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Agitation and aggressiveness in Alzheimer's disease: focus on neurotransmission mechanisms and pharmacological treatments

Agitazione e aggressività nella malattia di Alzheimer: focus sui meccanismi di neurotrasmissione e trattamenti farmacologici

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ABSTRACT IN LINGUA INGLESE

The aim of this thesis is to investigate two main behavioral symptoms in Alzheimer's Disease (AD): agitation and aggressiveness, the most common, challenging and severe ones, in relation to their pharmacological treatment, mechanism of action and main pathways of neurotransmission. After having introduced and described the Alzheimer's Disease, highlighting its current diagnosis, etiology and pathology, in order to give an overview of this clinical condition, the first chapter is focused on the current pharmacological treatment used to manage cognitive and behavioral symptoms in AD. In particular, the mechanisms of action, the effects and the neurotransmission mechanisms involved in the main categories of pharmacological treatments usually prescribed in AD, such as acetylcholinesterase inhibitors, antagonists for the NMDA receptor, antidepressants, benzodiazepines and antipsychotics, are deeply described. While the first two categories are useful to manage cognitive symptoms, the last three ones have effects on behavioral symptoms, such as agitation and aggressiveness. The second chapter, instead, analyzes the main side effects of AD drugs, pointing out the increased risk of falls in AD patients, that involves the autonomic nervous system and heart rate, usually affected by the acetylcholinesterase inhibitors, used to treat cognitive symptoms in AD. The third chapter describes deeper the behavioral symptoms in AD, focusing on their management and predictors. Specifically, it goes into detail regarding agitation and aggressiveness, analyzing their biomarkers that can be used as a diagnostic tool, as predictors of disease onset, for monitoring the progression of the symptoms and to identify possible treatment targets. In particular, in the third chapter are discussed agitation and aggressiveness' neuropathology, neuroimaging techniques, the pathways of neurotransmission involved, the genotype and neuroinflammation that usually augment the risk of developing agitation and aggressiveness. The main pathways of neurotransmission involved, such as the serotoninergic, dopaminergic and cholinergic ones, are also described in the last chapter, in order to analyze the effects of AD drugs on agitation and aggressiveness, their mechanisms of action and their clinical effectiveness on patients' wellbeing.

ABSTRACT IN LINGUA ITALIANA

Lo scopo di questo elaborato è di approfondire due tra i principali sintomi comportamentali nella malattia di Alzheimer (AD): agitazione e aggressività, i più comuni, impegnativi e severi, in rapporto al loro trattamento farmacologico, meccanismo d'azione e principali sistemi di neurotrasmissione. Dopo aver introdotto e descritto la malattia di Alzheimer, evidenziandone l'attuale diagnosi, eziologia e caratteristiche patologiche, con lo scopo di fornire una visione di insieme di questa condizione clinica, il primo capitolo è focalizzato sull'attuale trattamento farmacologico usato per gestire sia sintomi cognitivi che comportamentali nell'AD. In particolare, vengono descritti i meccanismi d'azione, gli effetti e i meccanismi di neurotrasmissione coinvolti nelle principali categorie di trattamenti farmacologici solitamente prescritti nell'AD, come ad esempio gli inibitori dell'acetilcolinesterasi, gli antagonisti del recettore NMDA, antidepressivi, benzodiazepine e antipsicotici. Mentre le prime due categorie sono indicate per trattare sintomi cognitivi, le ultime tre hanno effetti sui sintomi comportamentali, come l'agitazione e l'aggressività. Il secondo capitolo, invece, analizza i principali effetti collaterali dei farmaci per l'AD, evidenziando l'aumentato rischio di cadute nei pazienti AD, il quale coinvolge il sistema nervoso autonomo e il battito cardiaco, solitamente colpiti dagli inibitori dell'acetilcolinesterasi, usati per trattare i sintomi cognitivi nell'AD. Il terzo capitolo descrive in profondità i sintomi comportamentali nell'AD, focalizzandosi sulla loro gestione e sui loro predittori. Specificamente, entra nel dettaglio per quanto riguarda agitazione e aggressività, analizzandone i biomarcatori, che possono essere utilizzati come strumenti diagnostici, come predittori d'insorgenza della malattia, per monitorare la progressione dei sintomi e per identificare possibili target per il trattamento. In particolare, nel terzo capitolo vengono trattati la neuropatologia dell'agitazione e aggressività, le tecniche di neuroimmagine, le vie di neurotrasmissione coinvolte, il genotipo e la neuroinfiammazione, che solitamente aumentano il rischio di sviluppare agitazione e aggressività. I principali sistemi di neurotrasmissione coinvolti, come il sistema serotoninergico, dopaminergico e colinergico, vengono descritti anche nell'ultimo capitolo, allo scopo di analizzare gli effetti dei farmaci dell'AD su agitazione e aggressività, i loro meccanismi d'azione e la loro efficacia clinica sul benessere dei pazienti.

INTRODUCTION

In November 1901, Dr. Alois Alzheimer, a German neurologist, described the case of a 51 years old woman, Auguste D., who showed "untreatable paranoid symptomatology, with fast progression and intensity of sleep disorders, memory impairments, disorientation, hallucinations and aggressiveness" (Alzheimer, 1906). At first, A. Alzheimer thought that her symptoms matched the diagnosis of "dementia", but because of the fact that she was too young to display it, he understood that her condition could be called "presenile dementia" (Maurer, 1997). Four and a half years later, when the patient died, the Doctor described also the histopathological findings of her disease, and he reported "peculiar changes in the neurofibrils in the center of an almost normal cell", characterized by abnormal thickness and impregnability (Alzheimer, 1906).

In addition, G. Perusini, an Italian Doctor, described in 1909 four cases of psychiatric diseases of older people. He made a comparison between their case's history and the one analyzed by Alzheimer, and he found identical features like amyloid plaques and neurofibrillary tangles, but to distinguish them from the case of Auguste D., he defined their condition as "senile dementia" (Perusini,1909).

Thanks to E. Kraepelin, one year later, the previous cases were mentioned as "Alzheimer's disease" for the first time in his book Psychiatrie. He stated that their clinical condition was still unclear, because of the fact that "sometimes this form of senile dementia can start in the forties", showing illustrations of very similar fibrillary patterns (Kraepelin, 1910).

Today, it can be confirmed that the patients described previously were degenerative forms of dementia, and not vascular ones. In addition, the deposition of the plaques outside the nerve cells in the cerebral cortex turned out to be "β-amyloid protein", while the intracellular fibrils can be referred as "neurofibrillary degeneration" (Maurer, 1997).

0.1) Alzheimer's Disease (AD): diagnosis and clinical condition

Alzheimer's Disease (AD) is characterized by a progressive deterioration of cognitive abilities, that typically starts with a decline in the competence of creating new memories, but in the last stadiums of the pathology, it affects all the aspects of intellectual functioning, resulting in total reliance on others for essential daily activities, and early death (Mayeux et al, 2012). As the World Health Organization states, in the last years more than 55 million people worldwide live with AD, with around 10 million new cases every year. The risk of developing AD dementia increases dramatically with age: 3% of people age 65-74 years, 17% of people age 75-84 and 32% of 85 years old people, according to the Alzheimer's Association Report of 2020. As the Alzheimer's Disease International (ADI) states, these numbers are predicted to double every 20 years as a result of the population all over the world that continues to age (ADI, 2023). In addition, AD results to be the leading cause of dementia with impaired memory (60-70% of cases) and the seventh main cause of death.

As stated before, it is possible to distinguish between early and late onset dementia. AD late onset is the most common form of dementia, which usually starts after 65 years and is secondary to known genetic mutations in autosomal dominant form. However, there are many risk factors contributing to late onset dementia, for example environmental, genetic and age-related factors. The early onset dementia is very rare (2% of cases before 60 years old) and it's usually transmitted as an autosomal dominant gene with strong penetrance (Plassman, 1996). Autosomal dominant form refers to the inheritance pattern seen in some forms of genetic disorders. "Autosomal" means that the gene is situated on one of the non-sex chromosomes, while "dominant" means that having one only copy of the mutated gene, inherited from one parent, is sufficient to cause the condition. In fact, someone's child with an autosomal dominant condition has 50% chance of having the same pathology. Instead, autosomal recessive disorders require both copies of the gene mutated, one from each parent, to manifest the disorder (National Human Genome Research Institute, 2023).

Three genes, which will be discussed more in detail in the next paragraph, are associated with familial cases of Alzheimer's disease (AD): chromosome 21, presenilin 1 on chromosome 14, and presenilin 2 on chromosome 1. Chromosome 21 is linked to AD due to the presence of the amyloid precursor protein (APP). A fourth gene, apolipoprotein ε (APOE), with alleles ε2, ε3, and ε4, is associated with senile and sporadic AD, with the ε4 allele being a potential susceptibility factor for AD-related dementia (Greicius et al, 2002).

Senile AD is characterized by three pathological features: amyloid plaques, neurofibrillary tangles and neuronal loss. First one refers to extraneuronal aggregates of β-amyloid (Aβ) protein, while neurofibrillary tangles are aggregations of tau protein, which is predominantly found in neuronal cell bodies, aggregated with neurofilaments. Amyloid plaques and neurofibrillary tangles lead to neuronal loss. These findings are useful to make an accurate clinical diagnosis of AD and to predict the progression of the disease. As a result of genetic and other risk factors, it is today known that the pathological process of AD starts even decades before the diagnosis, but without evident cognitive deficits (Sperling et al, 2011). However, there is high heterogeneity among AD patients in terms of development of symptoms and clinical decline also because of the typical and atypical variants of AD. Indeed, the National Institute on Aging and Alzheimer's Association in 2011 made a distinction between amnestic AD, the typical form of AD, and nonamnestic AD, that includes specific features like language impairment, visuospatial deficits and executive dysfunctions (Atri, 2019). The classical form of AD is characterized, in the late dementia stages of the disease, by a gradual loss of language skills and spatial awareness. These features can be easily mixed up with atypical forms of AD, for example Posterior Cortical Atrophy (PCA) which affects spatial and visual processing, and Primary Progressive Aphasia (PPA), that involves difficulties in speaking and naming objects. Thanks to the availability of disease biomarkers, such as cerebrospinal fluid (CSF) Aβ-42, and thanks to neuroimaging techniques like Positron Emission Tomography (PET) amyloid imaging, it is possible to diagnose in vivo the pathology, in particular atypical, fast progressive or early onset dementia.

Typical AD can be categorized in three different phases: preclinical AD, prodromal AD and AD dementia (Sperling et al, 2011). The preclinical phase of AD corresponds to the asymptomatic phase of the disease and is an opportunity for potential early intervention on the pathology. However, the pathogenic mechanism is already in action, but most of the times it is not properly identified. The patients in this phase carry the gene mutations that are known to increase the risk of developing AD dementia, for example apolipoprotein ε (APOE), and are positive to biomarkers, but their symptoms are still blurry and hidden to make a diagnosis. In this first phase it's possible to sense subtle episodic memory loss usually assigned to fatigue and behavioral disturbances like irritability and apathy (Sperling et al, 2011). Instead, executive skills still appear to be intact (Caselli et al, 2011). In addition, in this phase is possible to find hippocampal and entorhinal cortex volume's reduction, anticipating the progression to the prodromal AD stage (Kaye et al, 1997). Moreover, thanks to Magnetic Resonance Imaging (MRI) studies, useful to detect hippocampal atrophy and brain morphology, preclinical AD patients usually show less brain volume, brain tissue, cortical thickness and grey matter (Wishart et al, 2006). In patients that carry APOE ε4 allele, it's possible to find reduced glucose metabolism in temporal, precuneus, parietal, and frontal regions thanks to PET imaging, using the radioactive tracer called fluorodeoxyglucose (Kennedy et al, 1995). PET studies also have found β-amyloid deposition in the striatum in cognitively regular old people, even 15 years before the prodromal stage (Villemagne et al, 2011). In fact, amyloid and tau biomarkers for AD are widely recognized diagnostic tools for the identification of AD even in preclinical and prodromal stages of the disease (Iaccarino et al., 2023). Indeed, PET imaging can be useful to detect amyloid deposition, brain metabolism and cerebral blood flow. However, while only one tau PET tracer has been approved recently and is still under research (Jie et al., 2021), PET amyloid scans are usually expensive and mostly used for atypical AD patients or in clinical trials (Lee et al., 2021). Thanks to cerebrospinal fluid biomarkers (CSF) it's possible to determine with 94% of probability the correct prediction on future AD patients, excluding all people suspected of having AD, that are positive to biomarkers, but that won't develop Alzheimer's disease (Caselli

et al, 2012). In fact, in APOE carriers, CSF levels of β-amyloid begin to fall in this early phase, predicting the trajectory of AD's development (Morris et al, 2010).

PET, Single-Photon Emission Computed Tomography (SPECT) and MRI are techniques used for conventional brain imaging, and are useful to identify subjects with an high risk of developing AD while they are in the early stages of cognitive impairment. The combination of these brain imaging techniques with CSF biomarker analysis, an invasive technique, augments the accuracy of the diagnosis of complicated cases. In fact, CSF indicates the amount of Aβ plaques and tau, and the level of tau in the CSF indicates the severity and progression of the AD pathology. Minimal invasive biomarkers are Electroencephalography (EEG), plasma and saliva, in particular EEG waveforms in AD are distinctly different from normal elderly individuals, in terms of reduction of high frequency waves and synchronization. Plasma, in addition to CSF, can be an useful tool too, because it's possible to find in AD patients typical proteins, while saliva can contain metabolites that predict the progression of AD (Gunes et al., 2022). However, while biomarkers provide valuable information, they have limitations and must be interpreted within the context of a patient's clinical presentation and other diagnostic assessments: indeed, due to variability in disease progression, due to the overlap with other comorbidities and because of the complexity and heterogeneity of AD, biomarkers aren't definitive and certain indicators of Alzheimer's disease (Bodaghi et al., 2023).

The prodromal stage of AD corresponds to symptomatic phase, in which is possible to recognize obvious episodic memory loss and personality alterations like attention, decision making and less insight and awareness, in terms of being unable to recognize changes in their behavior and emotions. This concept refers to "anosognosia", a frequent symptom in AD, in which the patients fluctuate from clearly understanding that they have a cognitive condition, to being unable to identify the presence and progression of the disease (Sanz et al., 2016). In addition, behavioral disturbances start to be more worth of attention, like mood swings, anxiety and irritability (Geda et al, 2008). AD prodromal stage is also referred to as "Mild cognitive impairment" (MCI), a clinical

condition of patients with a cognitive deficit that is greater than what would be expected based on the individual's age and education level, but they still don't meet the criteria for dementia. MCI is usually associated to an increased risk of developing dementia, at an annual rate of 15% (Dunne et al., 2020). However, the symptoms' extent is not enough to compromise patient's functional autonomy (Reisberg et al, 2008). While in the preclinical stage patients usually perform well on psychometric and mental status tests, MCI patients usually have low scores for example in Mini-Mental State Examination test (MMSE), a test usually used to determine intellective and cognitive impairments, but the performance is influenced by education and age. To determine if a MCI patient is developing dementia due to AD, it's important to verify if there is biomarker evidence of accumulating AD neuropathology (Albert et al, 2011). In fact, in this stage is possible to find complex patterns of brain atrophy and cerebrospinal fluid flow (CSF). A wider brain atrophy can indicate a bigger reduction of grey matter, and also a reduction in white matter in many regions like hippocampus, temporal, insular, orbitofrontal, posterior cingulate and precuneus (Fan et al, 2008). Reduced blood flow and metabolic activity can be also found in posterior cingulate and parieto-temporal cortex (Fan et al, 2008). So, in comparison to the preclinical AD stage, as the disease progresses, the pattern of AD pathology spreads to many more regions and with a higher extent. Mild behavioral impairment (MBI) is a clinical presentation that is part of the prodromal AD phase too, and it includes a cluster of symptoms, for example decreased motivation, affective dysregulation (anxiety, dysphoria), impulse dyscontrol (agitation, behavioral perseveration), social inappropriateness (loss of empathy, loss of insight), delusions and hallucinations (Ismail et al, 2017).

Dementia stage corresponds to the full-blown phase of the disease. The cognitive impairment is now clearly noticeable by the patient's family and even by unfamiliar people. Patients have short-term memory loss and sometimes even long-term memory, the repeating questions and poor ability to recall word list, objects or stories are typical. People in this stage manifest loss of verbal fluency and executive impairments. In this phase it's common to find behavioral disturbances like

irritability, anger, delusions and wandering (Fan et al, 2008). Usually, using the MMSE test, patients in the AD dementia phase score less than 23/30 points, while less than 27/30 is considered abnormal impairment (Rodriguez et al, 2021). At this stage, even motor and sensitive cortex are impaired.

According to the National Institute on Aging-Alzheimer's Association on diagnostic guidelines for AD (NINCDS-ADRDA criteria), in 2011 it was proposed a classification criterion to make a diagnosis of AD dementia: probable AD dementia, possible AD dementia and probable or possible AD dementia with evidence of AD pathophysiological process (McKhann et al, 2011). To diagnose probable AD dementia is necessary the presence of four different characteristics, which are insidious and gradual onset, a gradual progression in the worsening of cognition, the impaired personal autonomy and the deficit must be confirmed using neuropsychological tests. Possible AD dementia is diagnosed when the course of the pathology is atypical in terms of progressive decline, sudden onset or etiologically mixed pathologies (like Cerebrovascular Disease, Dementia with Lewy bodies or other medical comorbidities that complicate the diagnosis). The last criterion is referred to the pathophysiological process: biomarkers of Aβ-42, tau protein, hypometabolism and brain atrophy.

