IJHSR
ijhighschoolresearch.org
REVIEW ARTICLE

Bidirectional Association of Depression and Alzheimer's Disease, with an Emphasis on Memory and Antidepressants

Helena Wang

Basis Independent Fremont, 39706 Mission Blvd, Fremont, CA 94539, USA; helenawang49@gmail.com

ABSTRACT: Two seemingly independent disorders, depression and Alzheimer's disease (AD), are in fact interconnected in complex mechanisms. Although their association remains unclear, depression has been hypothesized to be a risk factor, prodrome, or accelerating factor of AD. This review discusses the bidirectional association between depression and AD, with a specific focus on their shared impact on memory deficits and the potential role of antidepressants in managing both conditions. AD, a neurodegenerative disease, causes cognitive decline, in which early diagnosis and intervention is key for preventing progression. Depression, commonly linked to AD, is associated with hippocampal atrophy, a hallmark of AD, and memory decline in AD, particularly in working memory (WM) and episodic memory. The potential role of antidepressants in managing depression and AD is also discussed, though findings remain inconclusive. While some evidence suggests that antidepressants can alleviate depressive symptoms and delay cognitive decline in AD, the overall impact on cognitive and functional outcomes is not definitive, promoting the necessity for further research. This review underscores the importance of early detection and specific treatments for addressing the common negative implications of depression and AD.

KEYWORDS: Behavioral and Social Sciences, Cognitive Psychology, Alzheimer's Disease, Depression.

Introduction

As life expectancy increases, population aging drastically rises, leading to an elevated risk for various diseases related to cognitive impairment. Cases of Alzheimer's disease (AD) and depression, as two of the said diseases, have been on the rise due to increased numbers of those in late adulthood. Both have significant negative implications on the aging population and are, in fact, bidirectionally associated according to recent evidence.

Alzheimer's Disease:

AD is an extremely common neurodegenerative disorder, with over 3 million cases across the United States. Individuals with this disease gradually lose basic cognitive abilities such as thinking, behavior, and most importantly, memory. The most commonly known risk factor of AD is old age, explaining the main cause of late-onset Alzheimer's where patients are 65 years and older. Early-onset AD is considered for those who have Alzheimer's before the age of 65. Many will not live over 20 years after being affected by Alzheimer's, as AD is a progressive disease, meaning that cognitive symptoms slowly worsen over the years.[1] The severity of symptoms often follows a progression of stages: asymptomatic, in which biological changes are occurring in the brain but cognitive symptoms have not yet surfaced, mild cognitive impairment (MCI), in which patients can still maintain independent lives but will most likely develop dementia premise of brain changes, mild, in which early-stage symptoms start to interfere with daily activities but are not yet greatly noticeable, moderate, in which symptoms of low judgment, emotion influxes, and memory loss are more pronounced, and severe, in which patients need 24/7 assistance to maintain their daily lives and lose the ability to respond adequately to the environment and others.[2]

Much before AD symptoms are present and discernable in patients, changes in the brain have already taken place. The two major hallmarks of Alzheimer's disease are amyloid plaques of the protein amyloid beta (Aβ) and neurofibrillary tangles (NFTs) of the tau protein, and both have clear patterns of progression, spreading from regions of the brain important for memory function to other areas.[1] The accumulation of such plaques and tangles blocks communication throughout synaptic pathways, leading to widespread cell death and shrinkage of total brain volume, specifically the hippocampus. The hippocampus is a region in the brain significantly crucial for memory and learning. In hippocampal atrophy, hippocampus volume reduces, indicating correlated AD neuropathological changes and decline.[3] The irreversible death of neurons is the main factor for cognitive failure and memory loss in patients with AD.[1] A major present-day issue regarding Alzheimer's disease is the late diagnosis and, therefore, late treatment of AD. Biological changes often have occurred to the brain prior to noticing clear cognitive symptoms, when the disease has already progressed to relatively late stages and treatment has less effect. It has even been made clear that the pathogenesis of AD can start as early as decades before first symptoms emerge.[4] Current methods of diagnosis, including volume assessments, diffusion tensor imaging (DTI), positron emission tomography (PET) scans, and cerebrospinal fluid (CSF) and blood tests, are mostly insufficient by themselves to confidently determine the presence of AD and can only rule out possible incorrect diseases.[5] Therefore, it is crucial for researchers to identify risk factors and prodromes of AD for effective early diagnosis and treatment of the disease.

