# CURRENT KNOWLEDGE OF PAIN INVOLVEMENT IN ALZHEIMER`S DISEASE

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**Abstract:** Alzheimer`s disease is one of the most encountered dementia, since according to Alzheimer`s Association it represents approximately 60-80% of all types of dementia. It is a progressive neurodegenerative disorder which affects memory, cognitive processes, communication abilities and produces important mood changes.
A complex psycho-physiological process, pain, is a unique for every individual, being described by IASP (International Association for the Study of Pain) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”(1979).
There have been few studies made on pain involvement in patients with Alzheimer`s disease, making it a field that raises interest more and more.
In this way, patients with Alzheimer`s disease report less clinical pain than their cognitive intact peers. Moreover, patients suffering from Alzheimer`s disease are administered fewer analgesics, as compared with unaffected cognitive subjects with similar level of painful disease or injury. Also, according to the newer hypothesis, perception and pain processing are affected in Alzheimer`s disease and are not diminished as some older studies stated, raising questions about the ways that is dealt with pain in this highly dependent and vulnerable patient group.
However, it is still unclear whether the observed difference in pain report and management occurs as a result of impaired communication and memory of pain, and/or whether the perception and experience of pain is altered as a result of the progressive degeneration of cortical and subcortical regions involved in the transmission and processing of nociceptive information.

## INTRODUCTION

Alzheimer`s disease (AD) is characterized by a progressive cognitive decline, where memory of recent facts, spatial orientation, attention and executive functions are ones of the first affected. This is followed by speech and behavioural problems, which affect everyday life (Almkvist O,1996; Benedikz E et all 2009). Pain is a subjective phenomenon, described by IASP as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Alzheimer`s disease affects both cognitive and affective functions, and the global pain experience is known to result from a complex integration of sensory, cognitive and affective processes (*Melzack and Casey*, 1968). Assessment and management of pain in dementia is problematic for at least three reasons: first, there are difficulties in pain assessment in patients progressively less able to communicate; second, neurodegenerative changes affect pain processing at different levels; third, different subtypes of dementia show specific changes along the pain pathways(Scherder E et al,2009; Scherder E et al 2005; Carlino E et al, 2010).

Although it is a known fact that age is the highest risk factor for both dementia and pain, this issue has only recently started to be studied, despite its physiological and clinical relevance in the aging population(Scherder E et al,2009; Scherder E et al 2005; Carlino E et al, 2010) One of the major conclusion during the last 2 decades of studies focusing on the experience, assessment , and treatment of pain in older persons with dementia, is that pain is still undertreated in this population due to the complexity of reliable pain assessment, which is a prerequisite for effective pain treatment(Scherder E et al,2009; Nanda de Knegt et al, 2011).

The purpose of this article is to follow pain perception in AD, and its numerous aspects, through a wide range of studies and to highlight the necessity of understanding pain phenomenon in AD, but most important, to recognize it, so that methods of treatment can be performed.

## GENERAL ASPECTS OF ALZHEIMER`S DISEASE

Alzheimer disease-factors that arise or contribute to its occurrence

Alzheimer disease, one of the most common dementia, is characterized by pathological changes in the brain. They consist of abundant extracellular amyloid plaques (deposits of β-amyloid) and intracellular neurofibrillary tangles (NFTs), accompanied by synaptic and neuronal loss, and brain inflammation (Ball MJ,1977; Braak H et al,1991; Scheff SW et al,2007; Schultzberg M et al,2007; Benedikz E et al,2009).

Synaptic loss is one of the strongest reasons of cognitive impairment in patients with AD. Several lines of investigation support the notion that the synaptic pathology and defective neurogenesis in AD are related to progressive accumulation of Aβ oligomers rather than fibrils(Crews L et al,2010). Aβ is associated with the formation of reactive oxygen (ROS) and nitrogen (RNS) species, and induces calcium-dependent excitotoxicity, impairment of cellular respiration, and alteration of synaptic functions associated with learning and memory (Querfurth H.W et al,2010; Butterfield D.A et al,2014). The Aβ peptide can consist of 39-43 amino acid residues, but the two major forms are Aβ40 accounting for approximately 90% of all the Aβ released from cells and the longer Aβ42 accounting for only approximately 10%.