According to the Global Deterioration Scale (GDS) it's possible to distinguish 7 different stages that analyze deeper the preclinical, prodromal and dementia stages. Stage 1 corresponds to the absence of dementia signs, in fact people in this phase are free of symptoms of cognitive and functional decline, behavioral and mood changes. Stage 2 is characterized by the presence of subjective memory loss and recall, and symptoms are recognized by the patient but are not notable by the family. Stage 3 corresponds to the MCI phase, in which deficits are notable by close people, for example repetitive questions and less capacity to perform executive functions. Stage 4-7 specify better the dementia stage, that can be divided in "mild", "moderate", "moderately severe" and "severe". In mild dementia the diagnosis of AD can be made with high accuracy, it manifests itself as deficits in daily activities, hindering their ability to live independently, also in evident memory

loss, but patients can still recall significant current events (Alzheimer's Association, 2023). In moderate dementia, instead, the evident deficits in basic activities are evident and patients need supervision, and the typical reaction of the patients is behaving aggressively and suspiciously. Moderately severe dementia patients are not able to orient themselves in time and space, and often misidentify the family members, showing violent behavior because of the frustration and fear of the circumstances. In addition, the patient shows inabilities to communicate properly and articulate sentences. In fact, patients affected by severe dementia speak only single intelligible words, while they are not able to ambulate independently, but also to sit properly, with an increased probability of falling because of physical rigidity and loss of reflexes (Reisberg, 2022).

0.2) Etiology of AD

While the etiology of a minority of cases can be attributed to specific dominant genetic mutations, the majority of AD cases occur sporadically and are not linked to a single genetic factor. However, AD dementia is a result of genetic and environmental factors that augment the probability of developing the disease.

From the genetic point of view, three genes can be linked to the AD familial cases: Aβ precursor protein APP on chromosome 21, presenilin 1 on chromosome 14, and presinilin 2 on chromosome 1 (Greicius et al, 2002). All of them result in an excessive production of the most neurotoxic form of amyloid, Aβ-42. Chromosome 21 was the first AD related gene to be identified, because the precursor of the amyloid protein APP is located on this chromosome and it's linked to Down's syndrome. Indeed, every patient with Down's syndrome grow amyloid plaques at 40 years old. It has been noticed in people affected by Down's syndrome that they have a much higher probability to develop a cognitive decline, because they have three copies of chromosome 21, so if they have a mutation on this gene, it'll be expressed three times (St George-Hyslop, 1987; Salehi et al., 2019). Presenilin 1 (PS1) gene mutation causes most of the early onset AD cases, and has the same outcome as presenilin 2: a selective increase in the production of the peptide Aβ-42. PS1, in

particular, is involved in γ-secretase mediated cleavage of the amyloid precursor protein APP, that generally can be cleaved and cut by different enzymes, including β and α-secretase, to generate various fragments: specifically, it cuts the C-terminal transmembrane fragments of APP, the end of the protein (De Strooper et al, 1998, Liu et al., 2021). Presenilin 2 has the same role of PS1 but is located on the chromosome 1.

A fourth gene can be linked specifically to senile and sporadic AD: apolipoprotein ε, which codes for APOE. APOE has 3 alleles: ε2, ε3, ε4, and the last one is involved in dementia, even though it is not sufficient or necessary to develop Alzheimer's disease (Roses, 1994; Yamazaki et al., 2019). It can be considered as a potential susceptibility gene to develop late-onset AD (Greicius et al, 2002).

The greatest risk factor for AD is the age: as said before, AD is an age-related disease that in the majority of cases manifests itself beyond age 65, making it difficult to distinguish age-related physiological symptoms and disease-related symptoms. Females are associated to a greater risk for developing late-onset AD as compared to males, probably because of the protective effect of estrogen in premenopausal phase that decreases the risk of early-onset AD in women, but the risk increases in peri and post-menopausal phase as the estrogen level drops (Rahman et al, 2019).

Cardiovascular disease is extremely linked to an increased risk of AD and to dementia in general. High blood pressure, heart attacks and ischemia are all associated to AD, with an increased rate of 7% of new-onset dementia after a stroke because of the subsequent brain atrophy and hypoperfusion (Yang et al., 2018). Vascular diseases are usually caused by poor diet, obesity, high cholesterol and sedentary lifestyle, producing metabolic and oxygen's levels changes in the brain homeostasis (Uranga et al, 2010).

Type II Diabetes is a pathology comorbidity which directly affects Aβ amyloid because the excess of insulin in the bloodstream, due to insulin resistance, interferes with the brain's Aβ amyloid clearance. Additionally, the accumulation of advanced glycation end-products (AGE), that are proteins or lipids prevalent in diabetes, can be also detected in amyloid plaques and neurofibrillary tangles, giving rise to oxidative stress and neuronal death (Kong et al., 2020). An excess of adipose

tissue, moreover, results in a proliferation of substances like adipokines and cytokines, which can lead to insulin resistance (Mayeux et al, 2012) and to inflammatory processes. Obesity-associated systemic inflammation can lead to neuroinflammation in the brain, in particular the hypothalamus and hippocampus, resulting in negative cognitive outcomes (Boleti et al., 2023).

Sepsis-related inflammation and traumatic brain injuries represent additional risk factors for sporadic AD. Interleukin 6 (IL-6) is an inflammatory marker associated to a high risk of developing AD (Engelhart et al, 2004): greater levels of this marker is linked to faster cognitive decline, because of the activated astrocytes and microglia nearby amyloid plaques and neurofibrillary tangles (Navarro et al, 2018).
Other risk factors implicated in AD include pollution, stress and heavy metal exposure (Cacciottolo et al., 2017).

There are also protective factors that correlate with a reduced risk of AD. Cognitive reserve is the main one, and it can explain why some of the patients with AD don't show cognitive impairment, even if they already manifest accumulation of amyloid and neurofibrillary tangles (Aizenstein et al, 2008). People with educational or occupational acquirements have slower cognitive and language decline, coping more effectively with normal aging brain decline. Having a large-scale social network protects AD patients and elderly people too, engaging in productive activities, with 38% less risk of developing dementia (Mayeux et al, 2012).

Diet is also important to maintain a high cognitive functioning. For instance reduction of cholesterol level might reduce AD (Feringa et.al, 2021). Indeed, trans-unsaturated fats are associated to a 3 times higher risk of AD. Instead, omega-3 and vitamin D are essential for brain development and reserve (Dighriri et al., 2022). Mediterranean diet has also shown positive effects on cognition, thanks to a composite dietary pattern rich in nutritional components like vegetables, legumes, fruit and cereals (Mayeux et al, 2012). Paired to diet, physical activity is also fundamental, because it can enhance brain vascularization and neuronal circuitry, stimulating neurogenesis and brain plasticity

(Mayeux et al, 2012). In addition, exercise increases brain resistance and augments brain neurotrophic factor by modulating gene expression and reducing IL-6 levels (Ford, 2002).

0.3) Pathology of AD

The neuropathological hallmark of AD involves the progressive accumulation of extracellular amyloid plaques and cerebral amyloid angiopathy, neuritic plaques, intraneuronal neurofibrillary tangles and glial responses. Histopathology of AD also includes negative lesions such as loss of neurons and synapses, granulovacuolar degeneration and brain atrophy.

Three types of amyloid-related plaques can be identified: the first one is known as "diffuse plaques", which don't have an amyloid core but they contain stable amyloid proteins, representing the earliest stage of plaque formation. Typically, diffuse plaques can be found in non-symptomatic areas of brain affected by AD, such as the cerebellum. Second type of amyloid plaques are the classical neuritic plaques, that is a spherical structure bigger than a diffuse plaque that measures from 50 up to 200 micrometers in diameter. Neuritic plaques have a central amyloid core surrounded by two types of filaments: normal glial cells (in particular, astrocytes and microglia), and abnormal organelles (which are mitochondria and synaptic vesicles). Neuritic plaques also contain APOE, tau protein, and enzymes related to neurotransmitters. The third category of plaque is referred to as the "burnt out" plaques, composed of an amyloid core without surrounding neuritic components (Cummings et al., 1998; DeTure et al., 2019). Intraneuronal neurofibrillary tangles consist of a paired helical filament that is located in the cell body (most commonly in the large pyramidal cells) and can expand to dendrites, containing an abnormal phosphorylation of tau-protein (Cummings et al., 1998; Encyclopedia of the Neurological Sciences, 2014).

Neuronal cell loss is a consistent characteristic of AD, and it affects larger neurons in the superficial cortex, and it's more prominent in younger patients. Synaptic alterations are common too, with a

45% reduction in presynaptic terminal density (Cummings et al., 1998). In addition, cerebral amyloid angiopathy (CAA) differs from neuritic plaques in terms of location, in fact it is a type of cerebrovascular disorder characterized by the accumulation of amyloid in cerebral blood vessels, and not in the brain cells, and it is often associated to hemorrhagic strokes (Cummings et al., 1998; Malek-Ahmadi et al., 2019). Another histologic abnormality identified in AD, but rare in normal aging, is known as granulovacuolar degeneration, characterized by the presence of granules and vacuoles in the pyramidal cell layer in the hippocampus, altering the normal cell functioning (Cummings et al., 1998; Wiersma et al., 2020).

The relationship between amyloid plaques and neurofibrillary tangles in the pathogenesis of AD is still debated: the amyloid cascade hypothesis states that the formation of Aβ-amyloid triggers the aggregation of tau protein into neurofibrillary tangles, inflammation and oxidative stress and this cascade of events lead to AD pathology. This theory traces its origin in the chromosome 21's identification because Aβ-amyloid is located on it and, as a result, Glenner et al. in 1984 thought that APP gene on chromosome 21 is responsible for AD pathology (Wiseman et al, 2018). On the contrary, tau hypothesis states that the formation of neurofibrillary tangles is antecedent to the Aβ-amyloid plaques formation. There is evidence that supports this theory: tangles can be found in very early/mild dementia and without the presence of Aβ-amyloid plaques. Tau also correlates more with the progression of AD than amyloid plaques, probably because it results in neuronal death via inhibition of axonal transport (Combs et al., 2019). Indeed, Aβ-amyloid plaques can be found also in people who don't experience neurodegeneration (Mormino et al., 2018). Today the approach is multifaced because of the pathology's complexity: some researches state that amyloid and tau follow dual pathways (Small et al., 2008), while other scientists began to consider the role of inflammation and oxidative stress, caused by a declining mitochondrial function which in turn triggers the formation of amyloid, tangles, synaptic loss and oxidative stress (Swerdlow et al., 2010).

Also, inflammation, amyloid and tau can be induced by an acetylcholine dysfunction, which decreases its concentration and functioning in AD, giving rise to the Cholinergic Hypothesis, which identifies a consistent loss of cholinergic neurons in AD, in particular in the basal forebrain cholinergic nuclei (BFCN). (Chen & Mobley, 2019)

Figure 1: Neuritic plaques (Cummings et al., 1998)

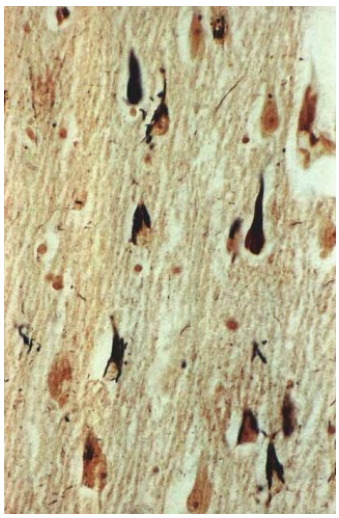

Figure 2: Neurofibrillary tangles (Cummings et al., 1998)

Even though the distribution of amyloid and tau deposits changes from one individual to another, it's possible to distinguish a characteristic pattern that permits the differentiation of AD in different stages, as a support for the diagnosis. In 1991 Braak & Braak classified AD's degree of pathology observing the neuropathological findings in 83 brains obtained at autopsy. It's possible to distinguish between three stages of amyloid deposition's progression: in stage A, initial deposits can be found in basal portions of the isocortex, in particular in the basal portions of the frontal, occipital and temporal lobe, without affecting the hippocampus. Stage B is characterized by amyloid deposition in all the association areas, while hippocampus is only slightly implicated without any involvement of the primary sensory area and motor area. In the final stage C all isocortical areas are involved, including sensory and motor areas. Stage C corresponds to the phase where patients are bedridden and unable to respond to external stimuli (Therriault et al., 2022).

Neurofibrillary tangles can be classified in 6 stages, which all follow the progression of the disease. Stage I and II are called as "transenthorinal" stage, because tau tangles originate in the transitional enthorinal cortex, which is a relay station between the cortex and the hippocampus, critical for memory. In this phases there are not visible external symptoms and mental testing shows minimal impairment. In stage II tau starts to aggregate in the hippocampus and in the cortex. Stages III- IV are the limbic stages, involving enthorinal, transentorhinal cortex, hippocampus and cortex. These stages correspond to the Mild Cognitive Impairment condition, in which patients start to experience AD symptoms. Stages V-VI correspond to moderate and severe dementia, because tau tangles have caused severe memory and cognitive impairment, and these stages are marked by isocortical destruction. Tau tangles have formed extensively in the transitional enthorinal cortex, hippocampus and cortex (Braak & Braak, 1991).

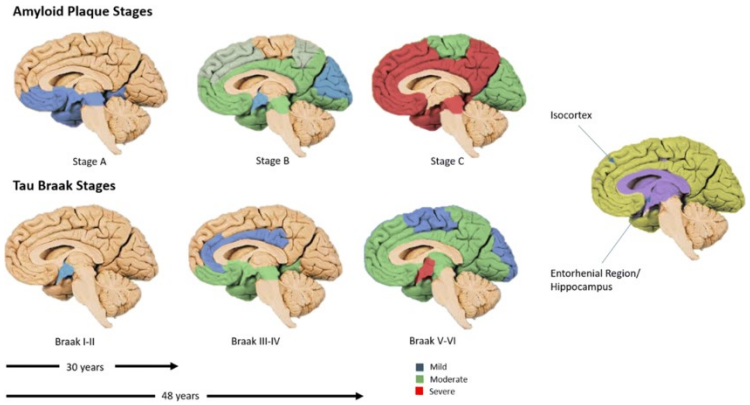

Figure 3: distribution pattern of amyloid deposits and neurofibrillary tangles (Swarbrick et al., 2019)

0.4) An insight into Serotoninergic and Dopaminergic pathways

With respect to the neurotransmitters involved in the pathogenesis of AD, the progressive decline in cholinergic, dopaminergic and serotoninergic neuronal functioning, follows the histopathological deposition of Aβ-amyloid and tau tangles. In fact, the interaction of amyloid with these neurotransmitter systems would induce cell dysfunction, neurotransmitter signaling imbalance, leading to the symptomatic aspects of AD (Lanni et al., 2021). In addition to the cholinergic system, serotonin (5-HT) is one of the most prominent and compromised neurotransmitter pathway, as it is

involved in emotional, cognitive and behavioral disturbances. The current treatment primarily targets the enhancement of acetylcholine loss, but this approach only restores memory and cognition in the short term, because it has no effect as the disease progresses. Indeed, it is necessary to prevent neuronal cell loss, otherwise this type of drugs would become ineffective, as there are fewer cells and synapses available (Geldenhuys et al., 2011). That's why the serotoninergic system has gained significance, representing a potential target for new therapies. Serotonin's functions are mediated by its interactions mainly with the cholinergic and dopaminergic systems. Serotonin's synthesis starts from the essential amino-acid tryptophan, with a brain pathway that begins in the raphe nuclei. Raphe nuclei are located in the brainstem and they have connections to neocortex, limbic system which includes amygdala and hippocampus, and autonomous nervous system, with several modulatory effects on neuronal firing (Aaldijk & Vermeiren, 2022). The progressive degeneration of sub-cortical nuclei, including raphe nuclei, deprives hippocampal and cortical neurons from innervation mediated by the monoaminergic system, which includes serotonin and dopamine. As a result, progressive denervation can cause the AD cognitive symptoms (Martorana & Koch, 2014). The decrease in total brain serotoninergic transmission in AD can be found, particularly, in temporal and frontal cortex (Štrac et al., 2016), while it is also altered in the cerebrospinal fluid (CSF) (Gallo et al., 2021). The action of serotonin is mediated by specific receptors located in brain areas involved in memory and learning functions. Generally, in AD, the serotonin receptors 5-HT1 and 5-HT2 are usually lowered in hippocampus, amygdala and in the neocortex, which was analyzed by Blin et al. in 1997 post-mortem in the patients' brains, but can also be demonstrated in vivo using PET (Nasser et al., 2023). However, a reduction in 5-HT1A receptor activity may contribute to increased agitation and mood disturbances that often occur in AD, while an overactivity of 5-HT2A receptors has been suggested to contribute to behavioral disturbances, as will be discussed later. In 2014 it was also discovered a correlation between aggressiveness and depressive symptoms in the hippocampus which can be attributed to low serotonin levels (Vermeiren et al, 2014), that's why SSRI and antipsychotic treatments show positive results on AD, namely anger and anxiety (Rodrìguez et al., 2012). In addition, it was

discovered that the long-term use of SSRIs lowers the risk of developing AD in depressed patients, representing a strategy to prevent AD (Kessing et al., 2009). Not only that: compounds with neuroprotective effects ideally change the progression of the disease, preventing the cell death or facilitating the recovery. For instance, 5-HT6 receptor antagonist P7C3 induces neurogenesis by inhibiting Aβ-amyloid toxicity (Geldenhuys et al., 2011), while 5-HT4 receptors have a role in modulating Aβ-amyloid by increasing APP precursor protein's levels in the hippocampus and cortex.