DOI: 10.36838/v7i4.23

Alzheimer's disease is the leading cause of dementia, accounting for 60-80% of all dementia cases. It affects a patient's working memory (WM), episodic memory, and executive function. Monitoring the decline in cognitive function of these memory mechanisms may serve as a signal of AD progression. Amnestic-MCI (a-MCI) adults have definitive episodic memory impairments, multiple domain a-MCI (a-MCI+) adults have episodic memory, WM, and executive function deficits, and nonamnestic-MCI (na-MCI) adults show cognitive impairments unrelated to episodic memory functions. It is shown that adults with a-MCI and early impairments in episodic memory, WM, and executive function are at higher risk for developing AD. Early-stage AD nevertheless consists of continuous executive function deficits.[6]

Depression:

Depression, or major depressive disorder, is a major mental health disorder with over 3 million cases in the United States. According to the Diagnostic and Statistical Manual of Mental Health Disorders, fifth edition (DSM-5), major depressive disorder may be diagnosed through the presence of symptoms, such as persistent low mood, reduced pleasure or interest in previously enjoyed activities (anhedonia), or hopelessness, for at least two weeks. Increased severity levels of distress and impairment should also occur for the diagnosis of depression.[7] The severity of symptoms greatly depends on the individual. Common risk factors of depression most likely fall under two categories: genetic or environmental. Individuals with a personal or family history of depression or significant alterations in life such as trauma or stress are more likely to develop depression. Comorbidities of depression and separate severe diseases are prevalent usually in mid-life or late-life depression, due to individual aging. Evidence suggests that such comorbidities lead to enhanced negative symptoms of both diseases. Depression is treatable, and symptoms can usually resolve within a few months, especially with early diagnosis and intervention. Psychotherapy and medication, or a combination of the two, are commonly used as treatment for depression.[8] Typical medication for treatment of depression is antidepressants, including but not restricted to selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs).

Depression has been shown to negatively influence emotional information processing in working memory (WM). Findings have demonstrated that depression-specific deficits are manifested in updating positive contents of a positive image to WM.[9] WM is a fundamental cognitive function involving temporary retention and management of a limited amount of information for a shorter period of time. This type of memory mechanism is responsible for executive functions such as planning, comprehension, reasoning, and problem-solving.[10]

Association between depression and Alzheimer's disease:

Recent studies and literature reviews have shown several different risk factors for the development of Alzheimer's. Previous research describes that the relationship between vascular diseases such as dyslipidemia, hypertension, tobacco consumption, and diabetes mellitus and AD primarily have links in regards to their vascular component and common inflammation mechanisms. However, novel research touches upon the association of neuropsychiatric disorders and symptoms to AD.[11] It is still unclear and somewhat controversial as to the exact relationship between depression and AD, but previous studies have concluded various feasible hypotheses. Firstly, there has been evidence that shows that depression is somewhat associated with an increase in the risk for dementia. Secondly, depression may also be an early sign or symptom that indicates the presence of Alzheimer's. Lastly, depression may also cause normal cognition to become MCI and MCI to dementia.[12]

In this context, this review paper aims to provide elucidation of the association between depression and AD and clarify possible confusions of the complex relationships whilst pointing clear directions for future research efforts. The paper begins with the bidirectional relationship of depression and AD, moving through three sections respectively: depression and AD as mutual risk factors, depression as a prodromal factor of AD, and depression as an accelerating factor of AD. Then, the effects of depression and AD on memory, both separately and collectively, are discussed. Finally, the independent and mutual effects of antidepressants on depression and AD are examined. The entire paper and conclusion highlight that the investigation into the understudied relationship of depression and AD can perhaps lead to the efficacious usage of treatments of depression for the prevention of AD or the early diagnosis and possible interventions of AD.