Aβ42 is more hydrophobic and more prone to aggregation than Aβ40 (Verdile G et al,2004), and is the predominant form found in the amyloid plaques of AD (Lippa CF et al,1998; Benedikz E et al,2009).

Increasing evidence suggests a role for caspase activation and apoptosis in AD neuropathogenesis (Holtzman DM et al,1997; Lunkes A et al,1998; Namura S et al,1998; Kim TW et al,1997; Loetscher H et al,1997; Barnes NY et al,1998; Kovacs DM et al,1999; Su JH et al,1994; Su JH et al,1997; Tesco G et al,2007; Haijun Shao et al,2014; .Mattson MP et al,2002; Raina AK et al,2003), even though the contribution of apoptosis to neuronal loss in AD remains debatable (LeBlanc AC et al,2005;Cribbs DH et al,2004; Haijun Shao et al,2014).

A recent study suggest that caspase activation even without apoptosis can contribute to AD neuropathogenesis (Haijun Shao et al,2014; Yao J et al,2009).

Mitochondrial dysfunction may also contribute to AD neuropathogenesis (Haijun Shao et al,2014;Querfurth HW et al,2010; Zhu X et al,2013; Louneva N et al,2008). Furthermore, a recent study has shown that AD patients may have an age-dependent decrease of gama-aminobutyric acid (GABA) currents in the AD brain, and this reduction was associated with decreased mRNA and protein levels of GABA receptor subunits(Limon A et al,2012).

A large body of evidence implicates oxidative damage in AD pathogenesis (Beal M.F. et al,2005; Solfrizzi V. et al,2006; Padurariu M et al, 2009). It is believed that oxidative damage to critical molecules occurs early in the pathogenesis of AD and precedes pronounced neuropathological alterations (Baldeiras I et al,2008; Lovell MA et al,2007; Halliwell B,2007; Padurariu M et al, 2009).

What is oxidative stress?

Oxidative stress is defined as the biomolecular damage caused by the attack of reactive species upon constituents of living organisms (Halliwell B et al,2004).

The oxidative stress refers to a serious imbalance between reactive species production and antioxidant defences (Halliwell B,2007; Sies H et al,1991). As described by Sies, oxidative stress is a disturbance in the pro-oxidant-antioxidant balance in favour of the former, leading to potential damage (Halliwell B,2007; Sies H et al,1991).Chemically speaking pro-oxidants are oxidant agents and antioxidants are reduction agents.

Chemical reactions of oxidation and reduction happen on a common basis in the organism and are named redox reactions. During redox reactions a process of giving and accepting electrons is taking place. In physiological conditions there is a balance between oxidation and reduction. When this balance is broken, oxidative stress arises. That is the moment when free radicals appear, producing oxidative damage.

What are Free radicals?

They are an atom or a molecule that have in their structure an unpaired electron. This fact causes their instability, and makes them possess a high energy. Their quest is to find a matching structure that will bring back the missing electron, the equilibrium state being characterized by paired electrons and therefore less energy. In nature there is a large variety of free radicals, making their classification difficult. Depending on their structure there are several types of free radicals, and most studied are: superoxide anion, hydroxyl radical, hydrogen peroxide, nitric oxide, peroxyl and reactive aldehyde. The difference between free radicals, which depends on their structural and biochemical features, is crucial because it confers the compound its oxidative power, i.e. its toxicity.

Depending on their oxidation power, there are two types of free radicals: free radical with lesser reactivity and more aggressive free radicals, with larger reactivity.