In association to cognitive decline, also extrapyramidal and behavioral symptoms are typical of AD patients, involving the dopamine (DA) dysfunction. Usually, in AD, a reduction of dopamine, DA metabolites and receptors can be observed. On the contrary, particularly in agitated and aggressive patients, it's possible to find an increase in DA neurotransmission. Indeed, in the Behavior and Psychological Symptoms of Dementia (BPSD), as defined by the International Psychogeriatric Associations, it's possible to find a positive association between polymorphisms of genes encoding for dopaminergic factors and psychosis and aggressiveness in AD patients (Holmes et al., 2001). In addition, the nigrostriatal pathway, deeply involved in the motor control, shows pathological changes, namely the presence of neurofibrillary tangles and Aβ plaques, and neuronal loss, but also an increase in DA neurotransmitter, specifically in agitated and aggressive patients. Dopamine is a catecholamine synthesized from tyrosine by the tyrosine hydroxylase enzyme and degraded by the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). The five dopamine receptors D1, D2, D3, D4 and D5 are divided in two families: D1 (that includes D1 and D5 receptors) and D2 (which includes D2, D3 and D4 receptors). Dopamine is produced by nuclei located in the midbrain, in particular in the substantia nigra pars compacta and in the ventral tegmental area, and they send their axons to the dopaminergic tracts, which are nigrostriatal tract, mesolimbic, mesocortical, and tuberoinfundibular tracts. So, while the nigrostriatal is connected to the motor functioning because of its projections to the basal ganglia, mesocortical and mesolimbic tracts project to hippocampus and neocortex and they have a key role in the reward system, but also

in pathological conditions like Parkinson's disease. Dopaminergic system is involved not only in the movement control, but also in the mood control and cognitive functions. Indeed, usually in AD it's possible to find a reduction in D1 and D2 receptors (in the prefrontal cortex and hippocampus), and also in the dopamine transporter and precursor L-DOPA (Storga et al., 1996; Shaikh et al., 2023). In addition, in AD patients there's a dopamine reduction in the CSF. In 2005 it was demonstrated a causative role for amyloid on dopamine dysfunction (Perez et al., 2005), and a role in memory and learning, because a restoration of DA transmission can have benefits on cognitive tasks, like object recognition memory (Guzmán-Ramos et al, 2012). In addition, in 1997 it was also demonstrated a protective role of DA, with anti-oxidant effects on the brain (Yen & Hsieh, 1997; Iuga et al., 2011).

According to the dopamine dysfunction hypothesis, it's possible to identify two mechanisms that are related to the dopaminergic dysfunction: Aβ-amyloid has negative effects on neurotransmission, causing neuronal death in the hippocampus and neocortex. In fact, amyloid can alter the synaptic plasticity, acting as a negative postsynaptic regulator, and it can modify excitatory glutamatergic neurotransmission at the synaptic level, reducing DA release in the prefrontal cortex and hippocampus (Martorana & Koch, 2014). In addition, dopamine receptors D1 and D2 can influence acetylcholine release in the cortex: the stimulation of D2 receptors can negatively impact acetylcholine transmission in the basal cholinergic neurons, while the activation of D1 receptors has the opposite effect of increasing the levels of acetylcholine release (Martorana et al., 2009).

The aim of this thesis is to analyze the available pharmacological treatments that are currently prescribed to AD patients, describing their mechanism of action and their side effects, which include an increased risk of falling. An additional aim is to dissect out their role and potential benefits. It will be also discussed the interaction between the neurotransmission pathways involved in AD underlying behavioral symptoms, like agitation and aggressiveness, and how they are modified by treatments, in order to identify potential new targets of prevention, like positively acting on anxiety.

CHAPTER 1

AD PHARMACOLOGICAL TREATMENTS

1.1) Treatment of cognitive symptoms

Today, there is ongoing research and development in the field of AD treatments, in particular disease-modifying pharmacological treatments. Because of the complexity and the heterogeneity of the disease, to date the approved treatments are effective to manage behavioral and cognitive symptoms typical in AD patients. Cholinesterase inhibitors is the most commonly used class of drugs, as it targets cognitive symptoms: in particular, memory-related symptoms, attention and concentration, and executive functions. Currently, approved cholinesterase inhibitors are donepezil, rivastigmine and galantamine. Another class of drugs is the N-methyl-D-aspartate (NMDA) receptor antagonist: memantine, which also targets cognitive symptoms, in several studies has showed to decrease excitotoxicity and neurodegeneration caused by an excess of glutamate, as will be discussed in the next paragraph (Conti et al., 2023). Moreover, antipsychotics, usually used to treat psychiatric disorders like bipolar disorder and schizophrenia, can have benefits on AD in order to manage behavioral and psychological symptoms. Benzodiazepines (BDZ) are sometimes used as an alternative to antipsychotic drugs. As a result of their high side effects like falls and cognitive deficits, is acceptable only an occasional use of BDZ in cases of extreme behavioral symptoms like agitation or aggression (Davies et al., 2018).

In 2014 it was also demonstrated a role of antidepressants, in particular Citalopram, to treat agitation in AD patients, but its practical application is limited because of its effects on cognition and cardiac system (Porsteinsson et al., 2014).

1.1.1) Galantamine

Galantamine is an alkaloid extracted, for the first time, in the 1950s from plant sources to treat neuropathic and paralytic diseases. Only in 1990s were discovered its acetylcholinesterase (AChE) inhibiting properties, opening the gates to new applications in the medicine field, for example in AD and Parkinson's disease. Indeed, in 2001 it was approved by the Food and Drug Administration (FDA) to treat AD patients' symptoms in the stages from mild to moderate AD. Typically, as said before, in AD patients the loss of cholinergic neurons in the basal forebrain is responsible for loss of memory and learning abilities, and correlates with the severity of dementia (Kalola & Nguyen, 2023). Galantamine's functioning includes the inhibition of the enzyme AChE in order to increase the availability of acetylcholine in the synaptic gap, by reducing the catalytic hydrolysis of acetylcholine, eventually compensating for the cholinergic impairment (Pesaresi et al., 2022). Indeed, galantamine is a selective, reversible and competitive inhibitor of AChE with a dual mechanism of action: it increases the acetylcholine neurotransmission, but also it directly modulates the nicotinic acetylcholine receptors (nAChRs), which have a role in cognitive processes too, and influence neuroinflammatory pathways (Mitra et al., 2020). In particular, presynaptic α7 nicotinic receptor's expression modulates astrocytes, microglial cells and anti-inflammatory cytokines, resulting in potential modulation of inflammatory responses. When its expression is altered, it contributes to the development of different pathologies (Piovesana et al., 2021). Moreover, nAChRs control the release of various neurotransmitters like Gamma-Aminobutyric Acid (GABA), glutamate, dopamine and serotonin, associated to memory, thinking and learning processes. Galantamine is an allosteric potentiator that binds to nAChRs in the allosteric site, triggering changes of the receptor that leads to an increase of the acetylcholine release, and augments the activity of serotoninergic and glutamatergic neurons. As a result, the cholinergic transmission is facilitated and the synergic action of other neurotransmitters may contribute also to behavioral symptoms typical in AD patients, like anxiety, agitation/aggression, disinhibition and hallucinations (Kalola & Nguyen, 2023).

Galantamine and, generally, all the cholinesterase inhibitors, are commonly prescribed for mild-to-moderate AD patients for a short-term use, nearly for less than one year (Hager et al.,2016) because it was demonstrated that its effects persist up to 5 years after the treatment (Hong et al., 2021). Compared to other AChEIs like rivastigmine and donepezil, galantamine was linked with the highest reduction in the risk for death and for severe dementia. However, as the disease progresses, cholinesterase inhibitors may lose their effectiveness because of the loss of cholinergic neurons, which results in a decreasing ability to create and use acetylcholine (Chen et al., 2022). Indeed, cholinesterase inhibitors can strengthen memory and cognition, but they can't prevent AD from destroying brain cells. As the disease progresses, usually other categories of drugs are prescribed, like glutamate regulators (in particular, memantine), which confers neuroprotection against glutamate-induced neurotoxicity in AD, due to the excessive activation of glutamate receptors (Kutzing et al., 2014).

1.1.2) Rivastigmine

Rivastigmine is a non-competitive, pseudo-irreversible, carbamate inhibitor of acetylcholinesterase that was developed in 1985, it is a semi-synthetic derivate of physostigmine, and was approved by the Food and Drug Administration (FDA) in 1997. In comparison to galantamine, rivastigmine also acts on butyrylcholinesterase (BuChE), a cholinesterase enzyme found in the glial cells (Patel & Gupta, 2023). Both in AD and Parkinson's disease, the upregulation of cholinesterase enzymes can be inhibited by both galantamine and rivastigmine, specifically in dementia. In particular, in mild to moderate AD dementia, patients showed significant improvement in cognitive performances with long-term rivastigmine treatment (Patel & Gupta, 2023). As rivastigmine is a dual inhibitor, it can provide longer sustained effects rather than selective inhibitors, and it can also prevent the formation of amyloid proteins by increasing in α-secretase that cleaves APP, enhancing neuronal activity (Ray et al., 2020). In addition, by improving mitochondrial enzyme activities, rivastigmine can also reduce oxidative stress in brain regions like striatum, cortex and hippocampus (Aborode et

al., 2022). Rivastigmine also showed to be effective for the improvement of behavioral and psychiatric symptoms of dementia (BPSD) in AD, Parkinson's disease and in dementia with Lewy bodies (DLB) (Kim et al., 2015).

1.1.3) Donepezil

Donepezil is a rapid, reversible and centrally active AChEI approved for AD treatment in mild, moderate and severe phases. Indeed, a combination of donepezil and memantine can improve cognition and behavior in moderate-to-severe AD dementia. Donepezil is also useful to reduce sedation associated with the analgesic use of opioids, and can improve outcomes in delirium due to dementia (Kumar et al., 2023). As rivastigmine, donepezil also has positive effects on both cognitive and behavioral symptoms in dementia with DLB, and can improve memory dysfunction in patients with traumatic brain injuries and it can enhance cognition in vascular dementia. In addition, it can improve executive functioning in dementia associated with Parkinson's disease (Kumar et al., 2023).
Donepezil has both cholinergic and noncholinergic mechanisms of action: indeed, donepezil upregulates also nicotinic receptors in cortical neurons, protecting against glutamate neurotoxicity and controlling cell survival (Kumar et al., 2023). In addition, donepezil inhibits the production of inflammatory cytokines induced by activated microglia, due to the formation of Aβ-amyloid, in hippocampal cells (Kim et al., 2014).

1.1.4) Memantine

Memantine is an antagonist of the NMDA receptors, which are ligand-gated cation channels activated by the excitatory neurotransmitter glutamate, preventing the over-activation of glutamine receptors. Indeed, an excessive activation of NMDA receptors would give rise to excitotoxic neuronal death, resulting in an excessive influx of calcium through the receptor's associated ion channel (Parsons et al., 2013). The accumulation of calcium leads to production of excessive

enzymatic processes and free radicals that would contribute to cell death. The mechanism of action of memantine is distinct from the cholinesterase inhibitors: indeed, memantine is proposed to be neuroprotective, in particular in moderate-to-severe AD dementia. Memantine is an uncompetitive antagonist that blocks the receptor-associated ion channels when they are excessively open, while it doesn't interfere when the synaptic transmission is normal and physiological for neuronal functioning (Kuns et al., 2022). The block of all NMDA receptors activity would, otherwise, give rise to dangerous clinical side effects because glutamate mediates critical synaptic transmission for the normal functioning of the nervous system (Chen & Lipton, 2006). The combined use of memantine and acetylcholinesterase inhibitors may bring additional benefits for the patients, for example acting on long-term behavioral and functional abilities. As will be discussed in the next chapters, memantine is effective in delaying clinical worsening and decreasing behavioral symptoms, like agitation and aggression.

1.2) Treatment of behavioral symptoms: Antipsychotics, Benzodiazepines and Antidepressants

In addition to cognitive and functional impairments, most of AD patients experience mood and behavioral disturbances. As mentioned before, these symptoms are referred as "Behavioral and Psychological Symptoms of Dementia" (BPSD). BPSD include a heterogeneous cluster of symptoms, like agitation, aggression, apathy, depression, anxiety, sleep disturbances, appetitive and motor disorders, hallucinations and delusions (Lee et al., 2023). These symptoms are associated with negative outcomes, for example earlier institutionalization, less quality of life, morbidity and an increased burden for the caregivers. Agitation is the most common and complex behavioral disturbance, that results from a complex interplay of biologic, psychiatric, environmental and neurologic factors that will be explored in the next chapter. ln 2023 the International Psychogeriatric Association (IPA) updated the criteria for the diagnosis of agitation in cognitive disorders, stating that the emotional distress linked to agitation exhibits in excessive motor activity,

verbal aggression and physical aggression, giving rise to significant impairments in the social functioning (IPA, 2023). The first-line treatment of agitation in dementia is usually non-pharmacological, but when it has failed due to limited economical resources, training requirements and staff availability, pharmacological drugs can be prescribed. The FDA approved pharmacological treatments include antipsychotics, antidepressants, anticonvulsants, sedative/hypnotics, anxiolytics and also acetylcholinesterase inhibitors, antagonists of the NMDA receptors (memantine), which will be discussed in a dedicated chapter to treat agitation.

Typical and atypical antipsychotics are widely used to treat agitation and psychosis in AD dementia. Typical antipsychotics, in particular haloperidol, were frequently prescribed in the 1950s to treat schizophrenia and by the 1970s they were a common treatment for the BPSD. Because of their adverse-effect profile, including a higher ratio for mortality for new users of haloperidol, by the 1990s atypical antipsychotics became the preferred option in AD patients (Davies et al., 2018). This category of drugs includes olanzapine, quetiapine, aripiprazole and risperidone, showing efficacy in the short-term management of aggressiveness. Although risperidone shows many beneficial effects, it is often associated to extrapyramidal symptoms, cerebrovascular adverse events and an acceleration in the rate of cognitive decline, compared to placebo (Ballard et al., 2009). According to recent studies, also quetiapine is well-tolerated and doesn't worsen parkinsonism symptoms (Carrarini et al., 2021). Recently, the atypical antipsychotic brexpiprazole is being investigated for agitation in AD patients, as it is already approved for schizophrenia and depressive disorders. Brexpiprazole is a partial agonist of D2, D3 and 5-HT receptors and it showed significant improvement in patients with frequent aggressive behaviors. It is also well-tolerated in comparison to other antipsychotics, with an incidence of emergent adverse events of less than 5% compared to placebo (Lee et al., 2023).

Antidepressants are an alternative pharmacological treatment that has shown positive results in lowering overall patient's agitation and caregiver stress. Citalopram and its enantiomer escitalopram (S-enantiomer), both selective serotonin reuptake inhibitors (SSRIs), are the most significantly

effective and relatively safe 5-HT antidepressant drugs to treat agitation in AD (Chen et al., 2023), with fewer adverse effects than antipsychotic drugs like risperidone (Qasim & Simpson, 2022). Although some studies have shown their efficacy in treating agitation, other antidepressant drugs like mirtazapine, sertraline and trazodone are not significantly efficacious when compared to placebo (Chen et al., 2023). Citalopram has also clinical and functional impact on reducing irritability, anxiety and delusions, but it is also associated to a modest reduction in cognitive function at the dose of 30mg/day evaluated by MMSE test (Porsteinsson et al., 2014), with increased sleep disorders and hallucinations (Lee et al., 2023). It was hypothesized that AD patients with more severe agitation and cognitive impairments have a higher risk of having these side effect, while patients with moderate agitation are more likely to experience benefits from antidepressant treatment (Schneider et al., 2016). Whit respect to citalopram, a racemic mixture of S- and R-enantiomers, the clinical effects are ascribable to the S-enantiomer, while R-enantiomer is associated to citalopram-related adverse effects and it can interfere with the pharmacologic activity of the S-enantiomer (Trkulja, 2010). Pharmacokinetic studies suggest that enantiomers may bind differently to protein or to other tissue receptor sites, resulting in differences in drug effects or distribution (Coelho et al., 2021). As a result, the same company that produced citalopram developed also escitalopram, stating that it is safer and more tolerable than citalopram, because it contains only the S-enantiomer (Trkulja, 2010). While the debate on the superior efficacy of escitalopram compared to citalopram is still under debate, several clinical trials have demonstrated that escitalopram can be considered a legitimate first-line treatment of agitation in AD patients (Ehrhardt et al., 2019). In addition to citalopram and escitalopram, data analysis also suggest that sertraline and mirtazapine have beneficial effects on BPSD symptoms (Carrarini et al., 2021).

