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Grey Matters: The Unique Landscape of Depression Treatment in Older Adults

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Abstract

Late-life depression (LLD), a potentially life-threatening disease that severely impacts older adults' health and quality of life, is a growing public health concern due to the aging global population. This review explores the challenges of treating LLD, including its unique presentation, underdiagnosis, and limitations of current treatment methods. It also examines the potential mechanisms underlying LLD, including cognitive changes in older adults, social stressors unique to their circumstances, and biological pathways that overlap with those of neurodegenerative diseases. Rather than viewing LLD as a singular medical condition, this review argues that it is the combined manifestation of a variety of underlying issues, including stress and age-related neurological dysregulation, inflammation, and oxidation, as well as social and cognitive alterations. New approaches to treatment and research are necessary, including innovative pharmacological research targeting shared neurobiological pathologies, holistic and personalized treatment plans, and standardized psychotherapy protocols. Some examples of emerging research incorporating this full-bodied approach are presented, and recommendations are given for future research and treatment. In conclusion, this review highlights the significance of recognizing LLD as a multifaceted issue to improve the aging experience.

Keywords

Late-Life Depression

1. Introduction

As the world's elderly population continues to grow, geriatric mental health problems, like depression, anxiety, and suicide, are becoming increasingly prevalent, severely impacting the quality of life of older adults. Late-life depression (LLD), which refers to the occurrence of major depressive disorder in older individuals

(usually those aged 65 and above), can affect up to 5% of older adults in community dwellings, with as much as 16% of older adults exhibiting clinical depressive symptoms (Taylor, 2014).

LLD is associated with high rates of medical morbidity, mortality, cognitive impairment, hospitalization, and disability (Parkar, 2015; Gundersen & Bensadon, 2023; Schulz et al., 2002). Depressed older adults often experience more pain, malnutrition, and drug side effects than their peers, and see less optimal recovery from common medical conditions, like stroke, chronic obstructive pulmonary disease, and arthritis (Katz, 1996). Conversely, the rate of LLD also rises with medical comorbidity, especially in primary care and hospital setting (Taylor, 2014). Most alarmingly, suicide ideation is not uncommon in depressed elders (Vannoy et al., 2007). Mood disorders, especially depression, are the most prevalent disorders among older adults who have died by suicide, and older adults have a markedly higher suicide rate compared to younger age groups in many countries (Van Orden & Conwell, 2011).

Thanks to ongoing research, evidence and literature continue to grow on the prevalence, risk factors, causes, and potential treatment methods of late-life depression. This literature review aims to examine current advancements in research on late-life depression (LLD), summarize the unique challenges of treating LLD, explore its underlying mechanisms from cognitive and biological perspectives, and suggest future directions in treatment and research.

2. Diagnosing and Treating Late-Life Depression: Unique Challenges

2.1. Presentation

Although late-life depression does not have its own diagnostic criteria in the DSM manual, it often presents differently from depression in younger adults in phenomenology, optimal treatment, etiology, and risks (Husain-Krautter & Ellison, 2021; Hall & Reynolds-III, 2014). This is especially true for older adults who had their first depressive episode after the age of 65, thus differentiating "true", late-onset LLD from early-onset/recurrent depression that happens to recur in later life, the former of which is the main focus of this paper. In late-onset LLD, patients are often less likely to exhibit affective symptoms, instead displaying more somatic and psychotic symptoms, cognitive deficits, and loss of interest in activities (Fiske et al., 2009; Husain-Krautter & Ellison, 2021). A past meta-analysis also shows that they may display more hypochondriasis/anxiety and more gastrointestinal symptoms, but less guilt or loss of sexual interest than younger depressed adults (Hegeman et al., 2012). The typical portrait of an LLD patient is thus often someone who is agitated, leans more towards anhedonia and hopelessness than depressive mood, and suffers from cognitive impairments that could not be resolved—interestingly, this kind of late-life depression appears to have a weaker association with family history, indicating that genetic influence, typically assumed to be a substantial factor in depression, may work dif-

ferently in LLD (Power et al., 2017).

2.2. Prevalence and Underdiagnosis

Gauging the exact prevalence of LLD is difficult, as LLD often shares somatic symptoms with other age-related illnesses (e.g. pain, fatigue, and sleep disturbance), making it difficult to diagnose. Diagnosis may also vary depending on factors such as the geographic region, economic status, and living situation of older adults, and even the health practitioners' choice of screening tools (Power et al., 2017; Kales & Valenstein, 2002).

