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THE CONSEQUENCES OF DEPRESSION IN ALZHEIMER'S: A LITERATURE REVIEW

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Abstract: Introduction: Alzheimer's disease (AD) is a neurodegenerative pathology of the central nervous system. In addition to cognitive disorders, depression stands out, which is another frequent aspect of dementia, causing anguish and reducing quality of life. **Objective:** identify the signs of depression in patients with Alzheimer's disease, its pathophysiology, and dementia in individuals who have depression in association with cognitive changes, whether these are reversible or not. **Material and methods:** A bibliographic review of the scientific literature was carried out, with searches in the Pubmed, Scielo, Google Scholar, Virtual Health Library databases. For this, five descriptors were validated on the DeCs/MeSH descriptors platform, namely: "Alzheimer's Disease", "Depression", "Mental Health", "Cognitive Dysfunction" and "Dementia". Subsequently, the descriptors inserted in the databases for searching for articles. The following inclusion criteria were used: period from 2018 to 2022, publications in Portuguese and English, articles and free magazines **Results:** 122 articles were found in Bireme, 111 in Pubmed, 247 in Google Scholar and no documents in Scielo, totaling 480 articles, which after the criteria were reduced to 15 (13 from Pubmed and 2 from Google Scholar), which were used to the making of this review. **Discussion/Conclusion:** The bibliographic survey showed evidence that depression can be an aggravating factor for AD due to the overlapping of significant symptoms between both pathologies.
Keywords: Alzheimer's Disease, Depression, Mental Health, Cognitive Dysfunction, Dementia.

INTRODUCTION

Alzheimer's disease (AD) is one of the most devastating brain disorders of elderly humans and a major public health problem, as AD accounts for up to 80% of all dementia diagnoses (CROUS-BOU, et al, 2017).

Defined as a chronic neurodegenerative disease with impairment of episodic memory, AD manifests itself slowly and worsens over time. This progression is characterized by massive synaptic loss and neuronal death in the brain regions responsible for cognitive functions, namely the cerebral cortex, hippocampus, entorhinal cortex and ventral striatum (SERENIKI; VITAL, 2008).

Due to the complexity of its early diagnosis, methodologies for tracking AD are based on the symptoms of dementia, divided into four stages: pre-dementia, initial or mild stage, intermediate stage and advanced stage (terminal) (DOS SANTOS, et al, 2020; MERTINS, et. al., 2020; PRICE et. al., 2015).

In the pre-dementia phase, the symptoms are subtle and there is the presence of memory loss, behavioral changes such as irritability, apathy and depression. In the mild stage we have symptoms of depression, temporal and spatial disorientation and difficulty in decision-making. In the intermediate stage, there is worsening of depression and signs of dementia, which affect activities of daily living, self-care, hallucinations, difficulties in semantic construction of sentences and loss of episodic memory (ABIEYV, et. al., 2022; DOS SANTOS, et al, 2020).

In its advanced stage, AD has altered episodic and semantic memory, resulting in inappropriate social behavior, severe depression, motor difficulties, inability to register and recognize information and name objects or people, and finally, it does not have the ability to perform any self-care or hygiene (MERTINS, et. al., 2020; MERTINS, et. al., 2020; DALGALARRONDO, p. 446, 2019).

Regarding the underlying etiology of AD, it still remains unknown and much research is directed towards its pathogenesis (MILANESCHI, et. al., 2016; MENGHANI

et al., 2021; ZENG et al., 2021). However, scientific evidence shows that prefrontal cortex and hippocampus regions are reduced in both AD and depression (SAMPATH, 2017).

In this context, studies indicate that most behavioral and psychological symptoms usually occur during the course of the disease. In addition to cognitive disorders, depression also stands out, which is another common aspect of dementia causing anxiety, reducing quality of life and increasing stress for everyone around them. Even at mild levels of depression, research suggests a significant increase in the functional and cognitive impairment of patients with dementia and, with increasing severity of depression, psychopathological and neurological changes and behaviors can worsen. (ORTEGA, el.al., 2017).

Due to the complications that depression can cause in AD, its treatment and knowledge is a fundamental clinical priority to improve the quality of life for both the person with dementia and the people around them (SUN et. al., 2018). In addition, AD is associated with high rates of comorbidity, and thus understanding its pathogenesis, comorbidities and early diagnosis are major targets of study in AD (WANG, 2017).