■ Discussion

Depression and AD as Mutual Risk Factors:

The first type of relationship between depression and AD to be discussed is depression as a risk factor for the pathogenesis of AD. It has been shown in the Maastricht Aging Study that depression and vascular pathology are linked together in leading to cognitive decline and later dementia.[11] Further evidence suggests that depression is associated with an increase in the risk for dementia, indicating a causal relationship for the two variables. Longitudinal studies have found a linear relationship between depressive symptoms and the risk of developing dementia, with hippocampal atrophy being prevalent in both late-life depression and Alzheimer's. This supports the hypothesis that long-term depressive symptoms may lead to reduced hippocampal volume, potentially causing the progression of dementia.[12] While earlier studies offered conflicting evidence on the link between depression and dementia (a few studies showed that individuals with depression or a history of depression were more likely to suffer from dementia later on in life and more studies indicated that depression only mildly affects the contraction of dementia or not even at all),[13] more recent research provides firm evidence on depression increasing the risk of AD. Specifically, older adults with clinical depression and mild cognitive impairment have been found to have accelerated rates to develop AD, and those with active depression within two years have an even higher risk to devel-

op AD. Based on a combined review of eleven studies,[11] there was a more than three-fold increased risk of AD for clinically significant depression, and yet another seventeen studies[11] showed a twofold increased risk of AD for just those with depressive symptoms.[11] Thus, depression is demonstrated to be a risk factor of AD.

Conversely, neurodegeneration in Alzheimer's causes dysfunction in brain regions responsible for regulating emotion and mood, which can lead to depression. According to the Ehrenberg *et al*. study, findings indicated a strong association between neurofibrillary tangle (NFT) burden and the development of certain neuropsychiatric symptoms (NPS), including depression, even in the early stages of AD when detectable cognitive decline is nebulous and not yet clear. This early NFT pathology occurs primarily in the subcortical regions of the brain.[14] The said region encompasses the thalamus, basal ganglia, hippocampus, amygdala, and nucleus accumbens, in which the amygdala, hippocampus, and thalamus are implicated in the brain of a depressed patient.[15] It is then valid to extract from findings on AD-related neurodegeneration in specific subcortical regions that such atrophy subsequently leads to the emergence of depression.[14] Therefore, AD can also contrarily be understood as a risk factor of depression.

Depression as a Prodromal Factor of AD:

Depression may also be an early sign or symptom that indicates the presence of Alzheimer's, suggesting a reverse causality hypothesis.[12] Once longer studies had been conducted, more evidence has originated from a cohort study[13] in that older individuals with depressive symptoms are more likely to develop dementia and/or AD, but more so depression being the prodromal stage of dementia.[13] Additionally, results from the Ehrenberg *et al*. study show that the first stages of AD may first manifest as neuropsychiatric symptoms such as depression. In some studies,[14] depression has been shown to be correlated with increased cortical plaques and tangles, which are also the hallmarks of AD.[14] In this context, depression can be considered to act as a sign for early diagnosis of AD.

Depression as an Accelerating Factor of AD:

Depression may also serve as an accelerating factor in the pathogenesis of AD, with evidence pointing to depression as responsible for expediting the process of MCI to AD. Studies indicate that depression is associated with more rapid progression from MCI to AD. Depression is said to be linked to disruption of hypothalamic-pituitary-adrenal (HPA) axis function and elevated glucocorticoid levels, causing accelerated brain atrophy in the hippocampus. Depression is also associated with chronic inflammation, which hastens the neurodegeneration process in patients with AD. Furthermore, the severity and frequency of depressive episodes and symptoms also play a big factor in exacerbating cognitive decline and advancement of AD.[12] Based on the above, it can be extrapolated that subsequent research can be concentrated on treatment of depression to prevent extremely rapid progression and slow such progression of AD. A clear representation of the overall reciprocal relationship of depression and AD is depicted in Figure 1.