As such, it is unsurprising that there is no consensus on the prevalence of elderly depression in the current literature, even in Caucasian communities in developed countries where LLD has been most extensively studied. A seminal review in 2006 found that the prevalence of major depression in older adults in this population could vary from 0.86% to 42%, while the prevalence of clinically relevant depressive symptom cases varied from 7.2% to 48%, depending on the specific community and the tools used (Djernes, 2006). In 2016, Guerra et al. expanded on the literature by examining LLD prevalence in nine low and middle-income countries using ICD-10 and EURO-D as their criteria; the former yielded a prevalence of about between 0.3% and 13.8%, while the latter yielded a prevalence between 1.0% and 38.6% (Guerra et al., 2016). More recently in 2021-22, Abdoli et al. reviewed 20 studies around the world and calculated the prevalence of major depression in older adults to be 13.3% globally, Zenebe et al. reviewed 42 studies and estimated the prevalence of depression in old age to be 31.74%, and Hu et al. reviewed 48 studies and found that 28.4% of the older adults screened positive for depression (Abdoli et al., 2021; Zenebe et al., 2021; Hu et al., 2022). These results combine to suggest that the average prevalence of LLD is around 10% - 30%, although all three reviews mentioned enormous heterogeneity among the data analyzed; therefore, actual rates can be much higher or lower in specific communities.

Depression is underdiagnosed across all age groups, and LLD is no different, as confirmed by recent population studies. For example, a community study conducted in Pella, North Greece, found that over 30% of the 160 subjects who reported no prior experience with depression were found to have moderate or severe depressive symptoms upon screening (Argyropoulos et al., 2018). Similarly, a study from Chile found that roughly 70% - 80% of older adults who screened positive for depression had never previously received a diagnosis (Moreno et al., 2022). Evidently, unclear prevalence and underdiagnosis of late-life depression remain a serious problem.

2.3. Treatment

Depression treatment in older adults, especially with antidepressants, has been drastically increasing since the last century (Gaboda et al., 2011)—however, undertreatment is still common whether in community living or primary care (Barry et al., 2012). In addition, undertreatment has been found to increase with age in

both hospital and home care settings (Szczerbińska et al., 2012). In a recent study of 30,000 older adults from 17 European countries, a striking 80% of European elders with late-life depression were not receiving adequate mental health treatment (Horackova et al., 2019). Worryingly, older adults who were inadequately treated for depression appear to have a worse prognosis than their younger counterparts, although evidence has been scarce and mostly comes from observational studies (Kok & Reynolds, 2017).

When depressed older adults do receive treatment, antidepressants remain one of the most common first-line measures, and all three kinds of antidepressants (TCAs, SSRIs, MAOIs) are generally effective and tolerated by older patients (Bottino et al., 2012). However, many patients do not respond to antidepressants at all (Gutsmiedl et al., 2020; Mallery et al., 2019) or see only limited benefits and no remission (Piel & Quante, 2023). Several factors specific to older adults may contribute to their treatment resistance, including comorbid medical conditions, functional changes in the brain during aging, poor adherence to treatment due to memory/cognitive decline, changes in drug metabolism, and suboptimal prescription of antidepressants (Lenze et al., 2008; Kok & Reynolds, 2017). Antidepressants can also be overprescribed, particularly newer ones used for non-specific psychiatric symptoms and subthreshold diagnosis (Bobo et al., 2019). This is especially pertinent because any antidepressant medication for older adults should be prescribed cautiously due to their frailty and the possibility of interaction with other medication; in fact, irresponsible use of TCAs and SSRIs could potentiate older patients for negative events like kidney and cardiovascular failure, hyponatremia, or falls (Sultana et al., 2015).

While there are also studies on nonpharmacological interventions for depressed older adults, a systematic review of their effectiveness is difficult. A 2019 review found only five studies with comparable data, which indicated the potential usefulness of interventions like mindfulness, memory training, and collaborative care (Krause et al., 2019). For treatment-resistant late-life depression, augmentation with other psychopharmacologic medication, electroconvulsive therapy, transcranial stimulation, and novel medical treatments like ketamine/esketamine are also potential solutions (Subramanian et al., 2023); however, all these measures require further testing before they can be implemented in large populations.

3. Possible Mechanisms of LLD: Toward a Systemic Explanation

3.1. Cognitive Mechanisms

With age come numerous social and cognitive changes, some of which may explain these differences in the phenomenology of depression in older people compared with younger adults. As individuals age, older adults often experience significant changes in their external social roles—for example, the loss of a valued career or caretaking role can lead to a decrease in overall social engagement, while

bereavement and reduced independence make isolation a common occurrence in older adults—all these factors can subsequently become major contributors to geriatric depression (Allan et al., 2014).