Even with so many efforts to understand AD, there is no test or questionnaire to detect depression in AD. And to obtain the diagnosis, it is necessary to investigate the patient's history with both the patient and their family members, in addition to complementary examinations such as physical and mental (WELLER & BUDSON, 2018).

Mood disturbances in depressed older adults who have prominent cognitive deficits as part of the depressive syndrome are at increased risk of developing dementia. Thus, the objective is to carry out a bibliographic review on depression in patients with AD, its pathophysiology, and dementia in patients who have depression in association with cognitive changes, whether these are reversible or not.

MATERIAL AND METHODS

This study is a bibliographic review. To select the works used for this article, the Pubmed, Bireme, Scielo, Google Scholar and Inapós Institution Library databases were accessed from 2018 to 2022. The following descriptors were used on the DeSC/MeSH platform (Figure 1): "Alzheimer's Disease", "Depression", "Mental Health", "Cognitive Dysfunction" and "Dementia".

For the platforms Pubmed, Bireme, Scielo, Google Scholar and Library of the institution Inapós, the search used validated descriptors and separated the articles and/or magazines with information regarding depression in patients with AD, its pathophysiology, and dementia. in patients who have depression in association with cognitive changes, whether these are reversible or not.

It was adopted as an inclusion criterion all works published in the period between 2018 and 2022, written in Portuguese and/or English, being available free of charge, that addressed topics related to Alzheimer's Disease, Depression, Mental Health, Cognitive Dysfunction and Dementia, with the use of AND in the search for the descriptors. As an exclusion criterion, studies with a publication date prior to the year 2018 were applied, as well as those that were not available in full and did not address the topics of the descriptors concomitantly in the same article and/or journal.

RESULTS

Through searches in the databases, 122 articles were found in Bireme and 111 in Pubmed, 247 in Google Scholar and no documents in Scielo, totaling 480 articles,