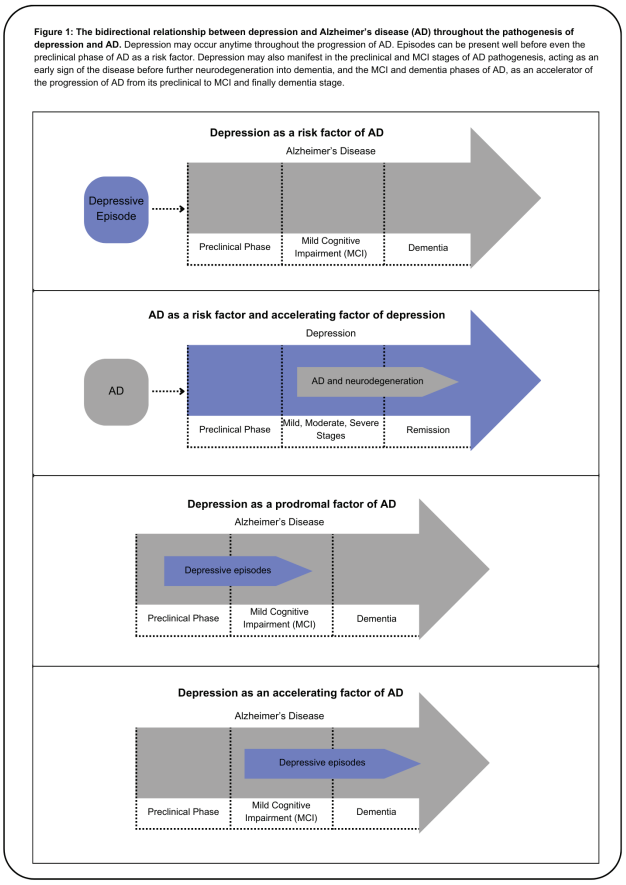

Figure 1: The bidirectional relationship between and Alzheimer's disease (AD) throughout the pathogenesis of depression and AD. Depression may occur anytime throughout the progression of AD. Episodes can be present well before even the preclinical phase of AD as a risk factor. Depression may also manifest in the preclinical and MCI stages of AD pathogenesis, acting as an early sign of the disease before further neurodegeneration into dementia, and the MCI and dementia phases of AD, as an accelerator of the progression of AD from its preclinical to MCI and finally dementia stage.

Effects of Depression and AD on Memory:

Both depression and AD have significant roles in the progression of dementia and corresponding memory deficits. This section will explore how each disease affects working memory (WM) and episodic memory separately and subsequently identify how they correlate with each other. Depression specifically has negative implications on working memory, and deficits in WM itself can also conversely act as a vulnerability factor and key cognitive dysfunction signal for depression. Studies have shown that those with depression struggle to complete assigned tasks associated with WM functions compared to healthy controls. Even those with only depressive symptoms and do not meet the diagnostic criteria for clinical depression have decreased WM ability and increased mind-wandering in WM while presented with task-irrelevant distractors.[9] Furthermore, patients with depression already in remission, or able to return to adequate daily activities, are still continuously affected by established WM impairments from previous depressive episodes.[15] According to the results of the Zhang *et al*. study, more severe depressive symptoms

DOI: 10.36838/v7i4.23

are correlated with more significant differences in reaction times between updating positive and neutral content in WM, demonstrating the tendency for WM impairments to act as a vulnerability factor for the development of depression. In AD, WM deficits act as a signal from normal aging to MCI, which is, to some degree, a prodrome of AD, and adults with MCI tend to develop AD much more quickly than those who are healthy. Even though WM deficits in MCI are not prevalent enough to interfere with daily activities, such impairments are clearer than the WM dysfunctions originating from normal aging. It was previously shown that adults with a-MCI were more likely to progress from MCI to AD, but recent evidence suggests that WM impairments can also be an early sign for AD. The Clément *et al*. study[22] consisted of fourteen participants (a-MCI and a-MCI+) split evenly into two groups: MCI higher-cognition and MCI lower-cognition, and each group was asked to complete a manipulation task, divided attention task, and focused attention control task. Consistent with the predicted hypothesis, results showed that the MCI higher-cognition group completed the divided attention task with higher performance quality and greater activation in the anterior cingulate cortex, which is primarily responsible for WM, whilst the MCI lower-cognition group appeared to have underactivation in corresponding brain regions. Before diagnosis of AD, one of the first symptoms to appear is divided attention, especially apparent in MCI adults with WM impairments. Furthermore, AD progression is often accompanied by WM and executive function deficits.[6]

Next, the association between depression and AD regarding episodic memory will be discussed through the Bierman *et al*. study. The study included forty-four late-life adults in early-stage AD as participants; their episodic memories were measured through the Auditory Verbal Learning Test (AVLT) with anxiety, depression, and confounding variables once and a follow-up one year later. Previous research points to comorbid hippocampal atrophy in both depression and AD greatly contributing to memory function decline. Therefore, the study aimed to test the predictive qualities of anxiety and depression for late-life early-stage AD. Surprisingly, results demonstrated no association between depressive symptoms and memory decline in both learning and recall in the AVLT and no significant association between depression and memory decline in the participants. In the one-year follow-up, depressive symptoms did not fluctuate significantly ($p = 0.24$), mean learning score decreased ($p = 0.04$) and mean recall score had insignificant changes ($p = 0.15$). These unexpected results may imply that depression does not, in fact, exacerbate memory and memory-related function decline in patients with AD.[16] The absence of a strong link between depression and episodic memory impairments in AD directs further research in a clear path: focuses on the association between depression and other memory mechanisms, exploration of different levels of depression severity, and attention directed towards WM impairments as vulnerability or signaling factors in depression and AD.