A corresponding change can be noticed internally, in the way older adults regulate emotions, their cognitive style, and biases. An example of this is the often-acknowledged existence of a "positivity bias", whereby aging adults attend more to positive than negative stimuli (Knight & Durbin, 2015; Gray et al., 2021). This positivity bias has been demonstrated to exist in various areas of cognition—as people age, they may start to recall more false positive than false negative memories (Fernandes et al., 2008), adopt more passive and less reactive strategies in the face of interpersonal conflict (Charles et al., 2009), or demonstrate less attention fixation on negative study materials (Livingstone et al., 2018). It is important to recognize cognitive changes like these as they may contribute to the unique qualities of late-life depression discussed previously. In addition, they also highlight the need for more targeted diagnosis and treatment methods for older patients with depression. For instance, as older adults tend to self-report more positive emotional affect and more emotional regulation than younger adults overall (Gross et al., 1997), the result of depression diagnosis using self-report questionnaires from older adults may be skewed. Another study, which concludes that older adults suffer a decline in their ability to utilize emotional regulation strategies like detached reappraisal, but improve when it comes to using strategies like positive reappraisal (Shiota & Levenson, 2009), demonstrates that older adults may need more targeted therapy and training programs tailored to their cognitive style.

Closely tied to cognitive modifications are changes in older adults' psychological "resilience", a factor that plays an important role in moderating mood disorders as it pertains to various "mental, social, and physical factors that lead to optimal outcomes of improved quality of life, happiness, and wellbeing as well as reduced depression" (Macleod et al., 2016). Contrary to traditional definitions of resilience as a stable, trait-like quality, current research recognizes it as a process that can change and develop over time—that is to say, resilience is theorized to be a multifaceted and evolving ability, the qualities of which may change throughout a lifetime of interaction between internal and external factors (Laird et al., 2019). One study that investigated psychological resilience in older (over 64) versus younger (under 26) adults, for example, found that older adults demonstrate more resilience in emotional regulation and problem-solving, while younger adults display more resilience when it comes to social support; additionally, physical and mental illnesses affected resilience differently in the two age groups, suggesting the involvement of divergent psychological processes or at least new developments in resilience across the lifespan (Gooding et al., 2012). The unique set of adverse life events as well as protective factors experienced by older adults likely explains this phenomenon; as such, ongoing studies are now focusing on developing a new scale to assess resilience in older adults, designing psychological treatments based on such measures, and exploring factors that enhance or

detract from it (Li & Ow, 2022).

Finally, poor mental health literacy in the elderly population and pessimistic views on geriatric depression are more specific cognitive factors that might contribute to difficulties in diagnosing and treating LLD. Compared to younger adults, older adults are less knowledgeable about common mental health problems and, therefore, less likely to recognize symptoms of depression: research shows that they are less accurate at characterizing symptoms as either anxiety or depression, and have a higher tendency to characterize them as neither (Wetherell et al., 2009). In primary care settings, both medical professionals and patients share a pessimistic perspective that late-life depression is "natural" or "untreatable". A qualitative study shows that primary care practitioners generally see depression as a routine aspect of old age rather than as a clear medical diagnosis, and both practitioners and patients often view clinically low mood in older patients as "justifiable". The patient group, in particular, can have limited expectations about the effectiveness of treatment, or not view depression as a legitimate illness to bring up to their GP (Burroughs et al., 2006). This, perhaps, explains why older adults often try managing symptoms independently without seeking professional help, until finally "muddling through" to some form of treatment when symptoms become severe (Nair et al., 2019; Berard et al., 2020). While it is probable, even likely, that the diagnosis and treatment of geriatric depression may require a different approach than the traditional medical model, it can still be concluded that a lack of mental health awareness is discouraging older depressed patients from seeking medical attention, thus resulting in underdiagnosis or less effective treatments.

3.2. Biological Mechanisms

Much like the etiology of depression in general, the precise biological mechanisms underpinning late-life depression are not fully understood. However, recent studies are shedding more light on the complicated nature of this problem. A significant development is a growing number of studies suggesting a reciprocal—or at least intertwined—relationship between LLD and neurodegenerative diseases like dementia, Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Particularly, there is growing evidence that LLD may share common pathological pathways with these neurodegenerative illnesses; certain subtypes of LLD may even be their prodrome or by-product.

This section seeks to explore and highlight this relationship by examining evidence from both structural-functional and neural-molecular perspectives. For a visual summary, please refer to **Figure 1**. It is important to note that these pieces of evidence should not be viewed as representing separate and independent pathways. Indeed, it is more likely for one biological change to result from another, or for all pathways to act in concert to contribute to the development of depression and neurodegeneration in aging. A more detailed understanding of this process is needed in order to improve treatment approaches and outcomes for individuals suffering from both late-life depression and neurodegeneration.