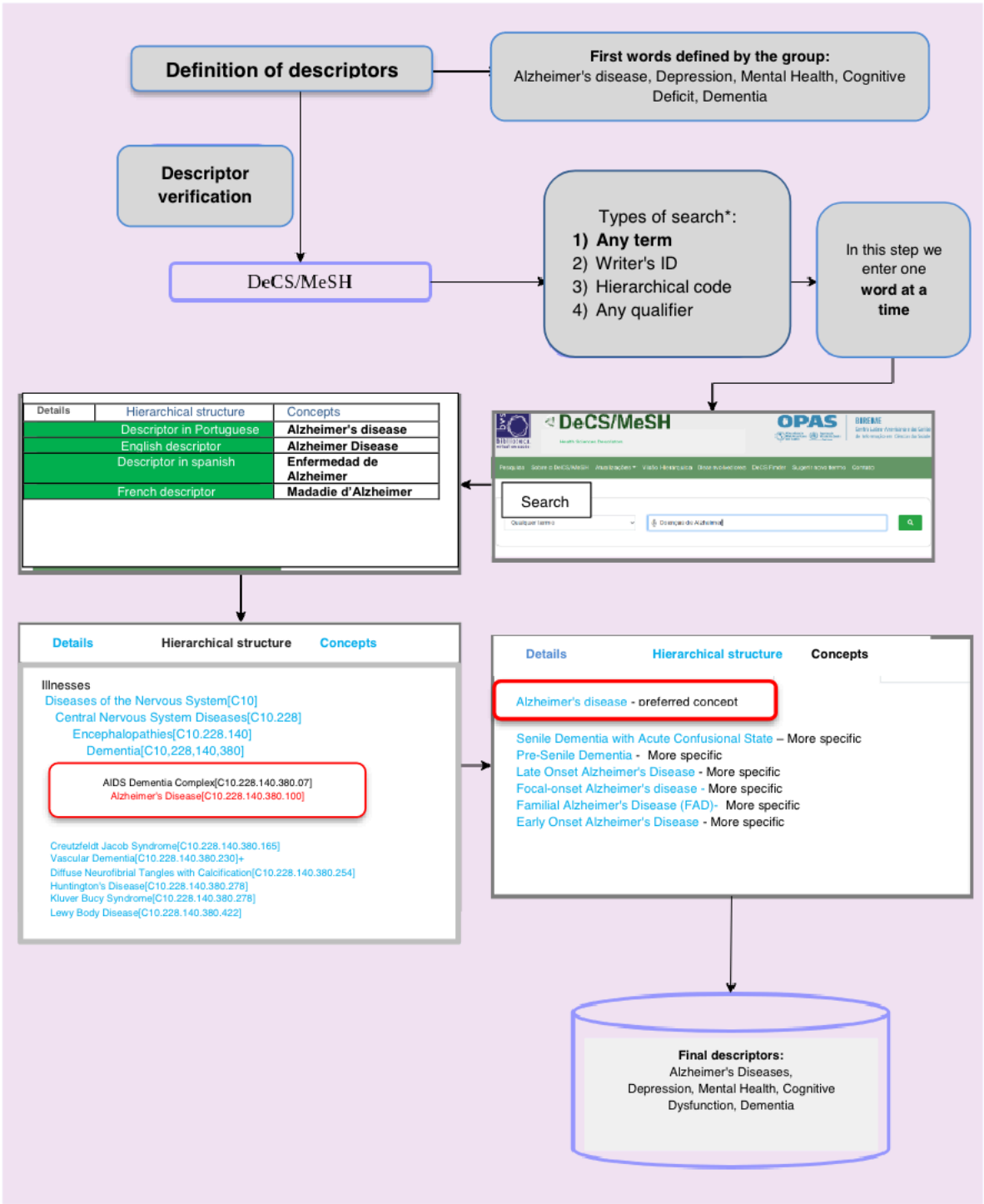

Figure 1: Workflow for validating descriptors on the DECS/MeSH platform.

which after the criteria were reduced to 15, which were used for the preparation of this review; being them, 13 from Pubmed and 2 from Google Scholar, in English and Portuguese.

At the end, the articles were divided into groups, namely (Figure 1).

In this process, articles were also selected, which contained data on drug treatment for AD and depression (Figure 2).

And, finally, data were organized regarding signs and symptoms of patients with AD and mental health comorbidities (Table 1).

DISCUSSION

The strong heterogeneity of depressive disorders likely contributes to the high levels of comorbidity reported with Alzheimer's Disease (AD). The heterogeneity of the depression phenotype is evident from its wide range of signs and symptoms and the likely existence of several subtypes of depression. This may explain how the extent of genetic overlap can be large for less polygenic AD but very small for depression, which fits with numerous reports that depressive disorders are an important predictor of AD pathology, while the opposite is less true (ROMERO-SANCHEZ et al., 2020; NALLEBALLE et al., 2020).

Studies show that some subtypes of depressive disorders have more comorbidities with AD than others, consistent with indications that subtypes of depressive disorders have significantly different genetic architectures (VINDEGAARD & BENROS, 2020). Also, if associated with neurobiological data, it would be of great value to determine the progression and effects of depression in AD (DINAKARAN et al., 2020; ZHANG et al., 2020; HELMS et al., 2020).

Another important aspect is that depression can lead to severe impairment of short-term memory, with repercussions on measures of global cognitive functioning, in addition to the possibility of being one of the first manifestations of dementia or a reaction to cognitive decline. Still, they present depressive symptoms as the first manifestation, and dementia and depression and the use of polypharmacy may coexist (CARDOSO et. al., 2020; FERREIRA, 2022).

In this context, the associated use of medication for the treatment of depression and AD is still being discussed, showing a strong indication of correlation between the two pathologies.

Dopaminergic drugs that act in the nucleus accumbens with inhibitory projection neurons called medium spinous neurons and

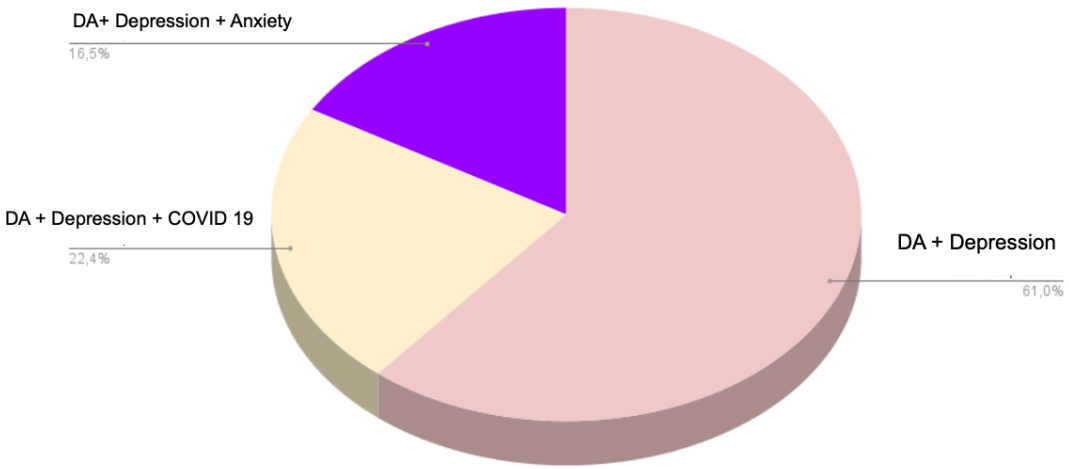

Figure 1: Articles related to Alzheimer's disease, depression and anxiety.