Sources of free radicals

The sources of reactive oxygen species are many and varied and have not yet been fully identified. The free radicals are the result of diverse physiological and pathological processes not only endogenous but also exogenous, such as aging, excessive caloric intake, infections, inflammatory states, environmental toxins, certain drugs, emotional and psychological stress, tobacco smoke, ionizing radiation, alcohol or unbalanced nutrition (Ranjana et al., 2012). One of the main endogenous source of free radicals is the respiratory chain that takes place in the mitochondria, but they can also be synthesized by activated microglia. Microglial activation is a type of immune response to some brain lesions, a process that involves the generation of cytotoxic compounds such as superoxides that maintain a vicious cycle of neuronal damage (Nakajima et al., 2001; Padurariu M et al,2013).

Effects of oxidative stress

Cells show a wide range of responses upon exposure to reactive species, ranging from increased proliferation, prevention of cell division, senescence, necrosis, apoptosis, or cell death mechanisms with features of both (Halliwell B et al,2004; Tang SY et al,2004). The effects are to some extent cell-type-specific, being influenced by such parameters as the presence of certain cell-surface receptors and signal transduction mechanisms, as well as antioxidant defence levels (Halliwell B et al,2004; Halliwell B,2003; Burdon RH et al,1990; Burdon RH et al,1995).
Most free radical injuries concern lipidic structures, in particular the polysaturated fatty acids, which are produced from the lipid peroxidation reactions (Padurariu M et al, 2013).It should be noted that there are also other structures vulnerable to oxidative attack, of which DNA and proteins are definitely worth mentioning (Padurariu M et al, 2013). DNA oxidative changes may include alterations varying from nitrogenous base losses to DNA repairing system damage. The highly toxic hydroxyl radical can easily access the cell nucleus causing the degradation of various nitrogenous bases such as guanine, adenine and pyrimidine, with the formation of toxic compounds such as hydrodeoxyguanosine, hydroxiadenine, peroxide thymine or glycol thiamine (Padurariu M et al, 2013 ).
The oxidative stress theory explains neuronal death as caused by free radicals that attach and change composition of neuronal fat molecules, altering membrane fluidity and permeability and disturbing some of the membrane functions, such as transport and barrier-like functions. The consequences of these disturbances are directed mainly towards the traffic of $Ca^{2+}$ ions that cross the membrane structure, with the alteration of the signal transduction processes (Rowan et al., 2004; Padurariu M et al, 2013).
It is now understandable that free radicals are involved in many diseases, including cancer and atherosclerosis, chronic inflammation and diabetes (Halliwell & Gutteridge 2007; Evans 1993). The role of oxidative stress in neuropsychiatric disorders is well known, including schizophrenia, Parkinson`s Disease, Alzheimer dementia, anxiety or bipolar affective disorder (Uttara et al., 2009; Padurariu et al.,2010, Ciobica et al, 2010,2011,2012, Stefanescu et al., 2012).
Brain is particularly vulnerable to oxidative stress as a result of the relatively low levels of antioxidants, high levels of polysaturated fatty acids and increased need of oxygen (Padurariu M et al, 2010; Burdon RH et al,1990).

Antioxidative system

Against the oxidative attack the organism has its own developed mechanism to fight it. It consists of an arsenal of processes that offer protection against oxidative stress, called the antioxidative system. The elements that compose the antioxidative system are: antioxidant enzymes and non-enzymatic factors. Between the antioxidant enzymes most mentioned are superoxide dismutase (SOD), glutathione peroxidise (GPX), catalase or aldehyde dehydrogenase. These enzymes catalyze the reaction of reduction of free radicals, conducting to diminishing their power and also the oxidative cytotoxicity.

Non-enzymatic factors may be considered homeostatic role molecules that act as “scavengers” towards the pro-oxidant compounds. Their origin has been described as endo- or exogenous and they include: uric acid, glutathione, lipoic acid, bilirubin, melatonin, ascorbic acid, beta-carotene, bilirubin, selenium, NADPH mannitol, benzoate, reduced CoQ10 or tocopherol. Glutathione appears to be most important, reducing lipid peroxidation processes by directly blocking the activity of reactive species. Also, it maintains vitamins E and C in reduced forms, conferring them antioxidant proprieties (Singh et al., 2004; Padurariu M et al, 2013).