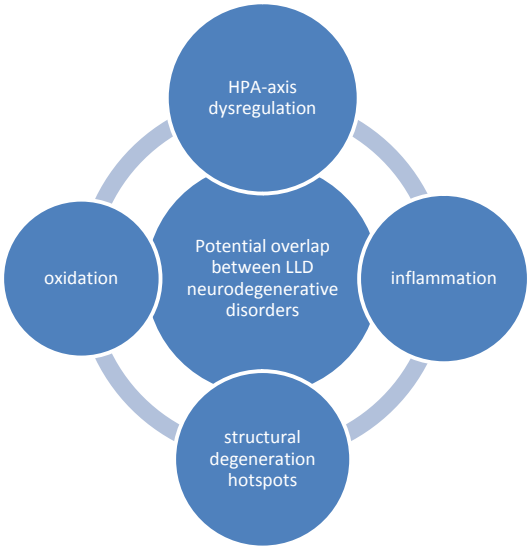

Figure 1. Summary of mechanisms mentioned.

3.2.1. Structural and Functional Changes

The development and expression of age-related neurodegenerative disorders and geriatric depression have been shown to affect similar brain regions, including frontal-subcortical networks, the hippocampus, and white matter microstructure.

In older adults, depression frequently co-occurs with conditions that affect the subcortical structures of the brain, such as vascular dementia, PD, and HD (Alexopoulos, 2019). As such, Alexopoulos et al. proposed a specific type of depression-executive dysfunction (DED) syndrome characterized by symptoms like clinical depression, poor response to antidepressants, and declining cognitive abilities (e.g. problem-solving, verbal fluency, working memory, psychomotor agency). All of the above are symptoms closely tied to the disruption of the frontal-subcortical region, indicating that a certain subtype of LLD patients may suffer from pathological mechanisms closely related to those of vascular dementia and PD.

It is not uncommon for LLD patients to have white matter lesions and hyperintensities in the aforementioned subcortical structures and their frontal projections (Taylor et al., 2003). Research even suggests that white matter hyperintensities (WMH) could be one of the biological mechanisms underlying the cognitive and affective problems LLD patients suffer (Kim & Han, 2020). Linking this to other neurodegenerative disorders is the fact that WHM is also a well-established predictor of dementia, as well as cerebrovascular events overall (Debette & Markus, 2010). Increased WHM can generally be considered an indicator of both vascular risks and cognitive decline (Newton et al., 2023). Therefore, it can be reasonably hypothesized that the existence of WMH may indicate the presence of small-vessel cerebrovascular diseases that can cause, be caused by, or have reciprocal relationships with the cognitive and affective impairments seen in both LLD and dementia (Butters et al., 2008; Brickman et al., 2009; Alexopoulos,

2019). While the evidence is not as robust, grey matter volume has also been found to be significantly altered in age-related neuropsychiatric and neurodegenerative conditions, including AD, PD, HD, and major depression (Luo et al., 2019).

The hippocampus is a brain region that shows marked atrophy in both depression and other neurodegenerative disorders. Hippocampal atrophy is very noticeable in patients with AD; in fact, decreasing hippocampal volume and hippocampal atrophy rates are recognized as features that may mark the transition from mild cognitive impairment to the full onset of AD (Falgàs et al., 2019; McRae-McKee et al., 2019). Hippocampal atrophy is also prominent in patients with late-life depression, as a meta-analysis study observed that LLD patients had significantly smaller hippocampal volumes when compared to controls, a change which, interestingly, is more pronounced in patients with "true" late-onset LLD than early-onset depression (Geerlings & Gerritsen, 2017). Such evidence is complemented by research showing that depressive symptoms may be both a risk factor for and a prodrome of AD (Gutzmann & Qazi, 2015). As such, it is quite possible that the hippocampus is an important neuroanatomical link between depression and dementia.

3.2.2. Neural/Molecular Changes

Stress plays a critical role in both depression and neurodegeneration. Prolonged stress can result in neurological and molecular changes such as hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, overproduction of pro-inflammatory cytokines and glucocorticoids, and oxidation. Current findings suggest these mechanisms may significantly impact the development of major depression, while also being involved in the pathogenesis of neurodegenerative disorders such as AD, PD, and HD.

The HPA axis is sometimes called "the final common pathway in the stress response" (Swaab et al., 2005), and its hyperactivity is a characteristic feature of major depression. Many biological changes associated with this hyperactivity have been identified through extensive research, including heightened secretion and reactivity of cortisol, elevated levels of corticotropin-releasing hormone (CRH), as well as impairment of the glucocorticoid-mediated negative feedback loop of the HPA axis itself (Zunszain et al., 2011). While less intensively studied, it is recognized that HPA-axis dysregulation is also present in AD, which is indicated by elevated levels of glucocorticoids in AD patients (cortisol in humans and corticosterone in mice); high cortisol levels may then contribute to an increase in Aβ deposits, which is a hallmark of AD (Ahmad et al., 2019). The brain, therefore, enters a vicious cycle where the progression of AD triggers further dysregulation of the HPA axis, which in turn exacerbates AD pathology (Canet et al., 2019). Review articles on whether HPA-axis pathology mediates comorbid depression in AD, PD, and HD presented preliminary evidence that HPA dysregulation is also present in the latter two diseases (i.e. non-depressed early-stage PD and HD), but the scarcity of large cohort human studies and sub-

stantial results means that no concrete conclusion can yet be drawn (Du & Pang, 2015; Galts et al., 2019).