With regard to anticonvulsants, carbamazepine, used in many forms of epilepsy, as a mood stabilizer for bipolar disorders and to treat aggressive outbursts in episodic dyscontrol syndrome (EDS), has shown to be effective in the treatment of agitation and aggressiveness in AD patients. However, other studies haven't demonstrated efficacy in the treatment of BPSD symptoms

(Konovalov et al., 2008) because of potential drug-drug interactions and due to its ability to increase the activity of the CYP 3A4 enzyme, which has a critical role in the metabolism of several psychotropic drugs (Davies et al., 2018). An increased metabolism means that the drug is processed more quickly than usual, leading to a decrease in drug concentration levels in the bloodstream, which can affect therapeutic efficacy. Changes in the metabolism of psychotropic drugs can alter drug levels and pharmacological effect (Susa et al., 2023) However, in patients resistant to or unable to take antipsychotics, carbamazepine can be a potential drug, as it has less mortality risk than antipsychotics (Lee et al., 2023).
Moreover, valproic acid also targets BPSD and it is commonly prescribed in people with dementia even though, according to recent studies, the risk of adverse events related to valproic acid are known. Indeed, valproic acid can worsen functional decline and increase brain atrophy (McDermott & Gruenewald, 2019). Both carbamazepine and valproic acid inhibit voltage-gated sodium channels, obstructing the entry of sodium into neurons, leading to decreased neuron excitability and firing rate. In addition, they stimulate the activation of GABA receptors producing a sedative effect (Iannaccone et al., 2021).
Gabapentin, in addition, is a voltage-gated calcium channel blocker developed originally to treat forms of epilepsy, but studies have also demonstrated its effectiveness in the treatment of BPSD and anxiety symptoms. Gabapentin lacks potential cytochrome P-450 pharmacokinetic interactions and it has a high level of tolerability (Davies et al., 2018).

Benzodiazepines (BDZ) also work by enhancing GABA neurotransmission, at the $GABA_A$ receptor. As a result, benzodiazepines produce a sedative and hypnotic effect, but also anxiolytic and anticonvulsant effect, in addition to muscle relaxant properties. Retrospective studies have demonstrated that an exposure to BDZ longer than three months can increase the risk of developing dementia, in particular BDZ with a long half-life, causing a limitation in cognitive reserve capacity (Defrancesco et al., 2015). Instead, BDZ with short half-lives, like oxazepam, have shown positive results in treating agitation in AD. However, it is recommend to prescribe a limited duration of BDZ

treatment, even though their use is often chronic. In details, long-term treatment is associated to a cluster of symptoms which include the risk of drug dependence, behavioral disinhibition, risk of falls, amnesia, confusion, insomnia and adverse drug reactions (Sterke et al., 2012). In addition, BDZ might also increase intraneuronal Aβ-amyloid accumulation (Tampelini et al., 2010), cognitive worsening, especially in the elderly (Tennenbaum et al., 2012) and pneumonia (Rochon et al., 2017). Several studies have shown a significant improvement of acute behavioral disturbances after BDZ use, including agitation: in particular, a randomized and double-blind study of 272 patients in 2002 has demonstrated benefits two hours after an intramuscular administration of lorazepam and olanzapine (Defrancesco et al., 2015). In a review conducted in 2021 by M. Amore and other researchers, were analyzed five prior studies that have shown that the combination of lorazepam and haloperidol is superior to both the agents alone, while another study comparing olanzapine and lorazepam, showed that olanzapine was superior to lorazepam, but both superior to placebo (Amore et al., 2021). Thus, based on the heterogeneous results of the published studies, it can be concluded the occasional use of BDZ is acceptable in cases of extreme and acute agitation or aggressive behavior, and when other interventions are ineffective (Amore et al., 2021).

In order to investigate the role of anxiolytics in AD, a study conducted by Burke et al. in 2018 highlighted that patients with MCI and co-occurring anxiety and irritability have a doubled risk of developing AD-related dementia within a 3-years period, as they have abnormal levels of tau tangles and Aβ-amyloid accumulation in their spinal fluid (Burke et al., 2018). This may be a result of the allostatic load of pathological anxiety which can lead to oxidative stress, synergistically with the risk due to APOE ε4 genotype (Goldstein, 2012). In these patients, anxiolytics like alprazolam, diazepam, lorazepam could moderately reduce MCI and AD development by reducing anxiety. Moreover, the combination of GABAergic agents and antagonists of the glutamate receptor, NMDA, may have positive anxiolytic effects (Zarrabian et al., 2016).

Recently, research on new types of pharmacological treatments for BPSD symptoms has been expanded. Cannabinoids, which activate endogenous CB1 and CB2 receptors that are largely

expressed in the central nervous system, may have positive effects on agitation by increasing serotoninergic signaling, inhibiting glutamate release and acting as neuroprotectors (Lee et al., 2023).

Additionally, a novel sedative-analgesic agent, dexmedetomidine, a selective α_2-adrenergic receptor agonist, has been designed to treat acute agitation in schizophrenia and dementia, without severe adverse effects (Lee et al., 2023).

Furthermore, the antitussive dextromethorphan, modulates glutamatergic neurotransmission by acting as high affinity σ-1 receptor agonist, by inhibiting presynaptic glutamate release, by acting as low affinity NMDA receptor antagonist, and by modulating post-synaptic glutamate response (Kongpakwattana et al., 2018; Lee et a., 2023). Additionally, it is an inhibitor of serotonin and norepinephrine and it is a nicotinic receptor antagonist (Lee et al., 2023). Usually, it is combined with bupropion, an antidepressant, or quinidine, an antiarrhythmic, to prevent CYP-450 metabolism, increasing its bioavailability to treat agitation and depressive disorders (Parincu & Iosifescu, 2023; Lee et al., 2023).

Masupirdine is an antagonist of the serotonin 5-HT6 receptor, used to treat cognition disturbances and agitation/physical aggression in patients with moderate AD (Nirogi et al., 2022), concomitantly treated with donepezil and memantine.

Recent neurobiological studies have suggested that aggressiveness related to dementia may involve enhanced responsiveness to norepinephrine at the α1-adrenoreceptor. As a result, prazosin, an antagonist of α1-adrenoreceptor, may reduce agitation by decreasing excess activity of norepinephrine (Tampi et al., 2022).

In conclusion, while the availability of actual pharmacological therapies is still limited, due to side effects, advances in diagnostic and therapeutic fields have been remarkable. Indeed, the pathogenic mechanisms of agitation and aggressiveness in AD still remain elusive, but recent pharmacological intervention studies are promising, and lay the bases for the development of safe, well tolerated and efficacious medications for BPSD symptoms.

CHAPTER 2

SIDE EFFECTS OF AD PHARMACOLOGICAL TREATMENTS

In some cases, side effects related to pharmacological treatments get better after two weeks of taking the medication, while in some other cases drugs can potentially be life-threatening. That's why it's necessary to keep monitored with routine MRI and functional magnetic resonance imaging (fMRI), that can detect brain changes after a short period of treatment, in particular by showing how they modulate brain areas and networks. Indeed, fMRI allows to observe cerebral functions during the performance of specific tasks and in task-free approaches in resting-state (Canu et al., 2018). While task-based studies have limitations due to the type of task, the severity of the cognitive impairment and the patient's attention and motivation, resting-state techniques are useful to measure functionally-related brain regions at rest (Grieder et al., 2018). This method can be used to measure pharmacodynamics changes induced by the use of AD drugs (Goveas et al., 2011), but also to explore how resting state networks like the default mode network (DMN). In particular, the DMN is a set of brain regions related to cognitive functions, that usually increases activity while the subject is not doing tasks and it decreases during cognitive activity (Ibrahim et al., 2021). Several studies have demonstrated alterations of the DMN in AD, especially a moderate decrease of DMN connectivity within the posterior cingulate cortex, the central node of the DMN, reflecting the impairment of cognitive functions, memory and attention that typically occur in AD (Leech et al., 2014).

2.1) Common side effects of AD drugs

Relatively to acetylcholinesterase inhibitors, common side effects are dose-related. Therefore, the prevalence of adverse drug reactions (ADRs) increases with ascending doses and, as a result, doctors usually increase the dosage gradually based on patient's tolerance.

As said previously, current AD typical treatment involves both glutamatergic (memantine) and acetylcholinesterase, the enzyme responsible for the degradation of Ach, inhibitors (AChеIs). The rising use of AChеIs results in increased adverse effects, which include gastrointestinal and cardiovascular adverse reactions, due to overstimulation of central and peripheral cholinergic and muscarinic receptors. Over the last ten years, it was reported an increase of severe adverse reactions up to 50-70%, with a rate of 2,3% of fatal cases (Ruangritchankul et al., 2021). Commonly, 17% of adverse reactions are neuropsychiatric symptoms, while 16,2% are gastrointestinal and 11,2% are cardiovascular (Ruangritchankul et al., 2021). Indeed, the overstimulation of muscarinic and nicotinic receptors is secondary to the inhibition of acetylcholinesterase (Adeyinka et al., 2023). An excessive accumulation of ACh at the neuromuscular junctions and synapses causes toxic symptoms like cramps, nausea, tremor, insomnia and vagotonic effects like bradycardia and syncope (Lott et al., 2022). The toxicity related to AChеIs is dose-related, and they present a narrow therapeutic index (Ruangritchankul et al., 2021). Regarding to gastrointestinal adverse effects, the oral administration of AChеIs increases gastric acid secretion of hydrochloric acid, that can lead to gastrointestinal ulceration and bleeding, especially when there is concomitant use of AChеIs and non-steroidal anti-inflammatory drugs (NSAID), that can cause mucosal injury by reducing a protective bicarbonate mucus barrier in the stomach and small bowel, due to cyclo-oxygenase inhibition that reduces prostaglandins production (Ruangritchankul et al., 2021).

Cardiovascular side effects are caused by an increase in the availability of choline in the heart and vagotonic effects via muscarinic receptors (Ruangritchankul et al., 2021). As a result, older patients treated with AChеIs are more prone to develop conduction dysfunction that can increase mortality risk. Sinoatrial and atrioventricular block, severe sinus bradycardia, atrial arrhythmias and QT interval prolongation are uncommon cardiac side effects, which can all result in adverse health outcomes, which include syncope, hospitalization, falls, fractures and pacemaker insertion (Ruangritchankul et al., 2021).

Neurological side effects usually result from excessive activation of nicotinic receptors, causing dizziness, dyskinesia, convulsion, vivid dreams and muscle cramps. While convulsions are very

rare, they can be caused by metabolic and nutritional disorders such as hyponatremia (Ruangritchankul et al., 2021). Moreover, bronchospasms can be considered as pulmonary side effects of ACheIs, in addition to urinary incontinence and irritant contact dermatitis due to local skin patches of rivastigmine (Ruangritchankul et al., 2021).

Furthermore, pharmacokinetics and drug-drug interactions are risky factors of developing adverse reactions to AChеIs. With regards to pharmacokinetics, age-related changes in absorption, distribution, metabolism and excretion play an important role in clinical outcomes. Specifically, gastrointestinal changes like hypochlorhydria and reduced blood flow can slower oral absorption of AChеIs. Moreover, changes in body composition in older patients, in terms of reduced muscle mass and increased body fat, can impact the volume of distribution AChеIs. Additionally, the CYP enzyme system, responsible for drug metabolism, undergoes age-related changes, resulting in higher concentrations of AChеIs in patients due to reduced metabolism. Decreased renal function, typical in older AD patients, can also impact drug excretion and cause prolonged drug half-life (Ruangritchankul et al., 2021).

Regarding to drug-drug interactions, pharmacoepidemiologic studies have also revealed that anticholinergics, antidepressants, cardiovascular drugs, antipsychotics and NSAIDS are common co-medications prescribed with AChеIs, and the concomitant use can be associated to psychodynamic drug interactions. In particular, the use of anticholinergic and antipsychotics in patients that already present a reduction in the number of cholinergic and dopaminergic neurons, may interfere with the activity of AChеIs. In fact, anticholinergic drugs inhibit cholinergic activity by blocking the action of acetylcholine at muscarinic receptors, while AChеIs increase acetylcholine levels, giving rise to opposite effects on the cholinergic system and leading to side effects, including further impaired cognition in AD patients and 18% of increased risk to experience falls (Carter et al., 2021). It is also known that patients that assume both AChеIs and risperidone often manifest rigidity and parkinsonism symptoms, which disappear after risperidone discontinuation (Ruangritchankul et al., 2021). Furthermore, the concomitant use of beta-blockers,

calcium channel blockers or antiarrhythmics and ACheIs, may result in cardiovascular effects like bradyarrhytmia, syncope and QT prolongation (Young et al., 2021).

Instead, several studies have demonstrated that memantine-related side effects are less common and less severe with respect to cholinesterase inhibitors. Indeed, it is usually well tolerated, even though it can increase dizziness, vertigo, fatigue, insomnia, headaches and muscle cramps (Alva & Cummings, 2008). W ith respect to the mechanism through which memantine may cause dizziness, the main adverse effect, it is hypothesized that it is related to its modulation of glutamate transmission, involved in the regulation of neuronal excitability. Memantine, as an NMDA receptor antagonist, works by blocking the excessive glutamate activity present in AD. As a result, the balance of excitatory neurotransmission can be altered, affecting the processing of sensory information related to balance and spatial orientation (Limòn et al., 2021). Although memantine has some side effects, it is the only NMDA antagonist that has passed phase III clinical trials and is commercially available for treatment (Tang et al., 2023). Moreover, the combination therapy of memantine and the AChеIs has shown superior clinical efficacy in terms of cognitive symptoms, daily activities, global assessment and neuropsychiatric symptoms (Guo et al., 2020). Indeed, the extended-release memantine treatment demonstrated significant benefits on behavioral symptoms like agitation/aggression, irritability, delusions and nighttime behaviors, typically associated with increased severity of dementia, in addition to improvements in semantic fluency (Kishi et al., 2017). Glutamate plays a role also in the development of anxiety. A balance is generally maintained between gabaergic and glutamatergic transmission. This GABA-glutamate balance, which typically consists of low levels of GABA and normal-to-high levels of glutamate, also plays a role in the development of generalized or social anxiety disorders. Sometimes, sedative drugs that are responsible to increase GABA, such as diazepam, are used to raise GABA in order to optimize the balance between the stimulatory glutamate and inhibitory GABA. Given memantine's capacity to lower glutamate activity, memantine may also be able to lower anxiety levels, without the need for

a sedative medication. Lowering glutamate levels may allow to GABA levels to be more effective in controlling and reducing generalized or social anxiety disorder symptoms (Schwartz et al., 2012)

Regarding to Antipsychotics which, as said before, are the first-line pharmacological treatment for the neuropsychiatric symptoms of AD, the efficacy is limited due to their association with the risk of several adverse outcomes. Indeed, they can increase the risk of mortality in patients with dementia, and they are often associated with pneumonia, cerebrovascular events, thromboembolism and parkinsonian symptoms (Rogowska et al., 2023). Antipsychotics have also been associated with an elevated risk of depending on long-term care and institutionalization. First generation antipsychotics (FGA), act on the D2 receptors in the mesolimbic system: while managing agitation and aggressiveness, acting on the dopaminergic pathways can cause side effects like extrapyramidal symptoms, emotional numbing and hyperprolactinemia. (Rogowska et al., 2023) Instead, second generation antipsychotics (SGA), while they act on D2 receptors too, they have a wider receptor building properties such as serotoninergic, muscarinic, histaminergic and adrenergic receptors. Indeed, this class of antipsychotics is less associated to dopaminergic side effects and to a minor mortality risk, but the main effects are linked to sedation, weight gain, blood glucose and lipid-related abnormalities. (Rogowska et al., 2023).
In particular, brexpiprazole, the SGA drug described in the previous chapter, has shown a modest therapeutic effect during trials of 12 weeks (Stummer et al., 2020; Grossberg et al., 2020), but it is also frequently associated to side effects like somnolence, dizziness and headaches, while extrapyramidal effects are not significant (Rogowska et al., 2023). Instead, haloperidol, an FGA drug, has been linked to a higher mortality risk compared to placebo, due to stroke and fractures (Ralph et al., 2018). Indeed, American Psychiatric Association (APA) established that haloperidol's use should be reserved for emergencies and delirium only (APA, 2016).

Moreover, the co-prescription of antipsychotics and other medications like antihypertensives and antidiabetics, can increase the risk of cardiovascular mortality, due to lower blood pressure that can cause falls, while the interactions with antidepressants, benzodiazepines and acetylcholinesterase

inhibitors increase the mortality risk, and it augments as the number of interactions increases, causing sedation, cytochrome P-450 inhibition and anticholinergic effects (Liperoti et al., 2017). However, several studies demonstrated that mortality risk is highest at the beginning of treatment, gradually lowering after three and six months of treatment (Maxwell et al., 2018). Furthermore, factors like male sex, dementia diagnosis at a younger age and the severity of symptoms can increase mortality risk (Nielsen et al., 2017).

Additionally, pneumonia and venous thromboembolism can be associated to the use of antipsychotics, due to their effects on D2, cholinergic and histamine receptors, leading to extrapyramidal side effects, sedation and altered movements (for example, dyskinesia). These factors, combined with changes in pulmonary secretion in older people, can result in pneumonia (Rajamaki et al., 2020), while muscle rigidity and prolonged bedridden, related to the blockage of nigrostriatal D2 receptors, can increase the risk of vein thrombosis and pulmonary embolism, (Beeber et al., 2022).

In conclusion, antipsychotics are also linked to an accelerated cognitive decline in patients with mild to moderate AD, and the risk increases if the patients are APOE ε4 carriers (Dyer et al., 2021), while a study conducted in 2020 found an association between the use of antipsychotics and the risk of head injuries in the first three months of treatment, due to orthostatic hypotension and sedation (Tepiainen et al., 2020).