Effects of Antidepressants on Depression and AD:

Although unanticipated, antidepressants have been shown to have positive implications on the intervention processes of both depression and AD. This section will cover the independent but somewhat interrelated effects of all types of antidepressants on depression and AD. The main function of antidepressants is reflected in their alterations of neurotransmitter levels in the brain, particularly serotonin and norepinephrine from SSRIs and SNRIs, respectively. In depression, these newer types of antidepressants have greater efficacious and positive effects on reducing depressive symptoms and reviving declined cognitive function than older MAOIs and tricyclics, which have larger side effects due to lower affinity for acetylcholine (a neurotransmitter in which low levels are responsible for memory disorders) and amine receptors. Additionally, substantial use of antidepressants may lead to increased brain-derived neurotrophic factor (BDNF), which is a protein important for learning and memory functions. This suggests that BDNF administration can also contribute to regulating depression. However, despite the meritorious effects of antidepressants on depression, there are nevertheless potential side effects and varying effects in improvement of the symptoms.[17]

The effects of antidepressants on AD will be examined through the discussion of two studies. It has been shown that antidepressants have a positive impact in the decrease of dementia incidence, particularly AD. Long-term use of SSRIs can lead to improved cognition for depression and delayed cognitive decline or onset of AD.[18] The Borda *et al*. study investigated long-term effects of antidepressants on one-hundred ninety-six patients with AD over five years, focusing on cognitive and functional decline, measured by Mini-Mental State Examination (MMSE) and the Rapid Disability Rating Scale-2 (RDRS-2), respectively. Results showed that the use of antidepressants was not statistically significant enough to demonstrate a clear effect of the medication on cognitive and functional decline in AD. However, results on a specific type of antidepressant, SSRIs, suggest that the use of SSRIs, in fact, slows the progression of cognitive decline than no use.[19] To further confirm conclusions from the former study, a second somewhat homogenous study will be discussed. Similarly, the Caballero *et al*. study analyzed the long-term effects of antidepressants on patients with AD, although more closely examined the cognitive aspect of specific brain mechanism dysfunctions. Comparable results were found, with an insignificant difference in cognitive decline between AD patients who took antidepressants and those who did not. Specifically, cognitive decline measured annually was similar between AD patients on SSRIs and those not on antidepressants, with a mean decline of 2.55 points on the MMSE for those on antidepressants versus 2.27 points for those not. Particular types of SSRIs studied, that is, sertraline ($p = 0.37$) and citalopram ($p = 0.85$), appeared to have no significant changes in cognitive decline. Furthermore, the literature review presented in the study also demonstrated mixed results regarding the positive and negative implications of antidepressants on AD.[20] Therefore, these ambiguous results indicate the necessity for future research to focus on either specific types of antidepressants

other than sertraline and citalopram or therapeutic approaches as more effective treatment for depression and AD.

Future Directions:

Future research regarding the bidirectional association between depression and AD could look into other possibilities that explain the relationship between the two diseases beyond and based upon the foundation of the focus on memory mechanisms and antidepressants. For example, the role of olfactory markers and neuroinflammatory pathways could be particularly investigated as potential advancements to identifying more effective treatments for both conditions. Recent research has shown that impaired olfactory functioning linked to depression may serve as a prodrome to AD progression. Additionally, inflammatory cytokines, which are signaling proteins involved in immune responses, such as interleukins and tumor necrosis factors, affect the buildup and disposition of Aβ plaques and NFTs. Furthermore, future studies could examine the effectiveness of antidepressants in their potential neuroprotective effects through mechanisms including BDNF regulation and hippocampal regulation in not only depression, but also AD.[21] Exploring the use of advanced imaging techniques to track fluctuating brain activity in specific regions, such as the hippocampus and olfactory bulb, and utilizing such means to establish early indicators or biomarkers for both disorders may also be a potential area of future research. More thorough investigation of these targeted approaches could increase the efficacy of the detection of high-risk individuals, preventative strategies, and pharmaceutical and therapeutic interventions specific to both depression and AD.