Another product of stress that is implicated in both depression and other neurodegenerative diseases is inflammation. Pro-inflammatory cytokines such as TNF-*α*, IL-1, IL-6, and IL-8, which increase due to stress, can negatively impact glucocorticoid receptors in the HPA axis's negative feedback loop, leading to the system's hyperactivity as mentioned earlier (Kuo et al., 2021). Additionally, these cytokines may contribute to depression by causing brain damage and reduced availability of the neurotransmitter 5-HT i.e. serotonin (Catena-Dell'Osso et al., 2011), disrupting neurogenesis and neuroplasticity, and impairing brain networks (Forbes et al., 2021). Many cytokines, including the aforementioned TNF-*α*, IL-1, IL-6, and IL-8, are also elevated in AD; while exact pathways are unclear, these cytokines are known to contribute to the hyperphosphorylation and aggregation of the tau protein, another hallmark of AD pathology as misfolded tau can clump into neurofibrillary tangles, accumulating in brain cells and contributing to AD toxicity (Gao et al., 2018). Higher levels of cytokines like TNF-*α*, IL-6, and IL-8, are also observed in PD patient, especially PD patients with comorbid LLD; early stages of HD is likewise marked by higher concentrations of plasma cytokines and well as other inflammatory markers like microglia accumulation (Galts et al., 2019). Overall, it is highly likely that inflammation plays a key, if not causal, role in the progression of all three illnesses by causing increased brain damage and environmental toxicity.

While these pieces of evidence remain circumstantial and cannot prove any causal relationship between stress-related neuronal changes, LLD, and neurodegenerative diseases, it is likely that a common stress/inflammation-related pathway aggravates a cohort of different illnesses. Aging comes with its own group of unique stressors, such as bereavement/widowhood, social isolation, loss of social roles, pain, and even elder mistreatment, potentially leading to the brain pathology involved in both types of disorders (Alexopoulos, 2019). Therefore, it is possible that stress-induced hyperactivity of the HPA axis, as well as over-secretion of stress-related hormones, contribute to the degeneration underlying both geriatric depression and cognitive decline.

Another common occurrence in old age is increased oxidative stress (OS), which may impact LLD, neurodegenerative illnesses, as well as cardiovascular diseases. Research shows that inflammation and OS, which feed into each other, combinedly contribute to necrosis/apoptosis, decreased plasticity, and finally, brain-damaging events like stroke and traumatic brain injury in aging (Shao et al., 2020; Jelinek et al., 2021). While its role in cerebro-cardiovascular damage is quite established, the role of OS in psychiatric disorders is still being explored. Shao et al. proposed that OS may be at the crossroads between aging, LLD, and stroke; similarly, Luca et al. proposed that OS plays a key role in the pathogenesis of both psychiatric and cardiovascular disorders (Luca et al., 2020). Relevant literature offers promising evidence for these hypotheses. In LLD, the role of OS

is substantiated by preliminary research showing that depressed older adults suffer from more oxidative DNA damage (Vieira et al., 2021). In AD, OS is believed to lead to mitochondrial dysfunction, which increases Aβ production, while the toxicity Aβ further exacerbates oxidative stress within the brain; at the same time, OS can cause DNA damage, suppression of DNA repair, and epigenetic changes, which may underlie cognitive decline (Ionescu-Tucker & Cotman, 2021).

In conclusion, the relationship between late-life depression and neurodegenerative diseases like AD is a complex interplay worthy of intensive research. A summary of emerging evidence discussed here is presented in **Figure 1**. Currently, research from both a structural-functional perspective and a neural-molecular perspective suggests that these conditions may share underlying biological mechanisms, or be exacerbated by similar environmental pathways. Developing effective pharmacological treatments will likely require a multifaceted approach.

4. Analysis and Emerging Research

4.1. Analysis

In Part 2 of this article, unique challenges were presented regarding geriatric depression. In Part 3, the potential mechanisms underlying the disorder were also discussed. Combined, the evidence surrounding LLD suggests several traits that need to be taken into account when developing better treatment options that are more suitable for the elderly population. These include the unique cognitive styles of older adults, interacting neurodegenerative and cardiovascular illnesses, pharmacological complications, unique social stressors, inflammatory and oxidative mechanisms, and more. Of course, non-geriatric factors that are thought to influence major depression, such as genetics and dysfunctional cognitive processing, still need to be considered (Husain-Krautter & Ellison, 2021). For a comprehensive summary, see **Figure 1**.