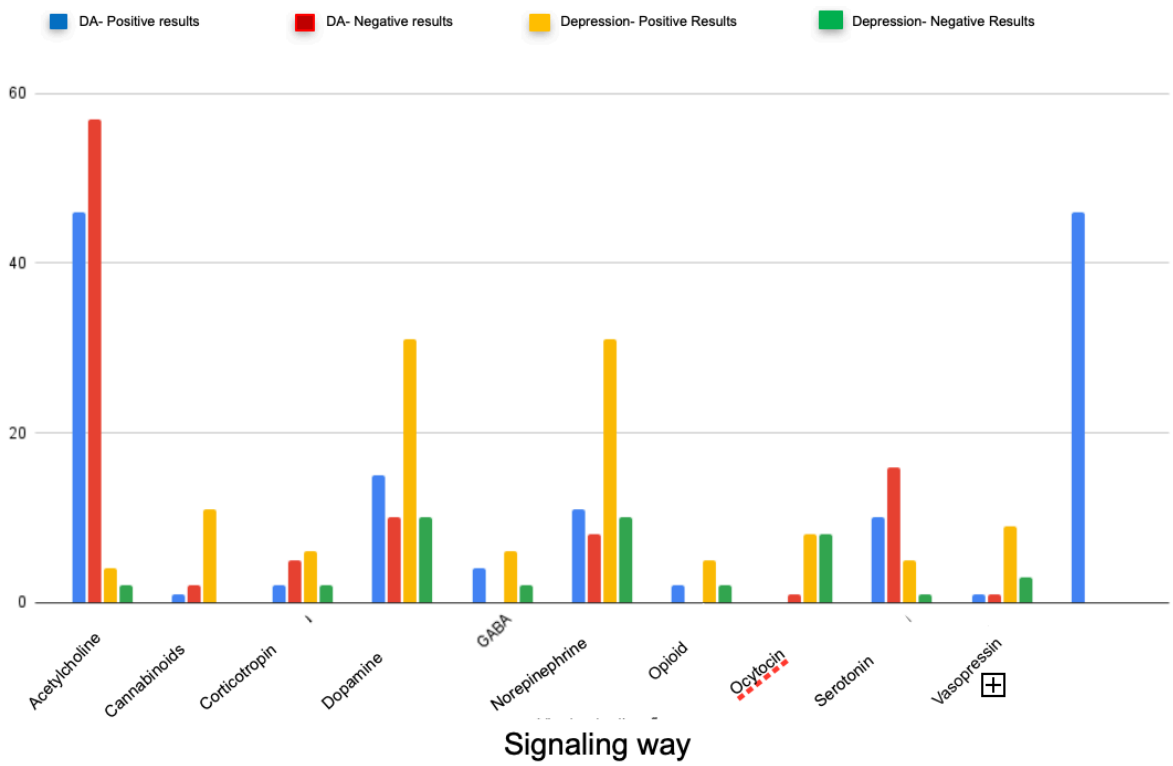

Figure 2: Polypharmacy of drugs for Alzheimer's Disease and Depression.

Author	Results
Cai et al., 2020	Percentage of subjects who reached the cutoff value of the scale: – Overall: 54.8% – Depression: 38.1% – PTSD: 31% – Anxiety: 22.2% – Anxiety and depression: 11.9%
Dinakaran et al., 2020	Evidence of neuropsychiatric manifestations: – Delirium: 4 studies – Psychosis: 2 studies – Mood swings: 1 study – Increased psychological distress in individuals with pre-existing epilepsy and psychiatric disorders: 2 studies
Helms et al., 2020	Prevalence of symptoms: – positive CAM-ICU: 65% – Agitation: 69%
Liguori et al., 2020	Prevalence of symptoms: – Sleep impairment: 49.51% – Depression: 37.86% – Anxiety: 33.01% – Confusion: 22.33%