Biological indicators of oxidative stress are determined in various biological fluids (such as blood, cerebrospinal fluid ,urine, saliva, tissue level) since measurement of free radicals isn`t possible, we follow the resulting compounds of the oxidative process. The DNA oxidation markers 8-oxo-2`-deoxyguanosine and 8-oxoguanine and lipid peroxidation markers represented by 4-hydroxynonenal, malondialdehyde or F2 isoprostanes. Furthermore, increases in the specific activities of antioxidant enzymes, such as SOD2 in the hippocampus, especially in CA1 region and the amygdale (Massaad et al. 2011) have been observed (Padurariu M et al, 2013).

The causal relationship between oxidative stress and the changes identified in dementia has not yet been fully elucidated. It is not known which is the primary etiological factor, whether oxidative stress is a consequence if the degeneration processes of dementia or the oxidative compounds produce the characteristic lesions in dementia (Padurariu M et al, 2013).

## PAIN- GENERAL ASPECTS

What is pain?

Pain is a subjective multidimensional experience that can have a marked impact on both physiological and psychological state of an individual. The IASP(International Association for the Study of Pain) definition of pain considers it more than a purely sensory modality but as a perception that needs cognitive processing for pain to be consciously experienced (Burdon RH et al ,1995).

Pain mechanism

At somatic and visceral level there are receptors, named noxic receptors or nociceptors composed of free arborescent endings of afferent fibers. Nociceptors can be divided into two general types. A-fiber nociceptors have lightly myelinated axons, conduct action potentials rapidly, and have medium to large-diameter cell bodies. A-fibers mediate the fast, pricking quality of pain. C-fibers have unmyelinated axons, conduct action potentials slowly, and have small-diameter cell bodies. C-fibers mediate the slower, burning quality of pain. C-fibers comprise around 70% of all nociceptors.

Two classes of C-fibers have been identified. One class contains a variety of neuropeptides, including substance P and calcitonin gene-related peptide, and expresses trkA receptors, the high-affinity receptor for nerve growth factor (Stucky C et al,2001).These neurons project to the outermost region of the spinal dorsal horn (lamina I and outer lamina II) and terminate largely on spinal neurons that project to higher-order pain centers in the brain(Stucky C et al,2001). The other class contains few neuropeptides but expresses a surface carbohydrate group that selectively binds to a plant lectin called isolectin B4 (IB4). This subpopulation of neurons is supported by glial-derived neurotrophic factor during early postnatal development (Stucky C et al,2001). The IB4-binding neurons project to a different region of the spinal dorsal horn (inner lamina II) that contains primarily local spinal interneurons (Stucky C et al,2001).

In addition to the Aδ and C fibres that carry noxious sensory information, there are primary afferent Aβ fibres that carry non-noxious stimuli. Each of these fibre types possesses different characteristics that allow the transmission of particular types of sensory information. Aδ and C fibres synapse with secondary afferent neurones in the dorsal horn of the spinal cord. The dorsal horn can be divided histologically into ten layers called Rexed laminae. Aδ and C fibres transmit information to nociceptive -specific neurones in Rexed lamina I and II, in addition to projections to other laminae. Primary afferent terminals release a number of excitatory neurotransmitters including glutamate and substance P. Complex interactions occur in the dorsal horn between afferent neurones, interneurones and descending modulatory pathways. These interactions determine activity of the secondary afferent neurones. Glycine and gamma-aminobutyric acid (GABA) are important neurotransmitters acting as inhibitory interneurones. There are two main pathways that carry nociceptive signals to higher centres in the brain.

The spinothalamic tract: secondary afferent neurones decussate within a few segments of the level of entry into the spinal cord and ascend in the contralateral spinothalamic tract to nuclei within the thalamus. Third order neurones then ascend to terminate in the somatosensory cortex. There are also projections to the periaqueductal grey matter (PAG) (Danielle Reddi et al, 2014).The spinothalamic tract transmits signals that are important for pain localisation.