Conclusion

Recent research has emphasized the prevalence of depression and AD and their significant challenges on society. This review has discussed in depth the complex relationship between these two common diseases, focusing on the implications for memory mechanisms and the potential role of antidepressants in managing both conditions. Early diagnosis of AD is especially crucial due to its often undetectable onset, steady progression from MCI to AD, and irreversible nature, implying a clear path for future research: focusing on the elucidation of early detection and intervention strategies for AD. Depression surprisingly shares a complex relationship with AD.[22] This review emphasizes three key categories of the association between depression and AD: depression as a risk factor, prodromal factor, or accelerating factor of the progression of AD. The connection in common hippocampal atrophy in both depression and AD further highlights the relationship between the two diseases. Both depression and AD have profound impacts on memory function, specifically on WM and episodic memory.[16] Studies have shown that depression impairs WM with effects even well into remission, and WM deficits may indicate the progression from MCI to AD.[15] In patients with AD and comorbid depression, research into episodic memory decline has remained inconclusive. Similar mixed results have also been demonstrated by studies that investigated the effects of antidepressants on depression and AD. While particular antidepressants, specifically SSRIs, have shown positive improvements in depressive symptoms and possibly a slower rate of AD pathogenesis, results are nevertheless ambiguous,[2,20] in which future studies are recommended to focus on clarifying these effects or experimenting with newer antidepressants. This review highlights the significance of clarifying the association between depression and AD. Early diagnosis and intervention continue to be significant in facing irreversible damages in the brains of the aging population, with a priority in treatment and prevention strategies in AD based on depression or in depression based on AD.

Acknowledgments

I would like to sincerely thank my mentor, Dr. Hannah Tarder-Stoll, and her teaching assistant, Monika Rybak, for their immense aid and professional comments for helping guide this paper. I would also like to thank the Indigo Research team for their support, resources, and this opportunity. I also want to thank my parents for their continuous support and encouragement.

References

1. Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*, *25*(24), 5789. https://doi.org/10.3390/molecules25245789
2. Scheltens, P., Strooper, B. D., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & van der Flier, W. M. (2021). Alzheimer's disease. *Lancet (London, England)*, *397*(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4
3. Van De Pol, L. A., Hensel, A., Barkhof, F., Gertz, H. J., Scheltens, P., & Van Der Flier, W. M. (2006). Hippocampal atrophy in Alzheimer disease: Age matters. *Neurology*, *66*(2), 236–238. https://doi.org/10.1212/01.wnl.0000194240.47892.4d
4. Cantón-Habas, V., Rich-Ruiz, M., Romero-Saldaña, M., & Carrera-González, M. del P. (2020). Depression as a Risk Factor for Dementia and Alzheimer's Disease. *Biomedicines*, *8*(11), Article 11. https://doi.org/10.3390/biomedicines8110457
5. Bomasang-Layno, E., & Bronsther, R. (2021). Diagnosis and Treatment of Alzheimer's Disease: *Delaware Journal of Public Health*, *7*(4), 74–85. https://doi.org/10.32481/djph.2021.09.009
6. Kirova, A.-M., Bays, R. B., & Lagalwar, S. (2015). Working Memory and Executive Function Decline across Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. *BioMed Research International*, *2015*, 748212. https://doi.org/10.1155/2015/748212
7. Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*, *75*(4), 336. https://doi.org/10.1001/jamapsychiatry.2017.4602
8. Richards, D. (2011). Prevalence and clinical course of depression: A review. *Clinical Psychology Review*, *31*(7), 1117–1125. https://doi.org/10.1016/j.cpr.2011.07.004
9. Zhang, Y., Boemo, T., Qiao, Z., Tan, Y., & Li, X. (2022). Distinct Effects of Anxiety and Depression on Updating Emotional Information in Working Memory. *International Journal of Environmental Research and Public Health*, *20*(1), 544. https://doi.org/10.3390/ijerph20010544
10. Cowan, N. (2014). Working Memory Underpins Cognitive Development, Learning, and Education. *Educational Psychology Review*, *26*(2), 197–223. https://doi.org/10.1007/s10648-013-9246-y