Taken together, converging evidence suggest that geriatric depression may not be a specific mood disorder that the current medical model commonly presents it as, but rather exists as a collection of depressive symptoms resulting from many different pathological processes, which then manifest through various biological pathways. Hence, it is not optimal to diagnose, treat, or study geriatric depression separately from other mental or physical disorders that occur later in life, such as dementia. Instead, these conditions would ideally be studied together to seek common mechanisms, underlying pathology, bilateral influences, common resilience factors, and other relevant information. That is to say, research and treatment will benefit from a more systemic approach, where late-life depression should be treated as a group of symptoms reflecting an underlying, full-body problem instead of a singular medical disorder.

Similar models have been put forward in the last decade. For example, in 2013, McKinney and Sibille proposed the "age-by-disease interaction hypothe-

sis", suggesting that the clinical symptoms of LLD are the "integrated output" of 1) changes in gene expression with age and 2) contributing factors like genetic predisposition, environmental pressure, and biochemical changes that together "push" the patient into disorders like LLD (McKinney & Sibille, 2013). Their paper advised that researchers further investigate molecular processes of aging, and develop interventions that would either slow down aging for critical genes, or repair and maintain proper telomere length, in an interdisciplinary effort that brings together aging and neuropsychiatric research. In a similar yet perhaps more treatment-focused vein, this paper suggests that future research zone in on pharmacological remediations for shared pathological pathways, full-bodied treatment approaches that improves the overall health of older adults, and flexible psychotherapeutic methods that tackle can social and cognitive stressors in the elderly population.

It may seem daunting to provide such treatment without a complete understanding of the multiple pathways involved in LLD. However, recent research in this area already shows promise. While some of these studies that take a systemic mindset have already been mentioned in Section 3, this section aims to more specifically explore current depression research from the perspective of novel treatment approaches.

4.2. Emerging Systemic Treatment & Research

Studies on the commonality between Alzheimer's disease and late-life depression have yielded significant results in the past two decades. For example, the impaired signaling of certain neurotrophins, such as transforming growth factor β1 (TGF-β1) and brain-derived neurotrophic factor (BDNF), has been identified as a common feature of both depression and Alzheimer's disease. BNDF is highly expressed in the hippocampus, previously demonstrated to be an anatomical region heavily implicated in both AD and LLD, and it is found to be associated with antidepressant effects and improved cognition (Linnemann & Lang, 2020). Thus, some current efforts in developing new treatments are focused on enhancing neurotrophin signaling. In particular, pharmacological interventions like antidepressants, aspirin, and lithium have been proposed to support neurotrophin signaling in both LLD and AD (Caraci et al., 2010).

A more debated yet nonetheless promising research area is whether amyloid-β peptide (Aβ) deposition, a pathological characteristic of AD, is related to depression and can be modulated by antidepressants. So far, some evidence suggests that Aβ levels are significantly altered in patients with long-term depression in the same direction it is in AD patients (Yasuno et al., 2016), pointing to the possibility of a shared mechanism or causal relationship. Meanwhile, in many animal studies, acute and chronic administration of SSRIs such as paroxetine and citalopram have been shown to reduce Aβ levels; however, in some human studies, such change either wasn't evident, or was in the opposite direction (Cassano et al., 2019; Alexopoulos, 2019). Such contrasting evidence indicates the need

for more research on the relationship between Aβ, AD, depression, and antidepressants.

Research on oxidative stress and LLD have also taken strides in the last five years. In 2018, a study demonstrated that an imbalance between anti-oxidative and oxidative stress markers, especially lipid peroxidation, is heavily implicated in LLD (Diniz et al., 2018). More recently, researchers demonstrated in a small sample that 8-oxo-DG, a marker of oxidative DNA damage, is elevated in LLD patients (Vieira et al., 2021). Meanwhile, Juszczyk et al. examined the theoretical and factual basis of using antioxidants to prevent and treat AD and depression, citing natural and chemical compounds such as curcumin, selenium, and Vitamin E as having great potential (Juszczyk et al., 2021) and thus pointing a path toward future treatment research.