The spinoreticular tract: fibres also decussate and ascend the contralateral cord to reach the brainstem reticular formation, before projecting to the thalamus and hypothalamus. There are many further projections to the cortex. This pathway is involved in the emotional aspects of pain.

The somatosensory cortex is important for the localisation of pain. However, imaging techniques such as functional magnetic resonance imaging (fMRI) have demonstrated that a large brain network is activated during the acute pain experience. This is often called the 'pain matrix'. The commonest areas activated include the primary and secondary somatosensory(S1 and S2), insular, anterior cingulated cortex and prefrontal cortex, and the thalamus, demonstrating that these areas are all important in pain perception (Danielle Reddi et al, 2014).

## PAIN IMPLICATIONS IN ALZHEIMER DISEASE

Not surprisingly, several studies have shown alterations of both acute and chronic pain in AD and demented patients (Farrell et al., 1996). In an observation report of two patients with AD who had experienced trauma of different

kinds, neither of the patients exhibited normal pain behaviour or gave verbal reports of pain commensurate with the tissue damage they had incurred.

Although, various types of physical trauma have been observed occurring in patients- burns, fractures, invasive tumours, herpes zoster – all capable of creating different types of pain and involving a variety of different types of structures (nerves, soft tissue, bone, superficial skin, deep tissues and so on) none of them showed signs of normal pain perception (Fisher-Morris M. et al, 1997).

It has been observed that the incidence of headache following lumber puncture in demented patients is only 2% (Blennow et al., 1993) compared to 40% of non-demented patients (Knutz et al., 1992). Similarly, Cornu (1975) found a modification of the body image which resulted in a poor localization of noxious stimuli. In a recent study (Benedetti et al., 1999), it was found that tolerance to electric shock pain and ischaemic arm pain was increased in AD patients, whereas pain thresholds were unchanged compared with controls.

These data indicate that sensory-discriminative component of pain is preserved in demented patients whereas pain tolerance, which is associated with the affective-emotional counterpart of pain experience (Prince, 1988), undergoes significant changes. Porter et al. (1993,1996) found altered heart rate responses prior to, during and following venipuncture in elderly patients with poor cognitive abilities and in demented patients, suggesting altered emotional responses (Rainero I et al, 2000).

A study conducted by Rainero I et al, 2000, during which a series of clinical tests were ran on AD patients aimed at recording heart rate, systolic blood pressure and pain perception after electrical stimulation. The results of the investigation confirmed the notion that pain processing is altered in dementia, also stated in other studies (Cornu, 1975; Jonsson et al., 1997; Blennow et al, 1993; Farrell et al., 1996). The findings of Rainero I et al, 2000, indicate that the autonomic responses to noxious stimuli depend on stimulus intensity and not on the pain experience *per se*. When pain stimulation is mild autonomic responses are blunted and pain perception is normal, whereas when pain stimulation is strong autonomic responses are almost normal (e.g. blood pressure) and pain experience is blunted. This suggests that threshold for autonomic activation is increased in AD patients (Rainero I et al, 2000).

Cole et al, 2006, 2011 used pressure pain stimuli and found an increased threshold for just noticeable pain(Jensen-Dahm C et al,2013). Others have also suggested that the perception of acute pain is preserved, while the experience of chronic pain may be altered (Pickering et al., 2006; Cole LJ et al, 2006).

These contradictory findings might be attributable to methodological differences in regard to pain induction, pain assessment, and severity of AD. Another explanation is that it is unclear whether the methods are appropriate in patients with AD. Patients with AD have impairment of short-term memory and may have difficulties understanding simple instructions (Jensen-Dahm C et al, 2014).

In 2014, a study to evaluate some aspects of reliability (i.e. Coefficient of variation) to know if the prior used methods in different studies were appropriate, was conducted. The team examined the test-retest reliability and agreement of different pain sensitivity models using quantitative sensory testing, i.e. , assessments of thermal and mechanical thresholds, and assessments of tolerance to cold and pressure stimuli, in patient with AD. The results of the study concluded that patients with mild to moderate AD were able to reliably cooperate with standardized thermal and mechanical pain sensitivity tests, compared to age- and gender-matched control group. The pain thresholds did not differ between AD patients and control subjects, but a significantly lowered mechanical pain tolerance was observed in AD patients (Jensen-Dahm C et al, 2014).