DOI: 10.36838/v7i4.23

11. Lyketsos, C. G., Carrillo, M. C., Ryan, J. M., Khachaturian, A. S., Trzepacz, P., Amatniek, J., Cedarbaum, J., Brashear, R., & Miller, D. S. (2011). Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *7*(5), 532. https://doi.org/10.1016/j.jalz.2011.05.2410
12. Dafsari, F. S., & Jessen, F. (2020). Depression—An underrecognized target for prevention of dementia in Alzheimer's disease. *Translational Psychiatry*, *10*(1), 1–13. https://doi.org/10.1038/s41398-020-0839-1
13. Kuo, C.-Y., Stachiv, I., & Nikolai, T. (2020). Association of Late Life Depression, (Non-) Modifiable Risk and Protective Factors with Dementia and Alzheimer's Disease: Literature Review on Current Evidences, Preventive Interventions and Possible Future Trends in Prevention and Treatment of Dementia. *International Journal of Environmental Research and Public Health*, *17*(20), 7475. https://doi.org/10.3390/ijerph17207475
14. Ehrenberg, A. J., Suemoto, C. K., de Paula França Resende, E., Petersen, C., Leite, R. E. P., Rodriguez, R. D., de Lucena Ferretti-Rebustini, R. E., You, M., Oh, J., Nitrini, R., Pasqualucci, C. A., Jacob-Filho, W., Kramer, J. H., Gatchel, J. R., & Grinberg, L. T. (2018). Neuropathologic Correlates of Psychiatric Symptoms in Alzheimer's Disease. *Journal of Alzheimer's Disease : JAD*, *66*(1), 115–126. https://doi.org/10.3233/JAD-180688
15. Semkovska, M., Quinlivan, L., O'Grady, T., Johnson, R., Collins, A., O'Connor, J., Knittle, H., Ahern, E., & Gload, T. (2019). Cognitive function following a major depressive episode: A systematic review and meta-analysis—ClinicalKey. *The Lancet Psychiatry*, *6*(10), 851–861.
16. Bierman, E. J. M., Comijs, H. C., Jonker, C., Scheltens, P., & Beekman, A. T. F. (2009). The effect of anxiety and depression on decline of memory function in Alzheimer's disease. *International Psychogeriatrics*, *21*(6), 1142–1147. https://doi.org/10.1017/S1041610209990512
17. Peng, G., Tian, J., Gao, X., Zhou, Y., & Qin, X. (2015). Research on the Pathological Mechanism and Drug Treatment Mechanism of Depression. *Current Neuropharmacology*, *13*(4), 514–523. https://doi.org/10.2174/1570159X1304150831120428
18. Dolotov, O. V., Inozemtseva, L. S., Myasoedov, N. F., & Grivennikov, I. A. (2022). Stress-Induced Depression and Alzheimer's Disease: Focus on Astrocytes. *International Journal of Molecular Sciences*, *23*(9), 4999. https://doi.org/10.3390/ijms23094999
19. Borda, M. G., Jaramillo-Jimenez, A., Oesterhus, R., Santacruz, J. M., Tovar-Rios, D. A., Soennesyn, H., Cano-Gutierrez, C. A., Vik-Mo, A. O., & Aarsland, D. (2021). Benzodiazepines and antidepressants: Effects on cognitive and functional decline in Alzheimer's disease and Lewy body dementia. *International Journal of Geriatric Psychiatry*, *36*(6), 917–925. https://doi.org/10.1002/gps.5494
20. Caballero, J., Hitchcock, M., Beversdorf, D., Scharre, D., & Nahata, M. (2006). Long-term effects of antidepressants on cognition in patients with Alzheimer's disease. *Journal of Clinical Pharmacy and Therapeutics*, *31*(6), 593–598. https://doi.org/10.1111/j.1365-2710.2006.00778.x
21. Naudin, M., & Atanasova, B. (2014). Olfactory markers of depression and Alzheimer's disease. *Neuroscience & Biobehavioral Reviews*, *45*, 262–270. https://doi.org/10.1016/j.neubiorev.2014.06.016
22. Clément, F., Gauthier, S., & Belleville, S. (2013). Executive functions in mild cognitive impairment: Emergence and breakdown of neural plasticity. *Cortex*, *49*(5), 1268–1279. https://doi.org/10.1016/j.cortex.2012.06.004

Author

Helena Wang is a student at Basis Independent Fremont. She is passionate about the interdisciplinary studies of brain research and drug development to reduce the amount of side effects in the brain associated with current drugs to allow for increased use for medication to expedite treatment processes.