Among the non-antipsychotics drugs, SSRIs like citalopram and escitalopram are usually well tolerated with minimal effects on other neurotransmitters, such as dopamine, noradrenaline and norepinephrine. Indeed, unlikely other antidepressant classes like noradrenaline and dopamine reuptake inhibitors (NDRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), citalopram and escitalopram have minimal effects on other neurotransmitters, mostly due to their selectivity for the serotonin transporter, that reduces the risk of side effects associated with the modulation of multiple neurotransmitters (Chu et al., 2024). To compare citalopram and risperidone for the treatment of psychotic symptoms and agitation, a study conducted with 103 patients in 2007

demonstrated that all the patients, divided in two groups, had a significant improvement in agitation and psychosis, suggesting that citalopram and risperidone had similar efficacy, but side effects were significantly higher in the patients treated with risperidone (Pollock et al., 2007). An American study in 2014 evaluated citalopram-related effects for 9 weeks in comparison to placebo, increasing weekly the dosage and permitting the concurrent administration of cholinesterase inhibitors and memantine. Patients with dementia had a mean age of 78, diagnosed with dementia since 5 years and with a MMSE score of 17 (Pollock et al., 2007). Results suggest that by week 9, 80% of patients remained on treatment, indicating a high tolerance linked to citalopram, of which 40% had a significant improvement in symptoms. (Pollock et al., 2007) A re-analysis of these findings suggested that the predictors of best response to citalopram treatment were patients with an MMSE score between 21-28 (mild to moderate dementia) with an age of 76-82 years without acute agitation (Aga et al., 2019). Moreover, this study highlighted that citalopram, in comparison to quetiapine and olanzapine, was the most effective medication, with less side effects such as the occurrence of falls, hypotension and hospitalizations (Aga et al., 2019). Additionally, patients treated with citalopram were less likely to manifest new-onset anxiety, irritability and delusions, in particular if the treatment is continued for 9 weeks at least.

An analysis conducted on cases reported to the American Poison Control Center during the period 2000-2014, with the aim to define the mortality index and serious outcomes related to antidepressants, emphasized that citalopram has a lower mortality risk even at high doses, but in comparison to other SSRIs, it was associated to higher rates of cardiac conduction disturbances, seizures and electrolyte disturbances, even though most of the patients showed a benign side effects, including fever and weight loss, while only 16,7% of patients had falls (Nelson & Spyker, 2017).

The main adverse effects related to citalopram are cardiac conduction disturbances, in particular dose-dependent QT prolongation. Indeed, it is a measure of delayed ventricular repolarization. In particular, it represents the time from the onset of ventricular depolarization to the end of ventricular r repolarization, and it is measured by using an electrocardiogram (ECG). As the QT

interval increases, also the risk of arrhythmias increases, as a result of the heart muscle that takes longer than normal to recharge between beats (Danese et al., 2019). Pharmacodynamics' effects can impact the QT interval: this process involves not only citalopram, but also the co-administration of escitalopram and haloperidol that can have a role in drug interactions. On the other hand, pharmacokinetics refers to drugs that don't directly prolong the QT interval, but they have an impact on the clearance reduction and metabolism of a drug, which can ultimately lead to the prolongation of the QT interval (Nelson & Spyker, 2017). Moreover, citalopram can cause electrolyte changes, specifically affecting potassium levels, that can increase the risk of QT prolongation. This phenomenon is often dose-dependent, and it assumes greater importance in older people, as the concentration-to-dose ratio of citalopram doubles by the age of 65 and rises rapidly after the age of 80 (Aga et al., 2019). To prevent mortality, it is necessary to assess risks and to take corrective action: indeed, citalopram should be avoided in patients with bradycardia, congenital long QT syndrome or with recent myocardial infarction (Aga et al., 2019). Additionally, in 2015 the FDA added to the list of adverse effects of donepezil the risk of QT prolongation: as a result, if a patient is already on citalopram, donepezil should be avoided (Aga et al., 2019). Furthermore, as will be discussed later, bradycardia can occur with all cholinesterase inhibitors. In conclusion, for patients above the age of 60 years, doses of citalopram above 20 mg/day should be considered risky, while the recommended dose is 10 mg/day (Aga et al., 2019). Escitalopram, in comparison to risperidone and other SSRIs, was found to produce fewer adverse effects and to be more effective to treat agitation, even in short-duration trials, as it has a faster onset of action (Wang et al., 2018). Escitalopram may prolong the QT interval too but, according to the American Poison Control Center, it is four times less fatal than citalopram when patients are exposed to high doses, but its serum concentration-to-dose ratio is similar to citalopram one, so it is recommended a minimum effective dose of the drug. While the question of whether QT prolongation may be a class adverse effect that involves all SSRIs remains unanswered due to lack of sufficient evidence, it is known that all SSRIs are associated to night-time behaviors, in particular REM-sleep disorders (Wichniak et al., 2017).

Despite known harms, benzodiazepines (BDZs) continue to be used to treat neuropsychiatric symptoms associated with AD dementia. While clinicians tend to avoid prescribing benzodiazepines, in long-term care facilities the rate of benzodiazepine use is more than 30%, according to a Canadian study (Ma et al., 2019). BDZs are linked to well-documented harms, which include injuries due to falls, pneumonia and cognitive worsening, especially in already vulnerable patients (Rochon et al., 2017). In particular, pneumonia can be severe enough to result in hospital admission or death, with an higher risk within the first 30 days of treatment (Rochon et al., 2017). The mechanisms that support the connection between BDZs and pneumonia are several: BDZs produce sedation, which leads to hypoventilation. Moreover, BDZs can lead to reflux and aspiration due to a lowered pressure in the esophagus. BDZs can also suppress immune function, contributing to pneumonia risk (Rochon et al., 2017). The prolonged use of BDZs, specifically over 2 months, can cause also tolerance and dependence, due to an extension of drug half-life caused by a decrease of oxidative metabolism, typically associated with old age. Recent studies also reported that adverse effects of BDZs outweigh the benefits, especially in people older than 60 years. As a result, the use of BDZs should be avoided, or limited to short and specific situations (Rochon et al., 2017). Furthermore, elderly long-term consumers of BDZs show limited cognitive reserve capacity, due to BDZs' mechanism. Indeed, BDZs are positive $GABA_A$ receptor modulators, causing a decrease in brain activation and reduced synaptic plasticity, due to an interference in the functioning of excitatory synapses, which can affect cognitive functions and memory formation (Sakimoto et al., 2021). Another potential mechanism underlying the deleterious effects of BDZs on cognitive processes is related to the depolarization and depressive action of BDZ agonists, that can lead to brain energy metabolism deficit, in particular a diminution of glucose utilization in the brain (Ettcheto et al., 2020). For example, diazepam, lorazepam and oxazepam have anticonvulsant properties and are GABA agonists, which can cause a decrease of glucose utilization, while flumazenil, an antagonist of BDZs, increases glucose use (Ettcheto et al., 2020). A study conducted in 2019 also reported that midazolam, a BDZs agonist often prescribed as an anxiolytic drug, can increase significantly hippocampal tau phosphorylation (Whittington et al., 2019). This result

suggests that BDZs can be involved in the increase of AD development. Indeed, tau protein can be involved in the regulation of brain insulin signaling, that has a fundamental role in cognitive processes (Gonçalves et al., 2019). According to a 2011 study, APOE allele carriers can also be more sensitive to cognitive adverse effects of acute doses of BDZs which, as a consequence, shouldn't be prescribed in those patients (Ettcheto et al., 2020). Despite these negative effects, it can be hypothesized that BDZs can improve sleep quality and protect against the development of AD, as sleep disturbances can increase oxidative stress and an accumulation of amyloid due to neuroinflammatory processes (Ettcheto et al., 2020). Additionally, insomnia is often linked to hypertension and diabetes, which all contribute to AD development (Sadeghmousavi et al., 2020). Moreover, the enhancement of $GABA_A$ activity can inhibit glutamatergic neurotransmission, protecting against the excitotoxic effects of glutamate induced by amyloid (Allen et al., 2023). Indeed, amyloid may have indirect effects on the GABAergic inhibition pathways, by influencing the balance between inhibitory GABAergic transmission and the cholinergic and glutamatergic excitatory pathways (Nava-Mesa et al., 2014). Indeed, in 2010 it was suggested that the imbalance between excitatory and inhibitory systems underlies the synaptic dysfunction caused by amyloid. As a result, in order to compensate for aberrant increase in neuronal excitability, GABA enhances synaptic inhibition. As a result, $GABA_A$ agonists may have nootropic and neuroprotective effects (Nava-Mesa et al., 2014).

With regards to anticonvulsants, the risk of pneumonia is increased with the use of carbamazepine, valproic acid and gabapentin, specifically in older patients with AD. This effect may be related to sedative properties of these drugs, that increases aspiration risk. Even though these side effects are more prominent in early treatment, somnolence is also another common symptom. However, low doses of carbamazepine and valproic acid are effective in the treatment of BPSD symptoms. However, anticonvulsants are not first line treatments, also due to their drug interactions, as described in the previous chapter (Taipale et al., 2019).

The growing interest in the use of cannabinoids derives from the anxiolytic, antidepressant and anti-inflammatory effects that these compounds have shown. They can regulate neurotransmission and

circadian rhythms in agitated AD patients, while increasing cerebral circulation. However, the use of cannabinoids should be considered cautiously: indeed, high doses of cannabinoids can give rise to anxiogenic effects and potential drug addiction. Moreover, some cannabinoids, such as cannabidiol (CBD), are inhibitors of multiple cytochrome P-450 enzymes, potentially leading to altered blood levels and effects on the drug metabolism (Outen et al., 2021).

2.2) Increase of fall risk in vulnerable patients

AD patients have a high mortality rate, in particular due to cardiac failure and myocardial infarction. Dysautonomia, which is common in older people with neurodegenerative dementias, might lead to worse outcomes, as it manifests with orthostatic hypotension, syncope, falls and urinary tract symptoms (Tulba et al., 2020). Orthostatic hypotension, in particular, manifests with weakness, dizziness and fatigue and is caused by an extremely low heart rate (bradycardia) that can lead to low blood pressure (Lei et al., 2020). The most common autonomic dysfunction occurs in the cardiovascular control sphere and consists of an abnormal vasovagal response that leads to syncope (Sànchez-Manso et al., 2023). Several studies have investigated this aspect, suggesting that dysautonomia might occur before the onset of the clinical symptoms of dementia. Usually, dysautonomia worsens as the dementia advances, because recurrent episodes of hypotension and cerebral hypoperfusion can result in neuronal injury (Sànchez-Manso et al., 2023). Dysautonomia, that is mediated by the autonomic nervous system (ANS), arises in AD patients as a result of an impairment in the ANS by neuroanatomical lesions and neurochemical changes, and may be related to any disease that affects the peripheral or central components of ANS (Sànchez-Manso et al., 2023). Indeed, in addition to the impairment caused by amyloid and tau, the peripheral nervous system in AD has a role in autonomic dysregulation, as patients manifest less baroreflex sensitivity and decreased heart rate variability (HVR). HVR correlates with blood levels of acetylcholinesterase activity, suggesting that higher levels of acetylcholinesterase may be associated with a reduction in parasympathetic activity. This correlation may indicate that changes in

acetylcholinesterase levels could reflect an autonomic imbalance between the sympathetic and parasympathetic branches, leading to altered HVR that may aggravate heart diseases (Sànchez-Manso et al., 2023).

2.2.1) Bradycardia: a side effect that involves the Autonomic Nervous System (ANS)

The risk of falls and syncope, that is already high in AD patients due to dysautonomia, can also be worsened by the use of ACheIs. Indeed, increased levels of acetylcholine can augment parasympathetic tone in the sinoatrial node, slowing the sinus rate and electrical conduction (Young et al., 2021). The dose-dependent risk of bradycardia can also cause or contribute to syncope, in particular when and AcheI is administered at high doses. In addition, other ANS-related symptoms can occur in patients treated with AChelIs such as dizziness, syncope, atrial arrhythmias, myocardial infarction and sinoatrial and atrioventricular block (Young et al., 2021). Patients taking these drugs are in general old and vulnerable to age-related changes that can predispose them to orthostasis and syncope, abnormal baroreceptor and autonomic function and myocardial dysfunction. Moreover, when patients present pre-existent cardiac disease, AChelIs can give rise to bradycardia, or interact with concurrent medications like beta-blockers, calcium channel blockers, and anti-arrhythmic medications (Young et al., 2021). More serious complications of syncope and falls, like fractures or head injuries, can lead patients' hospitalization of even death (Young et al., 2021). To explore further the physiology of the autonomic nervous system (ANS), ANS is a subcomponent of the peripheral nervous system that regulates involuntary physiologic processes including heart rate, blood pressure, respiration and digestion (Waxenbaum et al., 2023). Along with the ANS, which has fast-acting and short-lived effects, the endocrine system coordinates the body's functions to maintain homeostasis during rest and exercise and to initiate and control movement thanks to its slow-acting and long-lasting effects (Waxenbaum et al., 2023). In particular, ANS serves as a control center for heart rate regulation: indeed, two branches of the ANS, the sympathetic and the

parasympathetic ones, work together balancing the heart rate and promoting homeostasis. The enteric nervous system, which works independently, is also part of the ANS, and is responsible for regulating digestive processes (Waxenbaum et al., 2023). Both sympathetic and parasympathetic systems contain afferent fibers that provide sensory input and efferent fibers that provide motor output to the central nervous system (Waxenbaum et al., 2023). Parasympathetic branch, in particular, releases acetylcholine at synapses with cardiac muscle cells and lowers the heart rate during times of rest (Gordan et al., 2015). When the parasympathetic nervous system, via the vagus nerve, increases in activity, bradycardia can occur (Capilupi et al., 2020). Focusing on the vagus nerve afferent activation, which originates peripherally, it can modulate efferent sympathetic and the parasympathetic functions centrally and at the level of the baroreceptor. ACh release from parasympathetic nerve terminals activates preganglionic nicotinic receptors that, in turn, activate postsynaptic muscarinic receptors (LeBouef et al., 2024).

2.2.2) The role of cholinergic system in heart rate and emotion regulation

ACh functions as a neurotransmitter in both the central nervous system and the peripheral nervous system. Focusing on the peripheral nervous system, acetylcholinesterase inhibitors prevent the normal breakdown of ACh, leading to an accumulation in the synaptic cleft, resulting in an increased parasympathetic activation (Colovic et al., 2013) The vagus nerve is responsible for the release of ACh to regulate heart rate and the excess of ACh caused by the activity of ACheIs activates muscarinic receptors in the pacemaker cells of the heart, in particular in the sinoatrial node (Liu et al., 2019; Ann Geriatr Med, 2021). Stimulation of muscarinic receptors in the sinoatrial node promotes the release of potassium ions that, in turn, causes hyperpolarization of the cell membrane (Dhein et al., 2001). As a result, hyperpolarization indirectly affects sodium channels, reducing their opening, and inducing the depolarization of the cardiac cells (Scicchitano et al., 2012). Calcium channels are modulated too: calcium influx in the presynaptic terminal triggers the release of the neurotransmitter ACh into the synaptic cleft and when ACh binds to muscarinic receptors, calcium

channels in the cardiac cells are modulated in terms of intracellular calcium levels (Soukup et al., 2017). As a result of this hyperpolarization process of the cells in the sinoatrial node, there is a decrease in the heart rate in generating electrical impulses, and the heart rate slows down, leading to bradycardia (Verkerk et al., 2013).

Moreover, autonomic dysfunctions can lead to an impairment in the heart rate variability (HVR), which is considered an index of autonomic nervous system functioning, as it reflects the balance between the sympathetic and parasympathetic processes. It also works as an indicator of integrity of the prefrontal cortex, limbic and brainstem regions, because it is involved in both autonomic nervous systems and top-down processes (Liu et al., 2023). HVR is managed by parasympathetic autonomic nervous system and higher levels of HVR, which correspond to effective regulation of vagal tone, and indicate adaptability to external stimuli (Liu et al., 2023). Lower levels of HVR, instead, are related to higher levels of psychopathology, worse cognitive functioning and neurodegenerative diseases can further alter it. Executive function and emotion regulation ability in patients with dementia, are reflected in the differences in HVR and it is hypothesized that these two processes underlie the development of neuropsychiatric symptoms, in particular agitation (Liu et al., 2023).

To test the hypothesis that HVR is a marker of agitation, a study conducted in 2023 investigated a composite number of subscales of agitation, including disinhibition, aggressiveness, irritability and aberrant motor behavior, which all together contribute to a broader agitation measure (Liu et al., 2023). Additionally, to understand if the association between HVR and agitation is related to mood disorders, psychosis or dysexecutive syndrome, were included in this study these three neuropsychiatric subscales (Liu et al., 2023). Results suggest not only a positive correlation between HRV and agitation solely due to AD, but also that agitated individuals, compared with non-agitated ones, were more prone to show a decline in HVR measures at follow-up (Liu et al., 2023). Moreover this study demonstrated that a decline in HVR values can be observed with normal aging, and authors also stated that the strongest influence of AD degeneration on autonomic system dysfunction was related to the locus coeruleus (LC) noradrenergic system. Indeed, LC is one of the

brain areas primarily affected by AD pathology. LC also plays a role in the autonomic nervous system by upregulating cortical arousal, increasing sympathetic nervous system activity and reducing parasympathetic activity in response to stress (Samuels et al., 2008). In AD, indeed, the loss of LC neurons results in increased parasympathetic processes and reduced sympathetic activity (Samuels et al., 2008). Furthermore, acting as a compensatory process to AD-related LC cells loss, the LC-noradrenaline system hyperactivity possibly predisposes to agitation by an impaired cortical and subcortical regulation of behavior, for example via prefrontal cortical compensatory processes induced by sympathetic hyperactivity (Cassidy et al., 2022). Moreover, results are consistent with the hypothesis that a general decline of HVR levels typically occurs with natural aging and reflects the dementia severity, suggesting that HVR levels changes can be a marker of agitation, and AD progresses. Finally, authors observed a positive relationship between increased HVR change with frontal subscale, that includes apathy, disinhibition and irritability, but not with mood or psychosis, supporting the involvement of frontal self-regulation dysfunction in agitated patients (Rosenberg et al., 2015).

