

A preliminary survey has been conducted in collaboration with the Calabrian Pharmacovigilance Territorial Service of the health district of Catanzaro (Calabria, Italy). The latter has taken into consideration the prescriptions of acetylcholinesterase inhibitors (AChEI) and memantine (N06D, according to the WHO ATC classification) provided by the Regional Health Service through Territorial Pharmacy and by direct distribution for the period ranging from July 2015 to June 2016. For the study, the percentage of demented patients treated against pain with non steroidal antinflammatory drugs (FANS; M01A), opioids (N02A) and anticonvulsants (N03A) have been monitored and evaluated statistically for difference (Chi-Square test) between the frequency of treatment before (pre) and after (post) the settlement of AChEI or memantine therapy.

Results

The results show that, out of the total 2294 patients (average age of 78.9 years), 256 (Established) were treated for dementia, while 2038 (Naive) underwent diagnosis and treatment with drugs against dementia within the considered time period. In order to evaluate the appropriateness of pain assessment and management in these patients suffering from dementia, the number of patients assuming both AChEI or memantine and painkillers, such as FANS (M01A), opioids (N02A) and anticonvulsants [including α2δ-1 ligands (also known as gabapentinoids)] used in neuropathic pain (N03A), was analysed. These analgesics were administered to 1388 demented patients. Furthermore, the frequency of use of the painkillers has not resulted significantly different after that the pharmacological treatment with N06D drugs had been set, as shown in **Figure 1**.

Discussion

The results gathered so far demonstrate that almost all the classes of analgesics have been prescribed suggesting that in Calabria region pain is assessed in demented patients and this does not appear to be largely underestimated and undertreated because 60.51% of all the patients subjected to prescription of AChEI and memantine were treated with analgesics. However, the assessment of pain should be more accurate because, according to these prescribed data, likely neuropathic pain is underdiagnosed. The prescribing appropriateness needs to be improved, as well. In fact, despite being endowed with remarkable side effects and lacking effectiveness in chronic non cancer pain, opioids should not be abandoned, because they are very useful when prescribed under appropriate indication (Scuteri et al., 2017). The latter deduction is even more important because FANS and α2δ-1 ligands are not devoid of serious adverse reactions. Another matter of interest is represented by the tight link existing between unrelieved pain and NPSs. Indeed, a safe pharmacological approach for the handling of these symptoms is not yet available. Pimavanserin, a selective 5-HT2A receptor inverse agonist and antagonist recently approved in the USA for the treatment of psychotic hallucinations and delusions in patients affected by Parkinson's disease, has been tested in a phase 2, randomised, double-blind, placebo-controlled study (ClinicalTrials.gov, number NCT02035553) in psychosis associated to AD (Ballard et al., 2018). This drug resulted effective in the management of psychosis only up to the 6th week of treatment (Ballard et al., 2018). On the other hand, among other options, aromatherapy with Melissa and Lavanda has

been proven to display the best, although not complete, control of agitation. The antinociceptive properties, demonstrated in preclinical settings, of the essential oil of bergamot (BEO) may represent a rationale for the study of its effectiveness in the management of NPSs and, mainly, agitation (Scuteri et al., 2018). BEO reduces the nociceptive response in inflammatory and neuropathic pain models and this pharmacological action may be due to its property to enhance, through its component D-limonene, basal and induced autophagy (Berliocchi et al., 2018). Derangement of this highly conserved process has been involved in neuropathic pain (Berliocchi et al., 2011), but also in the impairment of the autophagic-endocytotic-lysosomal axis, representing a risk factor for the development of AD (Parcon et al., 2018). Another interesting feature of this essential oil is that it can induce anxiolytic, though not sedative, effects (Rombolà et al., 2017) thus resulting in more suitable than benzodiazepines in demented patients (Scuteri et al., 2018). Therefore, a large clinical trial to assess the efficacy of BEO on NPSs and, in particular, agitation, is needed for an improvement of the quality of life of demented patients while waiting for the development of efficacious disease-modifying drugs.

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