Besides pharmaceutical interventions, there have also been advances in other treatment methods, a few of which deserve highlighting for their full-body approach to the problem. One treatment model that has proved highly effective is the Collaborative Care Model, where one primary care physician leads a team that includes psychiatrists and/or behavioral therapists to create a treatment plan and provide service for one patient. This model has proven effective for late-life depression management in many studies in the last two decades; its efficacy is sustained both in the US and low or mid-income countries, and across ethnicities (Unützer et al., 2002; Wagner et al., 2022; Scazufca et al., 2022; Chen et al., 2022). A possible interpretation is that older adults are perhaps one of, if not the most, suitable populations for collaborative care, as a collaboration between the primary physician and behavioral/psychiatric experts could help address the complex social, medical, and cognitive-behavioral risk factors in late-life depression.

The success of the collaborative care model psychotherapy also implies the efficacy of psychotherapy/behavioral interventions, whether as an augmentation of pharmaceutical methods, or a standalone treatment for patients with milder symptoms. While the benefit of psychotherapy is less easy to quantify in a large population compared to medication, as Power et al. rightfully pointed out, psychotherapy has no side effect, does not interact with medication, and can be flexibly adapted to address issues unique to the patient population, such as lack of activity, isolation, loneliness, and pain from the loss of physical and executive functions. As addressed in Section 3, these are all potential causes of late-life depression and may actually be areas where older adults need the most support.

Reminiscence therapy (RT), where older participants recall and interpret their past life experiences based on triggers and prompts provided by professional therapists, is one psychotherapeutic method that has been increasing in popularity. It has been found to not only improve mood and life satisfaction in cognitively-intact older adults (Tam et al., 2020), but could also be effective in improving cognition and quality of life in patients with Alzheimer's disease and dementia (Cuevas et al., 2020; Saragih et al., 2022; Lök et al., 2019). This suggests

that RT may stimulate or engage a comprehensive brain network or region that affects both mood and cognitive abilities. Preliminary analysis also shows that group reminiscence therapy can be more effective and cost-effective than individual reminiscence therapy—the interpretation being, of course, that group therapy provides more social connection and interactive opportunities that older adults need—although additional studies are needed to substantiate this difference (Liu et al., 2021). Despite its popularity, however, several systematic reviews found RT to have inconclusive or limited effectiveness (Hsieh & Wang, 2003; Thomas & Sezgin, 2021); this can probably be attributed to there being no evidence-based standard protocol for administering RT for large groups of people. To address these concerns, future trials of RT may benefit from a globally standardized application protocol, as suggested by Liu et al. (2021) and Saragih et al. (2022). Further research into the underlying mechanisms of why and how RT works could also provide additional insights to improve its efficacy.

Another full-body treatment that can potentially improve mood, as well as cognitive function in older adults, is exercise. Commonly-used physical interventions in the elderly include aerobics (e.g. walking), balance and flexibility training, and resistance/strength training, and the very versatile nature of physical training means that these components can be combined into diverse intervention programs to target individual needs (Angulo et al., 2020). A multi-analysis of 15 RCTs demonstrated that aerobic, resistance and mind-body exercises are all effective treatments for older adults with clinical depression (Miller et al., 2019). Another review showed that exercise resulted in a small but significant improvement in cognitive functions in patients across six psychiatric disorders, including AD, PD, and HD, as well as significant improvements in quality of life and mood; however, the review also noted much heterogeneity and mixed results in the studies analyzed (Dauwan et al., 2021). It is hypothesized that regular exercise can improve mood and cognition through a variety of pathways previously discussed in this paper, including regulating the HPA axis, reducing oxidative stress and inflammation, increasing BDNF and supporting neurogenesis, and mitigating comorbid cardiovascular issues (Veronese et al., 2019; Luca & Luca, 2019). Future research can help elucidate exercise's role in promoting overall brain and mood health through each of these pathways.

5. Limitations

When conducting studies on aging cohorts, it is common to encounter limitations that are specific to this population. A central problem is distinguishing between "normal aging" and actual pathology, as the two can have overlapping manifestations. In describing the presentation of LLD, this paper emphasized somatic symptoms, loss of interest, and cognitive deficits—however, these symptoms may be considered too common in older adults to signal a mood disorder. The frontal lobe and hippocampus, which are implicated in LLD, can decline even in healthy older adults, and some level of memory impairment and cogni-

tive decline is almost expected; evidence also suggests that inflammation is a prevalent mechanism that is naturally heightened in older individuals (Scheiblich et al., 2020). A qualitative study has suggested that there is in fact minimal distinction between subsyndromal depression and normal aging in the very elderly, although both remain distinguishable from syndromal depression (Ludvigsson et al., 2014). While that study was performed on a very small community sample, the findings still imply that either some form of mood changes may be a natural aspect of aging, or current psychiatric tools are too insensitive to identify pathological changes without the help of neuroimaging and invasive procedures. That being said, this paper holds that older adults can still experience clinical depression, even should their "normal" baseline mood differ from that of younger people. LLD is not an inevitable aspect of the aging process, as evidenced by the presence of non-depressed older adults. Thus, it is crucial to improve clinical measures to better diagnose syndromal and subsyndromal LLD, instead of signing it off as a normal part of aging.