CHAPTER 3

AGGRESSIVENESS AND AGITATION IN AD PATIENTS

3.1) Causes, predictors and management of behavioral disturbances in AD

Behavioral alterations are frequent in all major types of dementias, however, in AD, they are common in every stages of the disease, with a prevalence of 80-90%. According to a study conducted in 2018, 50% of patients usually manifest at least four BPSD symptoms at the same time (Cortès et al., 2018). BPSD symptoms can be divided in five categories: cognitive perceptual (delusions, hallucinations), motor (wandering, repetitive movements), verbal (repetitive speech, yelling, verbal aggression), emotional (depression, apathy, anxiety, irritability, aggressiveness) and vegetative (sleep and appetite disturbances). Considering the order of appearance of neuropsychiatric symptoms, depression and anxiety usually come first while, as AD progresses, aberrant motor BPSD and emotional behaviors like wandering, aggression, and irritability usually manifest during the dementia phase. That's why agitation and aggressiveness are usually associated with more advanced forms of AD and they become more frequent as the disease's severity increases. (Ruthirakuhan et al., 2018).

Several findings suggest that some BPSD, such as depression, anxiety, and apathy, can occur before the onset of cognitive decline in AD (Altomari et al., 2021) and could predict both cognitive decline and progression from MCI to AD (Ma et al., 2020). In a study conducted in 2022 in 3000 patients, authors confirmed that apathy was the most common symptom in the early phases of the disease, while agitation frequently manifested in late phases (Laganà et al., 2022).

The etiology for BPSD is heterogeneous. In 2010 it was proposed a biopsychosocial model that addresses neurobiological changes, cognitive symptoms, personal history, personality and social environment to neuropsychiatric symptoms and behavioral changes (Spector et al., 2010). With regards to external factors that may cause expression of psychiatric symptoms in dementia, unmet needs and lack of activity, environmental triggers, and the interactions between people with

dementia and their caregivers can contribute to BPSD. The Unmet Needs model refers to patients 'ability to communicate to caregivers and nursing assistants their needs, which include physical and mental discomfort, inadequate social contacts and environmental conditions. As a result of patients' frustration, this difficult interaction can lead to behavioral alterations. Specifically, verbal behaviors and aggressiveness were more likely to be manifested in patients that were feeling physical pain, discomfort and loneliness, while physical non-aggressive behaviors often occur when patients are not engaged in activities and feel lack of stimulation (Cohen-Mansfield et al., 2015).

Moreover, altered behaviors can be also a result of patients' reduced tolerance to stress, according to the Progressively Lowered Stress Threshold (PLST) model. Indeed, as the stress threshold lowers, there is an augment of anxious and dysfunctional behaviors, with a reduction of normative behaviors (Soylemez et al., 2016). The PLST model identifies six factors that contribute to stress in dementia: physical stressors, inappropriate stimuli, changes in the environment, external demands that exceed patients' abilities, fatigue and affective responses to loss.

Moreover, personality traits like pre-morbid neuroticism, that is characterized by a tendency to cope with daily challenges with exaggerated negative emotions like anxiety, depression and anger, can increase the risk of developing BPSD symptoms: indeed, people that manifest increased emotional reactivity and vulnerability to stress may be more prone to develop behavioral symptoms like agitation and aggression in response to daily challenges (Cloak et al., 2024).

Biological factors are also linked to BPSD. Indeed, agitation, disinhibition and psychosis are all associated with fronto-temporal and cortical abnormalities. In particular, AD-related agitation is associated to volume reductions and to decreased brain metabolism in the orbital and dorsolateral prefrontal cortex, anterior cingulate, insula and temporal lobes, that are areas involved in the emotional regulation, self-awareness and perception (Alves et al., 2017). Moreover, vascular lesions, often associated to white matter hyper-intensities, are linked to depressive symptoms in AD, while neuroimaging evidence shows that delusion, agitation and depression are often predicted by single structures, such as basal ganglia. Additionally, the advancement of the atrophy in

neocortical and parietal areas is related to the worsening of psychotic symptoms in MCI and dementia patients. A hypo-metabolism in parietal-temporal and posterior cingulate cortex are usually linked to apathy in prodromal AD stage (Alves et al., 2017). Furthermore, frontotemporal, limbic, temporal and occipital changes can affect multiple behavioral aspects: indeed, it is hypothesized that an early impairment in crucial areas like anterior cingulate and dorsolateral prefrontal cortex, both involved in emotional regulation, can lead to disturbances in self-monitoring and self-regulation, decreasing the management of daily challenges (Alves et al., 2017). Eventually, these alterations may also involve affective and personality changes, mostly due to prefrontal cortex dysfunction, as this area is also related to decision-making, social behavior and executive functions, potentially leading to higher levels of neuroticism, impulsivity and anxiety (Forbes et al., 2014).

In a 2015 study by Peters et al., that explored BPSD symptoms as predictors of progression of AD, confirmed that psychosis, agitation and aggressiveness were predictive of earlier decline to severe dementia and death, and are correlated with a greater likelihood of conversion from MCI to AD dementia. Moreover, depression can be a major risk factor for incidence of AD dementia, vascular dementia and even MCI. Indeed, patients with MCI and depressive symptoms have a higher load of amyloid and inflammation, resulting in a greater progression to AD in terms of cognitive decline and functional impairment, which comprehends also volitional and motor skill, necessary for functional autonomy. (Santacruz et al., 2019). Furthermore, sleep-wake alterations and REM disturbances at the first stages of AD can also predict functionality impairments, as patients manifest a higher number of amyloid plaques (Santacruz et al., 2019). Even though the causal association between these factors and their predictive associations is still not known, it can be hypothesized that psychosis, agitation, aggressiveness and affective symptoms may influence the care environment and relationships, conducting to worsening of the disease (Peters et al., 2015), while the augmented mortality risk may be linked to the use of pharmacological therapy, as mentioned before. Additionally, BPSD-related complications also involve increased hospitalization, hospital complications, earlier nursing home placement and increased rates of cardiovascular

disorders in caregivers, in addition to a higher risk of injuries in patients and caregivers due to agitation and aggressive behaviors (Cloak et al., 2024).

The management of BPSD symptoms involves choosing an appropriate setting, while providing an adequate environment to avoid discomfort, and establishing non-pharmacological interventions. Analyzing past medical history and observing patients' symptoms are the first steps to evaluate appropriate cares for every patient, also in order to train caregivers, which can reduce or delay nursing home placement (Cloak et al., 2024). Usually, while wandering and repetitive vocalizations rarely improve after pharmacotherapy, other BPSD symptoms like agitation, aggression and psychosis are often treated with psychotropic medications, as they are the most problematic and distressing symptoms of BPSD (Cloak et al., 2024). Indeed, a study conducted in 2014 identified specific BPSD domains and clusters, for example the affective domain, the apathy domain, psychosis domain, euphoria domain and, most importantly, the Hyperactivity-Impulsivity-Disinhibition-Aggression (HIDA) clusters of symptoms, that represent the most difficult set of behavioral manifestations to manage in AD (Keszycki et al., 2019). The HIDA domain accounts for the most of the burden of caregivers and nurses, as they are often concerned about safety and self-injurious behaviors. Impulsivity and executive dysfunctions are also correlated to increased wandering and disorientation, which can increase the risk of falls and mortality. As a result, patients with severe HIDA symptoms are more likely to be institutionalized by caregivers (Keszycki et al., 2019).

3.2) Biomarkers of agitation and aggressiveness

Amyloid and tau are well-established and widely studied biomarkers for AD. Investigating the association between agitation/aggression and the deposition of Aβ plaques and neurofibrillary tangles in AD patients may provide insight also into their potential as biomarkers of agitation and aggressiveness, not only as diagnostic tools and as predictors of AD onset, but also for monitoring

the progression of behavioral symptoms and to identify possible treatment targets. Agitation is the most common BPSD that is experienced by up to 60% of MCI patients and up to 76% of AD dementia patients (Jones et al., 2021). According to the International Psychogeriatric Association, agitation includes both emotional distress and behavioral manifestations, such as excessive motor activity, repetitive speech, verbal aggression or physical aggression. In a study conducted in 2018, five classes of biomarkers were identified in order to detect or confirm the presence or severity of behavioral symptoms, in particular agitation and aggressiveness (Ruthirakuhan et al., 2018).

3.2.1) Neuropathology

Ruthirakuhan et al. in 2018 highlighted that the accumulation of amyloid plaques and neurofibrillary tangles, that are known to worsen the process of neurodegeneration, would interfere with neuronal circuitry and connectivity. Moreover, the disruption caused by amyloid plaques and neurofibrillary tangles can lead to an imbalance between neurotransmitter systems , such as the cholinergic, serotoninergic and dopaminergic, which have also an important role in the regulation of behavioral symptoms, such as agitation and aggressiveness. Specifically, amyloid and tau tangles have been shown to accumulate in brain specific areas like frontal and temporal cortices. Changes or damage in these areas may contribute to alterations in behavior, including agitation and aggression, even though this association is not linear due to the influence of neurological, psychological and environmental factors, as described previously (Ruthirakuhan et al., 2018). Moreover, CSF levels of amyloid are negatively correlated to agitation and aggressiveness (Bloniecki et al., 2014). This result confirms that lower levels of CSF Aβ-42 usually reflect high levels of Aβ-42 plaque formation in the brain, meaning that amyloid is being deposited into plaques rather than circulating in the CSF. This process results in increased AD neuropathology, which may consequently affect neurotransmitter systems essential in regulating BPSD symptoms (Lewczuk et al., 2020).

Instead, CSF tau levels are positively correlated with AD severity, because phosphorylated tau is

released into the CSF early in the disease progression. Consequently, monitoring CSF tau levels can be a valuable biomarker for assessing the progression of AD pathology. Indeed, in 2014 Bloniecki et al. reported positive correlations between agitation severity and CSF tau levels (Bloniecki et al., 2014). Moreover, in two postmortem studies, were found elevated levels of phosphorylated tau in the frontal cortex of AD patients and neurofibrillary tangles in the orbitofrontal cortex and anterior cingulate cortex in AD patients that manifested agitation and aggressiveness, as assessed using the Neuropsychiatric Inventory (NPI) agitation subscale. Indeed, these areas are both involved in emotional regulation and behavior control (Ruthirakuhan et al., 2018).

Apart from the cingulate and the orbitofrontal cortex, other limbic areas have been associated to agitation and aggressiveness, such as amygdala and insula. Additionally, neuronal loss in the locus coeruleus, a brainstem nucleus involved in the regulation of arousal and stress responses, has been associated with aggressive behaviors (Van Dam et al., 2016). Moreover, increased hippocampal neurofibrillary tangles' load has been linked to increased severity of aggressive behaviors and to the presence of chronic aggressiveness (Van Dam et al., 2016).

3.2.2) Neuroimaging

Several studies have investigated the relationship between neuroimaging biomarkers of neuronal degeneration and injury in relation to agitation and aggressiveness. In particular, two cross-sectional studies using PET, which measures cerebral metabolism and cerebral blood flow, reported a hypometabolism in the frontal and temporal cortices in correlation to the agitation/disinhibition factor score on the Neurobehavioral Rating Scale (Ruthirakuhan et al., 2018). These findings were confirmed in a study conducted in 2017 by Weissberger et al. using a larger sample size: indeed, he reported that patients who scored positively on the agitation factor of the Neuropsychiatric Inventory (NPI), which included the agitation and irritability subscores, had hypometabolism in the right temporal, right frontal, and bilateral cingulate cortices (Weissberger et al., 2017). Indeed, not only the anterior cingulate cortex, but also the posterior one is involved, as it is the central core of

the DMN. Specifically, greater atrophy in the posterior cingulate cortex may reduce the capacity to process and regulate behavior properly (Trzepacz et al., 2013). Thus, an imbalance between the default mode network and the salience network, characterized by increased connectivity in the latter, is hypothesized in those patients with agitation and apathy (Rosenberg et al., 2015).

Moreover, two cross-sectional MRI studies using voxel-based morphometry (VBM), a computational technique that measures differences in local concentrations of brain tissues, explored how gray matter volume changes in AD patients with agitation and aggressiveness. Bruen et al. in 2008 reported that agitation/aggression was negatively correlated to gray matter volume in the insula and in the bilateral cingulate cortices (Bruen et al., 2008). Hu et al. in 2015 had similar findings, as they reported that agitation/aggression was negatively correlated with atrophy in the left frontal cortex and insula (Hu et al., 2015).

With regards to longitudinal imaging findings, that involve the use of techniques like MRI or PET scans to monitor structural and functional changes over an extended period of time, in a two-years longitudinal study conducted by Trzepacz et al. in 2013 it was discovered an increased amount of atrophy in the left hippocampus and in the frontal cortex in patients with AD, in association to agitation/aggression (Trzepacz et al. in 2013).

Instead, SPECT is an useful technique that assesses cerebral blood flow (CBF), as described in the first chapter. SPECT can be used to investigate the association between CBF and agitation/aggression in patients with AD. A study conducted by Hirono et al. reported that in AD patients with agitation/aggression (NPI-agitation subscale), there was a significant hypoperfusion in the left anterior temporal cortex, bilateral superior frontal cortex, and right superior parietal cortices, compared with AD patients who did not have agitation/aggression (Hirono et al., 2000). Lanctot et al reported also a hypoperfusion in the right medial temporal gyrus, in association to agitated/aggressiveness in AD patients. The right medial temporal gyrus includes the hippocampus, parahippocampus, and posterior amygdala (Lanctot et al., 2004).

Together, these results suggest that the hypoperfusion in the left anterior temporal cortex and the right medial temporal gyrus may be associated with the presence of agitation/aggression.

More recently, Banno et al in 2014 reported that physical agitation was associated with hypoperfusion in the right superior temporal gyrus and the right inferior frontal gyrus. Instead, verbal agitation was associated with a hypoperfusion in the left inferior frontal gyrus and insula (Banno et al., 2014). However, in one cross-sectional functional MRI study that compared amygdala responses between patients with mild AD and healthy controls, Wright et al., using a fMRI paradigm, reported a positive correlation between amygdala activity and the severity of agitation, aggression and irritability in patients with AD, during a viewing paradigm of neutral and emotional human facial expressions (Wright et al., 2007). This result confirms the role of the amygdala: indeed, amygdala atrophy is related to aberrant motor behavior, with potential relationship with irritability and anxiety, as confirmed also by one study conducted by Davidson (Davidson et al., 2002). Furthermore, amygdala atrophy is also similar to hippocampal atrophy in mild AD dementia patients, suggesting that these structures are both similarly and consistently affected. Amygdala also correlates with the severity of cognitive impairment, even in mild stages of dementia (Jaramillo-Jimenez et al., 2021).

Additionally, Rosenberg et al. in 2015 explained further the brain circuits associated to agitation in AD patients: the authors highlighted that a dysfunction in the frontal cortex, anterior cingulate cortex, orbitofrontal cortex, amygdala, insula and hippocampus overlaps with circuits that underlie intensified perception of threat and inappropriate control of responses. Thus, agitation in AD involves the miscalculation of the proportions of threats, followed by increased attention and vigilance and by an augmented reactivity to uncertain events (Rosenberg et al., 2015). This hyperactivity is also rooted in cognitive deficits: for example, damage to memory circuits can cause a patient to forget a routine event, leading the patient to overreact and to become agitated due to the unexpected threat. Similar to amnesia, if the circuits responsible for agitation are affected, a patient with agnosia may respond to a family member as if they were strangers, leading to increased

agitation (Rosenberg et al., 2015). Zhou et al. in 2010 also pointed out the relationship between the DMN and the salience network (SN), that are usually negatively correlated, in relation to agitation in AD patients: indeed, in AD, DMN connectivity is decreased, while the SN one is increased. SN function is primarily related to task selection and executive functioning, in order to guide attention to filter important or salient information from the environment. Insula and anterior cingulate cortex are key components of the SN and are also affected in patients with agitation: as a result, it can be hypothesized that agitation in AD is due to alterations in the balance of DMN and SN. An increased SN connectivity in AD patients can reflect compensatory changes in network connectivity that account for a reduction of the DMN connectivity (Zhou et al., 2010).