Patients with AD might express their pain and discomfort behaviourally, as agitation, aggression, pacing, wandering, screaming, yelling, and sleep disturbances, although these behaviours are often not recognized as symptoms of pain but instead as behavioural and psychological symptoms of dementia (Coehen-Mansfiel J et al, 2012) so that individuals with dementia are more likely to receive psychotropic medication and not pain medication, to treat these manifestations of pain (Kamble P et al, 2009).

A randomized controlled trial reported that the use of a stepwise pain protocol based on the treatment recommendations of American Geriatrics Society significantly reduced behavioural disturbances and pain in individuals with moderate to severe dementia (Husebo BS et al, 2011), indicating the adequate treatment of pain reduces behavioural disturbances, but currently available drugs for management of pain such as acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, antidepressants and antiepileptic drugs often not effective or cause serious adverse reactions in older persons.

Recent studies have demonstrated the potential of cannabinoids, including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), to manage the symptoms of pain and dementia (Lynch ME et al, 2011). Two canabinoid receptors, CB1 and CB2, mediate the psychoactive, behavioural and analgesic effects of cannabinoids. CB1 receptors are highly expressed in the cortex, basal ganglia, cerebellum and hippocampus whereas CB2 receptors are mainly expressed in the immune system (Baker D et al, 2003). Cannabinoids also interact with other receptors and neurotransmitters in the brain, such as acetylcholine, dopamine, gamma-aminobutyric acid, serotonin, glutamate, norepinephrine, prostaglandins and opioid peptides (Baker D et al, 2003). This wide range of interactions reflects the potential pharmacological effects of cannabinoids in the management of behaviour, mood, and pain(Ahmed A et al, 2014).

Accurate assessment of pain is crucial for adequate pain management. In turn, this requires a reliable and valid observational tool for assessing pain in nonverbal individuals with dementia in clinical and nonclinical settings (Ahmed A et al, 2014).

Many brain areas affected in AD are relevant for pain transmission, for example, the amygdala, the hypothalamus, the thalamic intralaminar nuclei, the prefrontal regions (Mann DMA et al, 1988). Enhanced fMRI pain-related activity in sensory and affective brain areas has been observed in mild AD (Cole LJ et al, 2006) and both facial responses to pain (Kunz M et al, 2007; Lints-Martindale AC et al, 2007) and nociceptive motor reflexes (Kunz M et al,2009) have been found to be preserved or even increased in heterogeneous group of cognitively impaired patients (Carlino E et al, 2010).

Patients on a psychogeriatric ward where pain prevalence and intensity were found to be lower than on a somatic ward, received less pain medication than patients on the somatic ward, even when these pain parameters were matched (Achterberg WP et al,2007; Scherder E et al, 2009).

In one study, patients with dementia (subtype not otherwise specified, NOS) recovering from hip fracture surgery received only 1/3 the amount of morphine sulphate equivalents administered to non-demented adults and 76% of patients with dementia had no standing order for post-operative analgesia (Scherder E et al, 2009; Morrison RS et al, 2000).

In another study, only 33% of AD patients received appropriate analgesic medication compared to 64% of non-demented adults (Scherder E et al, 2009; Scherder EJ et al, 1997).

## CONCLUSION

As most of the studies show, it is a fact that pain perception is altered in AD. Some argue that the patient doesn`t realise the amount of pain he is experiencing or he is experiencing less pain of a certain kind. Others believe that pain manifestations are different from the ones that non-demented persons experience. Altogether, the available studies, suggest undertreatment of pain in patients with Alzheimer disease, which is not a surprise considering the complexity of this cognitive disorder and the intricate pathways of the pain phenomenon.

Therefore, we emphasise on the need of further studies in this complex matter of pain perception in Alzheimer dementia, so that patients with AD suffering from pain can be treated adequately.

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