Another limitation concerns the methodology of geriatric studies overall and whether their findings apply to the broader elderly population. Aging studies that utilize large national census-type datasets are rare, and most studies, including those reviewed in this paper, rely on data from either a single community (e.g. a city or a care facility) or availability samples recruited through advertisements (Hultsch et al., 2002). The former makes it hard to generalize findings to a larger population, while the latter suffers from self-selecting sampling. Presumably, older adults who can transport themselves or be transported to a university lab are generally more mobile and knowledgeable about study protocols than their peers, meaning they may be healthier, wealthier, and well-educated. As expected, a study also found that the older study participants are, the less they are representative of their age group (Golomb et al., 2012). Fortunately, there is growing awareness about identifying and addressing barriers to representation. Knechel (2013) identified several modifiable barriers to recruiting older participants, such as lengthy and complex consent forms, transportation difficulties, and concerns about invasive procedures. For minority older adults, including those from ethnically and socially diverse or rural backgrounds, these barriers may be exacerbated by additional factors such as a history of racism in research, cultural differences, and fear of exploitation (Forsat et al., 2020; Indorewalla et al., 2021). Therefore, to achieve greater representativeness, researchers can aim to provide flexible appointment times, home visits, shorter assessments, better transportation, and financial compensation; for minority older adults, it is also advised to work closely with community-based care providers for referrals (Marcantonio et al., 2008; Indorewalla et al., 2021).

Finally, a limiting factor that is extremely complex yet still worth briefly mentioning is the existence of frequent drug-drug, drug-disease, and disease-disease interactions in LLD patients, given their increased medical burden and frailty. For example, antidepressants can interact with other medications being taken

(drug-drug interaction), increase the risk of negative events like cognitive decline, hyponatremia, bleeding, osteopenia, and falls (drug-disease interaction), or be less effective in frailer older adults due to potential interaction between illnesses (disease-disease interaction) (Nelson, 2018; Brender et al., 2021; Brown et al., 2021). A good example is a study by Sneed and colleagues, who found that LLD patients with deficient response inhibition (DRI) did worse on cognitive tasks when they started SSRIs, meaning there is a negative interaction between antidepressants, DRI, and LLD (Sneed et al., 2010). Such evidence, of course, is not an argument against antidepressants—the benefit of treating LLD may offset the cost of drug interactions (Brender et al., 2021), and indeed some drug side effects like pain relief and sedation can be beneficial for older patients (Nelson, 2018). It does, however, highlight the complication of interpreting LLD research results, which drug and disease interactions can significantly distort, especially in smaller cohorts.

6. Broader Implications

The findings of this literature review suggest several broad implications for future research, treatment, and health policies.

Treatment: As LLD is often underdiagnosed and undertreated, better mental health education is needed to increase awareness about LLD in both primary care providers and older adults themselves. Collaborative care models that bring together physical and mental healthcare providers to develop comprehensive intervention plans for older patients may also effectively improve the detection and treatment of LLD.

While antidepressants will likely continue to be the primary method of treatment for LLD, we must prioritize efforts to design more flexible, accessible, and low-risk interventions. Programs such as psychotherapy and exercise may be beneficial for older adults with depression not only because of how they target full-bodied underlying mechanisms of LLD, but also because they can provide relief from social stressors like isolation, loss of function, and loneliness. Developing and testing standardized, evidence-based protocols for these interventions is paramount.

Research: Since depression in older adults is often linked to shared pathological pathways in aging and neurodegeneration, such as inflammation, problems with central nervous system regulation, and prolonged and oxidative stress, future research should try to elucidate how these pathways contribute to LLD, and develop targeted interventions. Meanwhile, special attention should be given to how drugs and diseases interact in the elderly population and how these interactions impact research results. Other potential interventions for treatment-resistant depression, such as antioxidants, should also be further explored.

In addition, in order to improve representativeness in LLD research samples, steps should be taken to make it easier for older adults of all backgrounds to participate in scientific studies. These steps may include recruiting participants from

community outreach programs, providing more mobility support and compensation for transportation to research facilities, minimizing red tape, and making appointment times flexible.

7. Conclusion

Overall, this review highlights the need for a multifaceted approach to the research treatment of late-life depression that takes into account the unique circumstances and needs of older adults. New approaches to treatment and research, including innovative and interdisciplinary pharmacological research, personalized treatment plans, and flexible therapy tools, are presented and discussed. Future research should continue to investigate promising LLD interventions while improving access to mental healthcare and diversifying representation in geriatric studies. Recognizing the complexity of LLD is crucial to improving the quality of life for older adults and advancing the field of geriatric mental health.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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