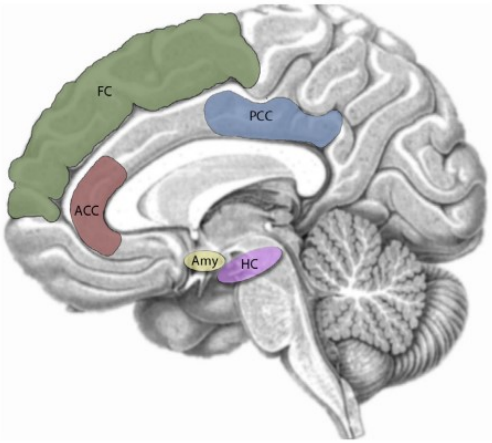

Fig. 4: brain regions implicated in agitation of AD network (Rosenberg et al., 2015)

3.2.3) Neurotransmitters

Neurochemical data on agitation in AD suggest that it is associated with a decreased acetylcholine neurotransmission. Indeed, cholinergic deficits appear more severe in AD patients displaying agitation or aggressiveness. Loss of choline acetyltransferase (ChAT) and increased acetylcholinesterase (AChE) enzyme activity has been reported in association with these BPSD symptoms. ChAT is the enzyme responsible for the synthesis of acetylcholine and is a marker of

cholinergic deficit: reduced ChAT activity is indeed negatively correlated to aggressive and overactive behaviors (Ruthirakuhan et al., 2018). Moreover, the loss of cholinergic neurons, in addition to decreased ChAT activity, contribute to the cholinergic deficiency typical of AD. Instead, the activity of the enzyme AChE, which is responsible for breaking down acetylcholine and is the target of AD drugs (AChEIs), is usually upregulated in AD patients, leading to an accelerated ACh degradation (Ruthirakuhan et al., 2018). These imbalances in the cholinergic system can affect mood and behavior, specifically agitation and aggressiveness. Indeed, acetylcholine has modulatory effects on arousal and alertness. Additionally, acetylcholine has modulatory effects on other neurotransmitter systems, including the serotonin and dopamine systems, which in turn are implicated in the regulation of mood and aggression (Ruthirakuhan et al., 2018). Thus, cholinergic dysfunction may contribute to alterations in the balance of these neurotransmitters, potentially influencing the development of aggressive behaviors. Moreover, several neurochemical studies have also linked serotonergic alterations with aggressiveness: reduced levels of 5HT and its metabolites were measured in the frontal lobes of aggressive AD patients (Solas et al., 2021), as described in the first chapter. Moreover, polymorphisms in the gene 5-HTT can affect the transcriptional activity of the 5-HT transporter, affecting the number of functional transporters available, that would impact negatively the serotonin neurotransmission. The 5-HTT gene has, indeed, a crucial role in the duration and amount of serotonin in the synaptic cleft (Ruthirakuhan et al., 2018). Two polymorphisms can be linked with susceptibility to manifest mood disorders, anxiety and stress responses: the 5-HTTLPR and the 5-HTTVNTR variants. Both refer to DNA sequence variations where a specific DNA segment is repeated in tandem within the gene 5-HTT. The number of repeats can vary between individuals, influencing the transcriptional efficiency of the 5-HTT gene and impacting serotonin levels (Ruthirakuhan et al., 2018). The 5-HTTLPR variant has two main allelic variants: the short and the long allele. The short allele is often linked to a more rapid reuptake of serotonin, potentially leading to lower serotonin levels in the synaptic cleft. This allele has been associated with increased aggressive behaviors in AD patients (Ueki et al., 2007). Moreover, 5-HTTLPR short allele carriers have greater amygdala response to emotional stimuli,

such as fearful and angry facial expressions, as the amygdala is a key brain region where the short allele genotype exerts its effects. In addition, short allele carriers also manifest structural differences in the amygdala, as they show smaller bilateral amygdala volumes, where smaller volumes are associated with higher activation of the amygdala (Kobiella et al., 2011).

These changes in the neurotransmitter pathways can be linked to the fundamental neurodegenerative processes of AD: indeed, corticothalamic network, as well as most circuits that connect deep brain structures to the cortex, predominantly exhibit inhibitory functions. Several evidence suggests that dysregulation of the corticothalamic network may be a common denominator that contributes to cognitive and behavioral alterations in AD. Indeed, in AD agitated patients, the decrease in cholinergic and serotoninergic neurotransmission implies a reduction in the inhibitory signals and control over the cortex. Consequently, agitation in individuals with AD may be a manifestation of the removal of inhibitory inputs that typically regulate behavior in the cortical circuits associated with agitation (Rosenberg et al., 2015). So, it can be proposed that circuits underlying neuropsychiatric disorders can give rise to BSPD either by intrinsic circuit dysfunction or by a dysregulation of circuits from ascending monoamine systems (Rosenberg et al., 2015).

On the other hand, dopaminergic alterations may also lie at the basis of aggressiveness and agitation in AD. As introduced in the first chapter, there are five receptor subtypes through which DA may elicit its mechanism of action: D1, D2, D3, D4 and D5. Specifically, several studies have investigated possible associations between the presence of aggressive behaviors and DRD1, the gene encoding for dopamine receptor D1. Indeed, carriers of the DRD1 B2 allele were more prone to manifest aggressive behaviors (Holmes et al., 2001; Pritchard et al., 2009). Moreover, the DRD4 gene, which codes for the receptor D4, is involved in behavioral and personality traits. Specifically, the VNTR polymorphism in the DRD4 gene involves the repeated sequence of nucleotides of the DNA, meaning that this sequence occurs consecutively multiple times. The number of repeats can vary between individuals, leading to polymorphism in the DRD4 gene. Pritchard et al. confirmed the role of this polymorphism in agitated and aggressive AD patients (Pritchard et al., 2009).

3.2.4) APOE genotype

It has been hypothesized that, because the APOE ε4 allele carriers are more susceptible of developing more rapid progression of AD and greater amyloid burden, AD patients carrying this allele may also manifest agitated and aggressive behaviors. Studies have demonstrated that agitation was a more prevalent symptom in homozygous ε4 allele carriers. This finding supports the idea that the prevalence and the severity of agitation and aggressiveness are associated to ε4 allele (Ruthirakuhan et al., 2018). Moreover, AD patients that possess at least one copy of the APOE ε4 allele manifest increased behavioral symptoms and increased frequency of agitated behaviors, including restlessness and vocalizations (Woods et al., 2009). Additionally, ε4 allele carriers that manifest agitated behaviors, anxiety and irritability increase the hazard ratios of incident dementia: the combination of behavioral symptoms and the genetic trait can be considered a useful strategy to identify MCI patients that are more vulnerable to convert to AD dementia (Valero et al., 2020).

3.2.5) Inflammation

As explored in the first chapter, pro-inflammatory cytokines are associated with increased cognitive impairment in AD. Several studies have pointed out the role of pro-inflammatory and anti-inflammatory cytokines in agitation and aggressiveness. The interleukin (IL)-1β is a pro-inflammatory cytokine that emphasizes oxidative stress and is associated with increased agitation, representing a possible monitoring biomarker (Higuchi et al., 2010). On the other hand, the IL-10 anti-inflammatory cytokine, which suppresses inflammation and inhibits the activity of immune cells, is the only one that is negatively correlated with NPI-agitation subscale and can be considered a possible diagnostic biomarker of agitation and aggressiveness in AD (Holmgren et al., 2014). Moreover, investigating the relationship between agitation, oxidative stress and neuroinflammation could help identifying novel targets for treatment of agitation in AD patients: one study conducted in 2019 by Ruthirakuhan et al. suggests that neuroinflammation may be associated to the severity of agitation in AD, while oxidative stress may be closely linked to the severity of cognitive impairment in agitated AD patients. However, oxidative stress and neuroinflammation are

interrelated processes that can worsen each other, but their relationship with agitation is still not deeply investigated (Ruthirakuhan et al., 2019).

CHAPTER 4

RELATIONSHIP BETWEEN PHARMACOLOGICAL TREATMENTS AND AGGRESSIVENESS AND AGITATION IN AD

In this chapter will be investigated how antidepressants, atypical antipsychotics, anticonvulsants, BDZs, AChEIs and memantine, the main classes of AD drugs, act on the main neurotransmission pathways involved in agitation and aggressiveness in AD. Moreover, will be analyzed studies and randomized trials demonstrating positive effects on agitation and aggressiveness, retracing the main AD pharmacological treatments and how they impact the patients' symptoms. Finally, will be investigated whether anxiety may be considered as a predictor of agitation and aggressiveness and potential correlation with the cognitive dysfunctions.

4.1) Modulation mechanisms of aggressiveness and agitation by AD drugs

As introduced previously, SSRIs like citalopram and escitalopram are first-line pharmacological treatments for agitation and aggressiveness in AD, as they are usually well tolerated, compared to antipsychotics. The mechanism of action of SSRIs involves the modulation of serotonin (5-HT): in particular SSRIs work by selectively inhibiting the activity of serotonin transporters (SERT), the membrane protein that transports serotonin from synaptic space into presynaptic neurons, thereby preventing the reuptake of serotonin into the presynaptic neurons (Arias et al., 2021). As a result of its inhibition, there is an increment of serotonin levels in the synapse, enhancing serotonin signaling and improving transmission of messages between neurons. When SSRIs increase 5-HT levels, they have effects on various serotonin receptors implicated in different physiological and behavioral responses (Slifirski et al., 2021). In particular, both 5-HT1A and 5-HT2A receptors are involved in mood regulation: while the 5-HT1A receptor is usually inhibitory, and its activation tends to have anxiolytic effects, the 5-HT2A receptor is primarily excitatory, and its activation has been linked to increased arousal, impulsivity and emotional reactivity (Slifirski et al., 2021).

Moreover, long-term citalopram treatment affects the dopamine and norepinephrine neurotransmission (NE), both involved in stress response. The norepinephrine (NE) system is, indeed, also implicated in agitation and aggressiveness in AD (Gutièrrez et al., 2022). In AD, the loss of NE neurons in the locus coeruleus has been well established, and usually worsens as AD severity increases. However, even if the role of NE in BPSD symptoms is still under debate, many studies have investigated the link between NE disruption and BPSD, suggesting that the loss of NE neurons with progression of AD would, in turn, result in increased NE activity, compensating for the loss of neurons (Herrmann et al., 2004). So, agitation and aggressiveness have been linked with increased NE activity and, as a result of the NE overstimulation, AD patients would no longer be able to focus attention, and their coping mechanism in response to external stimuli would be compromised. Even in the absence of stressful stimuli, the NE system would be active, accounting for the aggressiveness displayed in AD patients (Herrmann et al., 2004). Indeed, LC neurons mainly project toward the orbitofrontal and anterior cingulate cortices, deeply involved in agitated and aggressive behaviors (Carrarini et al., 2021). It has been demonstrated that chronic citalopram treatment suppresses the dopamine and norepinephrine systems in the prefrontal cortex, contributing to the therapeutic action of citalopram (Kaneko et al., 2016). On the other hand, while escitalopram may have a faster onset of action and may be associated with higher efficacy compared to citalopram, due to its S-enantiomer composition, both work primarily by inhibiting the reuptake of serotonin in the synaptic cleft. The target brain areas where citalopram and escitalopram act involve the limbic system, the frontal cortex and hypothalamus, as they are dense of serotonin receptors (Arce et al., 2007). Indeed, the amygdala, the anterior cingulate cortex, the frontal cortex and the hippocampus are the core areas linked to agitation and aggressiveness in AD, as described previously.

With regards to atypical antipsychotics, commonly used to treat agitation and aggressiveness in alternative to the use of SSRIs, they modulate different neurotransmitters, such as serotonin, dopamine and norepinephrine ones. Indeed, they differ from the typical antipsychotics, which act almost exclusively on the dopamine pathways (Grinchii et al., 2020). The atypical antipsychotic

olanzapine has effects on dopamine and serotonin receptor: it acts as an antagonist of dopamine D2 receptors in the mesolimbic pathways, blocking dopamine from potential action at the post-synaptic receptor, therefore helping to regulate the excessive dopamine activity that could contribute to agitation and aggressive behaviors (Thomas et al., 2023). The mesolimbic pathway is a neural circuit in the brain that plays a significant role in reward, motivation, and emotional processing. It involves the release of the neurotransmitter dopamine from neurons originating in the ventral tegmental area (VTA) and projecting to the limbic system, particularly the nucleus accumbens, amygdala and hippocampus, involved in agitation and aggressiveness (Serafini et al., 2020). Due to its projections to the limbic system and to the dysregulation of dopamine neurotransmission within the mesolimbic pathway, agitation and aggressiveness can arise. Moreover, olanzapine works similarly by antagonizing serotonin 5-HT2A receptors, reducing restlessness and agitation (Thomas et al., 2023). Even though usually agitation and aggressiveness are characterized by lower levels of serotonin, the therapeutic effects of olanzapine rely on the modulation of multiple neurotransmitters. Indeed, modulating one neurotransmitter system can have downstream effects on others. So, the overall outcome is influenced by a combination of factors, contributing to the therapeutic effects of olanzapine (Thomas et al., 2023). Quetiapine, similarly, works on both serotonin and dopamine receptors: in particular, it is an antagonist of the 5-HT2 serotonin receptor and it antagonizes D1 and D2 receptors. Moreover, its anxiolytic effects are due to the partial agonism on the 5-HT1A receptor and by inhibiting the norepinephrine transporter (NET). Both 5-HT2A and 5-HT1A receptors have a role in agitation and aggressiveness, as mentioned before. While an over activity of the postsynaptic 5-HT2A receptor may contribute to behavioral disturbances, there is evidence that an underactivity of serotonin postsynaptic 5-HT1A receptors may be associated with agitation and aggressive behavior (Slifirski et al., 2021).

As olanzapine and quetiapine, also risperidone has a similar mechanism of action, as it is an antagonist at D2 receptors, an antagonist of the 5-HT2A serotonin receptor and acts as an agonist at the 5-HT1A receptors (McNeil et al., 2023).

On the other hand, aripiprazole, an atypical antipsychotic, differs from the previous medications as it stabilizes dopamine activity: it acts as a dopamine receptor agonist in areas with low dopamine activity and as an antagonist in areas with excessive dopamine activity. Indeed, aripiprazole is a partial D2 agonist that binds to presynaptic receptors, while it acts as an antagonist on postsynaptic receptors (Tuplin et al., 2017). Moreover, similarly to olanzapine and quetiapine, it has partial agonist activity at the 5-HT1A receptor and partial antagonist activity at the 5-HT2A receptor. The overall impact of aripiprazole on dopamine and serotonin, may contribute to maintaining a more stable balance of the brain's signaling ending up in positive effects on agitated behaviors that occur in AD (Tuplin et al., 2017).

Brexpiprazole, as introduced in the first chapter, is a new therapeutic agent that acts as a partial agonist of D2, D3 and 5-HT1A receptors, and as an antagonist at 5-HT2A receptor. This drug has shown significant improvement in patients with frequent aggressive behaviors. Brexpiprazole is a derivative of aripiprazole, and compared to aripiprazole, is more potent at 5-HT1A receptors and provides improved efficacy and tolerability (McEvoy et al., 2016).

With regards to anticonvulsants, carbamazepine doesn’t act on serotonin or dopamine, but acts as a GABA agonist. Indeed, carbamazepine stimulates the activation of GABA receptors, inducing anxiolytic effects. GABAergic neurotransmission is involved in the regulation of various neural circuits, including those related to mood and behavior in AD. GABAergic neurotransmission, additionally, interacts with other neurotransmitter systems, such as serotonin and dopamine. Imbalances in the GABAergic system, particularly a decrease in inhibitory GABAergic activity, could lead to increased neuronal excitability. Indeed, carbamazepine additionally blocks voltage-gated sodium channels, stabilizing neuronal activity and excitability (Jo et al., 2014). In particular, it acts on amygdala and reduces agitation in AD patients, also by inducing mood-stabilizing effects. Moreover, it also inhibits the reuptake of serotonin, similarly to the SSRIs (Tampi et al., 2018). Valproic acid and gabapentin, similarly to carbamazepine, both enhance the inhibitory neurotransmission mediated by GABA, increasing its availability, and blocking gated sodium

channels (Romoli et al., 2019). Stabilizing neuronal activity can influence the functioning of the circuits involved in agitation and aggressiveness described previously.

With regards to BDZs, oxazepam, lorazepam and alprazolam act by augmenting the effect of GABA by increasing the frequency or duration of channel opening in response to GABA. This process augments the inhibitory tone in the brain, leading to a general reduction in neuronal excitability, and consequently reducing acute aggressiveness and agitation in AD.
Specifically, the anterior cingulate cortex, amygdala and hippocampus are the target structures for the anxiolytic effects of BDZs and anticonvulsants, as they have a significant density of GABA receptors (Schunck et al., 2009).

So, there is an overlap of brain areas where dopamine, serotonin and GABA pathways are active. These neurotransmitters interact and modulate neuronal activity in the same brain areas that are involved in agitation and aggressiveness, particularly in amygdala, in the anterior cingulate cortex, in the frontal cortex and in the hippocampus. This interconnectedness contributes to the effectiveness of various pharmacological treatments for agitation and aggressiveness.

Moreover, while AChEIs are primarily used to treat cognitive symptoms, there is some evidence that suggests that they have a positive impact on agitation and aggressiveness. Indeed, improved cognitive function and enhanced cholinergic neurotransmission could contribute to a more stable and regulated emotional state, also due to the cholinergic projections to amygdala, frontal cortex, anterior cingulate cortex and nucleus accumbens (Chandler et al., 2014).

Additionally, there is evidence that also memantine may reduce significantly agitation in AD, not acting on dopaminergic or serotoninergic pathways, but through a reduction of glutamatergic dysfunction. Indeed, by modulating the excitatory glutamatergic activity, memantine may have neuroprotective effects and protect neurons from excessive excitatory signals, and also prevent neurodegenerative processes (Fox et al., 2012). As described before, high levels of tau correlate with the manifestation of agitation and aggressiveness. Specifically, memantine may decrease tau

phosphorylation, consequently stabilizing mood, agitation and emotional distress, and also prevent the onset of agitation and aggressiveness (Liu et al., 2019).