Nalleballe et al., 2020	Prevalence of manifestations: – Overall: 22.5% – Anxiety and other related disorders: 4.6% – Mood disorders: 3.8% – Sleep disorder: 3.4% – Signs and symptoms of the emotional state: 0.8% – Suicidal ideation: 0.2%
Parra et al., 2020	Prevalence of symptoms: – Delusions: 100% – Orientation disturbances / attention: 60% – Auditory hallucinations: 40% – Visual hallucinations: 10%
Rogers et al., 2020	Evidence of neuropsychiatric manifestations: – Confusion: 5 studies – Anxiety and depression: 2 studies – Insomnia: 1 study
Romero-Sanchez et al., 2020	Prevalence of symptoms: – Insomnia: 13% – Anxiety: 8.1% – Depression: 5.2% – Psychosis: 1.3%
Varatharaj et al., 2020	Prevalence of manifestations: – Psychosis: 8% – Other psychiatric disorders: 5.6%
Vindegaard and Benros, 2020	Evidence of neuropsychiatric manifestations: – High prevalence of PTSD in patients with COVID-19 – Higher prevalence of depression in patients with COVID-19 than in quarantined individuals – Worsening of psychiatric symptoms in patients with pre-existing psychiatric disorders – Increased psychiatric symptoms in healthcare professionals – Lower psychological well-being and higher scores on anxiety/depression scales after the pandemic
Yuan et al., 2020	Increased immune response (white blood cell count, neutrophil count, and neutrophil-lymphocyte ratio) in the depression group compared to the control group
Zhang et al., 2020	Percentage of individuals with COVID-19 who reached the cutoff value of the scales: – Depression: 29.2% – Anxiety: 20.8% – Depression and anxiety: 21.1% Prevalence of depression was higher in patients with COVID-19 than in quarantined individuals

Table 1: Articles related to Alzheimer's Disease, Depression and other mental health issues.

their pharmacological action implicated in distress behaviors. The mesocortical pathway is considered essential for normal function and is involved in cognitive control, motivation and emotional response.

Thus demonstrating that this pathway of the dopaminergic system is probably involved in social functioning and affects both patients with AD and depression (PORCELLI, 2019).

Two other drugs used for the treatment of depression and AD are the GaBAergic drugs which have increased GABA activity serves as a filter of incoming sensory signals to increase discrimination of relevant sensory cues and maintain relevant core representations to facilitate behavioral responses. Finally, GABA plays a critical role in extinguishing conditioned emotional responses to stimuli previously associated with punishment and reward. It is norepinephrine that the drop in its brain levels is linked to depression and AD, as this neurotransmitter is responsible for keeping the body alert during the day (BREIJYEH & KARAMAN, 2020).

Due to different cognitive and psychological changes, studies show that excessive polypharmacy, defined as the concomitant use of 10 or more medications, was associated with a decline in cognitive ability measured by the Mini Mental State Examination (MMSE) compared to the non-polypharmacy group. And subsequently, this excessive use of medications may be related to the different levels of depression, anxiety and insomnia, which affect the mental health of these patients (KHAN et. al., 2020).

CONCLUSION

In conclusion, the bibliographic survey shows that both depression and Alzheimer's disease present pathophysiological alterations in the area of the frontal cortex, hippocampus and nucleus accumbens, these areas being pharmacological targets for the treatment of both pathologies. Still, it is pointed out that patients affected by Alzheimer's Disease (AD) have some depressive disorder at different levels (mild, moderate or severe). However, there was no possibility of associating levels of depression with the four phases of AD, moreover, all patients affected by AD and depression, have high levels of cognitive alterations, failing different cognitive tests, both episodic and semantic memory. In this context, no treatments were identified, even those performed with polypharmacy, or polypharmacy for regression or reversal of AD and depression. However, the use of dopaminergics, norepinephrine and acetylcholine show a period of stagnation of signs and symptoms of AD and depression.

FINAL CONSIDERATIONS

Thus, it is evident that this study provided more information about the pharmacological, neuroanatomical relationships between AD and depression, the evidence of overlapping of significant symptoms and neuropathological effects reflected in morphological changes in the brain, guaranteeing further research on the consequences and relationships of AD. depression in AD. However, it appears that the complex relationship between AD and depression will require future research to employ larger sample sizes, better metrics to determine different degrees of depression, and to associate them with different stages of AD. All this will influence the underlying biological mechanisms that explain the complex relationship between these disorders. Ultimately, this knowledge may provide a pathway to more effective treatments, thereby reducing the enormous burden that AD and depression place on patients and their caregivers.

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