4.2) Clinical effectiveness of AD drugs on agitation and aggressiveness: impact on patients' wellbeing

Agitated/aggressive Mild Cognitive Impairment (MCI) and Mild Behavioral Impairment (MBI) patients are usually treated with non-pharmacological interventions, as the symptoms they manifest are usually not severe enough to interfere significantly with daily life, and many patients diagnosed with MCI don't necessarily progress into developing dementia. However, the presence of anxiety, irritability and agitation may be associated with a faster progression of cognitive disorders. In particular, it has been suggested that the process of conversion from MCI to dementia is accelerated due to the presence of aggressive behaviors (Bidzan et al., 2023). That's why some studies explored the use of AChEIs and memantine in MCI patients to assess whether they might have a potential role in delaying or preventing the progression from MCI to dementia. In particular, a 3-years study conducted in 2005 tested whether donepezil could delay the diagnosis of AD dementia in patients with MCI, showing an improvement of agitation and aggressiveness during the entire trial in patients that carried the APOE allele (Petersen et al., 2005). The target areas of donepezil are, indeed, anterior cingulate cortex and frontal cortex both involved in agitation/aggressiveness and cognitive processes. Acting on these pathways may have benefits on both MCI and dementia patients. However, the results are still contrasting and the use of donepezil on MCI patients is still not approved by the FDA, mostly due to its side effects, while other AChEIs (rivastigmine, galantamine) and memantine have shown negative results regarding their potential role of delaying the diagnosis of dementia in MCI patients (Petrella et al., 2009).

With regards to dementia, instead, the evidence of clinical effectiveness of the pharmacological treatments mentioned above on agitated and aggressive behaviors is wider. Several studies have tested the efficacy of citalopram and escitalopram: the Citalopram for Agitation in Alzheimer

Disease Study (CitAD) involved 186 patients, that were randomized to receive either citalopram or placebo for 9 weeks, with a dose of 10 mg/day that increased up to 30 mg/day, based on response and tolerability. By week 9, about 80% subjects remained on treatment, indicating a high acceptability rate, and the patients treated with citalopram showed improvements in terms of agitation and caregiver distress, anxiety and irritability, even though at the dosage of 30 mg patients were more prone to develop QT prolongation (Porsteinsson et al., 2014). Moreover, a case study conducted on a 70 years old woman, who displayed a progressive cognitive decline (20/30 MMSE score) and high scores on verbal aggressiveness and restlessness (25/70 on the Cohen Mansfield Agitation Inventory), by week 8 with citalopram treatment her scores dropped to 12/70, and manifested only minimal restlessness and aggressive behaviors (Aga et al., 2019), confirming the positive effects of this SSRI on agitation and aggressiveness. The S-CitAD study, instead, is designed to test the efficacy and safety of escitalopram on agitated behaviors during a period of 12 weeks with a 15 mg daily dose (Ehrhardt et al., 2019). While the authors are still enrolling patients, positive results were demonstrated in a study conducted from January 2018 to January 2020 showing positive effects on agitated AD patients in terms of anxiety, emotional feelings and aggressive scores using the NPI subscales (Huang et al., 2021).

With regards to antipsychotics, despite their common side effects, there is evidence that olanzapine decreases agitation and aggressiveness. Indeed, a study conducted in 206 nursing home residents during a 6-weeks study with a dose of 5-10-15 mg/day demonstrated that low doses of olanzapine (5-10 mg/day) produced significant improvement compared to placebo in terms of clinically relevant agitation/aggressiveness, reducing also the distress of nurses (Street et al., 2000). These results were confirmed more recently, in 2021, by a study that enrolled up to 6090 participants to test both agitation and psychotic symptoms in AD. Results are consistent with the hypothesis that both olanzapine and quetiapine improve significantly agitation and aggressiveness, in comparison to typical antipsychotics such as haloperidol, despite their adverse effects, such as the increased risk of somnolence and extrapyramidal symptoms. However, the risk of serious adverse effects in relation

to haloperidol only increased slightly and was not significantly relevant in this study (Muhlbauer et al., 2021).

There is also evidence of the efficacy of carbamazepine and valproic acid in the management of agitation and aggressiveness. Several randomized controlled trials (RCTs) evaluated these drugs' efficacy: for aggressiveness, two RCTs with a mean dosage of 300-600 mg/day of carbamazepine for 6-8 weeks showed positive effects in terms of Overt Aggression Scale (OAS) total score, which comprehends verbal aggression, physical aggression against objects, against oneself and against other people (Yeh et al., 2012). Instead, for agitation, another RCT using a mean dosage of 300 mg/day of carbamazepine for 6 weeks showed efficacy using the Brief Psychiatric Rating scale (BPRS), in particular in the agitation subscale (Yeh et al., 2012). Regarding valproic acid, one RCT included 172 dementia patients, with a dosage of 1000 mg/day for 6 weeks: using the Cohen-Mansfield Agitation Inventory (CMAI) scale, results are consistent with the hypothesis that valproic acid is efficacious in the treatment of agitation and aggressiveness, in particular in the verbal agitation subscale of the CMAI (Yeh et al., 2012). These results were confirmed by other RCTs: using BPRS-agitation factor and a lower dosage of 820 mg/day of valproic acid (Yeh et al., 2012).

The use of BDZs in AD is recommended for the treatment of acute agitation and aggressiveness. Lorazepam (1 mg) and olanzapine (2,5 mg), both compared to placebo in a study conducted by Meehan et al. in acutely agitated dementia patients, administered intramuscular, after two hours after the injection, both produced positive effects on acute agitation and aggressiveness using the CMAI scale (Meehan et al., 2002). Another RCT, instead, compared the oral administration of alprazolam and lorazepam, highlighting that the treatment response was higher when patients were treated with alprazolam (42%) and 29% when they were treated with lorazepam (Defrancesco et al., 2015). Similar effects are attributed to oxazepam (10-60 mg/day) after 8 weeks: a study conducted by Coccaro et al. examined 52 patients with AD dementia, reporting a significant efficacy in terms

of verbal and physical aggressiveness, agitation and increased motor activity (Defrancesco et al., 2015).

In conclusion, while there is still an open debate regarding the role of AD drugs in the treatment of agitation and aggressiveness, mostly due to their side effects, there is wide evidence of drugs' efficacy on these BPSD symptoms at follow up.

4.2.1) Anxiety as biomarker and target for agitation and aggressiveness in AD

Anxiety can be considered a target of prevention of both cognitive impairment and aggressive behaviors in AD: indeed, several studies have considered agitation as an index of the external expression of anxiety, and anxiety can be considered as a risk factor for AD dementia, even independently from the presence of other BPSD symptoms. A large 4-years longitudinal study conducted in 2019 analyzed 4000 dementia-free people with a mean age of 55 years with anxiety at baseline. Authors observed a significant association between anxiety cases at baseline and AD dementia risk, confirming the role of anxiety as a predictor of dementia, as it increases the rate for conversion from MCI to dementia (Santabàrbara et al., 2019). Moreover, the presence of anxiety in older people is associated to an increased risk of developing MCI, predicting faster cognitive decline (Mortby et al., 2017). So, initial or prodromal anxiety may be most prominent among patients with early stages of AD, while anxiety in middle or late stages of AD may manifest as agitation and signs of emotional distress, with inappropriate/excessive vocal or motor activity and aggressiveness. Indeed, it has been hypothesized that agitation (an observed behavior) in AD individuals could be an expression of anxiety (a subjective feeling), implying that agitation could replace anxiety as AD progresses (Liu et al., 2020). That's why it was hypothesized that the presence of anxiety may be a contributing factor to agitation and aggressive behaviors, also due to the overlap of brain areas affected both by anxiety and aggressiveness, such as the hippocampus, temporal gyrus and insula. Moreover, anxiety is associated with early neurofibrillary tangle pathology in the entorhinal cortex in the presence of minimal cortical pathology (Mendez et al.,

2021). In MCI and AD, early neurodegeneration in right mesial temporal lobes, with entorhinal involvement, may lead to amygdala hyperactivity and heightened emotional contagion (Mendez et al., 2021). Furthermore, anxiety may be secondary to a release of emotion generating structures in the salience network. Amygdala and salience network are involved also in agitation and aggressiveness, as mentioned before (Mendez et al., 2021). Moreover, anxiety may be a consequence of unmet needs, giving rise to discomfort and stress, similarly to agitation and aggressiveness. Removing anxiety-producing triggers, responding to potential unmet needs, and maintaining a calm environment and steady routine can be most effective treatments in managing anxiety and resultant agitation/aggressiveness in later stages of AD (Mendez et al., 2021). However, if environmental interventions are insufficient, short-term use of BDZs or the use of a SSRI, usually are recommended to treat prodromal anxiety. Low doses trazodone, an antidepressant drug, particularly at bedtime, may be an alternative option when poor sleep or nocturnal anxiety occur (Mendez et al., 2021). Indeed, preventing and treating the manifestation of early anxiety may have positive effects on cognition and consequent agitation/aggressiveness. While this hypothesis is still under investigation, one study analyzed 272 agitation-free individuals at baseline to test the longitudinal relationship between baseline anxiety and the development of agitation in later stages of AD, and was found only a positive linear relationship between incident anxiety and agitation all over the study duration, using the Neuropsychiatric Inventory Questionnaire (NPI-Q) anxiety and agitation/aggression subscales (Liu et al., 2020).

Conclusively, some authors have suggested that the presence of anxiety in AD, a typical sign of the disease's preclinical stage, could be seen as a risk factor for the future ensuing of agitation and aggressiveness. However, studies have found mixed results regarding this recent hypothesis, and the debate is still open.

DISCUSSION

This thesis analyzed the available pharmacological treatments that are currently prescribed to AD patients, describing their mechanism of action and their side effects. An additional aim was to dissect out their role and potential benefits. It was also discussed the interaction between the neurotransmission pathways involved in AD underlying behavioral symptoms, like agitation and aggressiveness, and how they are modified by treatments, in order to identify potential new targets of prevention, like positively acting on anxiety.

Alzheimer's disease (AD) has gained attention representing a significant concern primarily due to the aging population: as people tend to live longer, the incidence of age-related diseases, including Alzheimer's disease, is prone to increase. The Alzheimer's disease is usually the result of both genetic risk factors and environmental components: APOE gene can be considered as a potential susceptibility gene to develop AD senile and sporadic AD (Quan et al., 2023), while the level of education, stress and the presence of comorbidities may increase the risk of developing dementia (Wallensten et al., 2023). AD is primarily characterized by the deposition of Aβ-amyloid plaques, tau phosphorylated protein, and by brain atrophy (Sperling et al, 2011). Tau also correlates more with the progression of AD, in comparison to amyloid plaques, probably because it results in neuronal death via inhibition of axonal transport (Combs et al., 2019). Moreover, Aβ-amyloid plaques can be found also in people who don't experience neurodegeneration (Sperling et al, 2011). Typical AD can be categorized in three different phases: preclinical AD, prodromal AD and AD dementia, where prodromal phase is transitional stage where individuals may exhibit mild cognitive impairment (MCI) or mild behavioral impairment (MBI) (Sperling et al, 2011). Usually, the primary focus regarding AD is related to cognitive symptoms, including the memory loss of recent events and semantic information in the earlier stages, that usually extends to episodic and autobiographical memory loss as the disease progresses. However, the present thesis is focused on two main Behavioral and Psychological symptoms of AD (BPSD), agitation and aggressiveness.

Both are the most common and severe symptoms in AD, due to their impact on the patients' quality of life and also on caregivers and nurses (Cloak et al., 2024). Indeed, agitated behaviors may be the result of unmet needs and lack of social activity, environmental triggers, and stressful interactions between people with dementia and their caregivers (Cloak et al., 2024). While the research on this field is still ongoing, studies have highlighted several factors that might be involved in the appearance of agitation and aggressiveness. Indeed, both these behavioral symptoms are characterized by a high amount of amyloid and tau tangles in frontal and temporal cortices (Ruthirakuhan et al., 2018), and by a distinct pattern of brain activations that usually underlie these behavioral symptoms, such as the anterior cingulate cortex, frontal cortex, orbitofrontal cortex, amygdala, insula and hippocampus (Rosenberg et al., 2015). Additionally, studies have demonstrated that agitation is usually a more prevalent symptom in homozygous APOE ε4 allele carriers (Ruthirakuhan et al., 2018). Moreover, neuroinflammatory processes may also have a role in agitation and aggressiveness: it has been demonstrated that interleukin (IL)-1β, a pro-inflammatory cytokine, can emphasizes oxidative stress and is associated with increased agitation, representing a possible monitoring biomarker (Higuchi et al., 2010). Agitation and aggressiveness are also characterized by neurotransmission pathways' imbalance: indeed, decreased cholinergic and serotoninergic transmission are typical in agitated AD patients (Ruthirakuhan et al., 2018). On the other hand, dopaminergic transmission is usually increased in agitated/aggressive patients (Pritchard et al., 2009), additionally to norepinephrine augmented transmission that compensates for the loss of noradrenergic neurons (Herrmann et al., 2004). These pathways represent the targets of current pharmacological treatments. While acetylcholinesterase inhibitors (AChEIs) and memantine (an antagonist of the NMDA receptor) are usually prescribed to improve cognitive symptoms in AD, other drug categories such as the antidepressants, antipsychotics, benzodiazepines and anticonvulsants are indicated for the treatment of behavioral symptoms. Several studies have also tested novel AD treatments, such as cannabinoids that in low doses may have positive effects on agitation and aggressiveness (Lee et al., 2023). While AChEIs usually increase cholinergic neurotransmission, memantine acts by improving glutamatergic transmission, as these two

pathways are compromised in patients that manifest cognitive symptoms. Moreover, memantine may also have neuroprotective effects against glutamate-induced neurotoxicity in AD due to the excessive activation of glutamate receptors, which is usually worsened by the accumulation of amyloid plaques. Therefore, memantine may provide to a potential mechanism for slowing down the progression of cognitive decline in individuals with AD. However, besides their impact on cognitive symptoms, AChEIs and memantine may also have positive effects on behavioral symptoms, as they target brain areas that overlap with the circuit involved in agitation and aggressiveness. (Kutzing et al., 2014), Similarly, also antidepressants, antipsychotics, benzodiazepines and anticonvulsants act on the brain areas involved in agitation and aggressiveness, but they have effects on different pathways of neurotransmission: antidepressants (in particular SSRIs) primarily act on the serotoninergic system, but their long term use may also impact dopaminergic and noradrenergic system (Kaneko et al., 2016). Comparably, atypical antipsychotics also act on dopaminergic, serotoninergic and noradrenergic pathways (Grinchii et al., 2020). Instead, anticonvulsants and benzodiazepines act on GABA transmission, that has inhibitory effects and can induce, indeed, anxiolytic effects (Jo et al., 2014). However, the use of pharmacological treatment in the management of agitation and aggressiveness is still under debate, due to the common side effects of AD drugs. Specifically, antipsychotics are the first line treatment for agitation and aggressiveness, but they have a high mortality risk and an increased probability to develop pneumonia, Indeed, due to their effects on dopamine neurotransmission, antipsychotics can lead to extrapyramidal side effects, sedation and altered movements (for example, dyskinesia). These factors, combined with changes in pulmonary secretion in older people, may lead to pneumonia (Rajamaki et al., 2020). Pneumonia is also a common side effect related to anticonvulsants, such as carbamazepine (Taipale et al., 2019). On the other hand, SSRIs are usually well tolerated, even though their main adverse effect is related to cardiac conduction disturbances, such as the delayed ventricular repolarization (QT prolongation) (Aga et al., 2019). Benzodiazepines, instead, are indicated for the treatment of acute agitation and aggressiveness: indeed, their chronic use may lead to cognitive worsening, to increased amyloid deposition and to

augmented risk of addiction (Rochon et al., 2017). With regards to acetylcholinesterase inhibitors and memantine, instead, the main side effect is related to the risk of falls and bradycardia (Young et al., 2021). Older people that manifest neurodegenerative diseases are more prone to develop autonomic dysfunction and abnormal vasovagal response, that may lead to syncope, falls and orthostatic hypotension (Sànchez-Manso et al., 2023). High doses of AChEIs may increase the risk of manifesting falls in vulnerable AD patients, as AChEIs can cause dizziness, syncope, atrial arrhythmias, myocardial infarction and sinoatrial and atrioventricular block (Young et al., 2021). However, when non-pharmacologic approaches are ineffective, pharmacological interventions are widely used, despite their negative complications, and their benefits have been tested by several studies demonstrating that, after the treatment, reduced agitation and aggressiveness has also positive effects on lowering the burden of caregivers (Porsteinsson et al., 2014). Moreover, the subjective feeling of agitation, anxiety, in prodromal stages of the Alzheimer's disease may be considered as a predictor of future onset of agitation and aggressiveness in later stages of the disease (Santabàrbara et al., 2019): while this hypothesis is still under debate, there is evidence of positive linear relationship between incident anxiety and agitation, discovered in a study conducted recently (Liu et al., 2020).

In conclusion, with the help of novel disease biomarkers that help better stratifying patients with higher risk of developing AD, and with the integration of more advanced neuroimaging techniques with novel pharmacological treatments, future approaches might improve or even prevent not only cognitive symptoms but also behavioral symptoms, in particular agitation and aggressiveness. In addition, concomitant non-pharmacological techniques, in particular individualized approaches on patients, such as cognitive-behavioral therapy and physical training, personalized nutrition plans and social group therapy, may provide additional positive effects on patients' and caregivers' wellbeing, in order to respond to patients' individual needs.

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