LUMEN ET VIRTUS
ISSN: 2177-2789

CHALLENGES AND STRATEGIES IN THE MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN THE ELDERLY: A SYSTEMATIC REVIEW OF COMORBIDITIES AND PHARMACOLOGICAL APPROACHES

https://doi.org/10.56238/levv15n41-044

Submitted on: 11/09/2024 **Publication date:** 11/10/2024

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ABSTRACT

Objective: The general objective of this study is to compile and evaluate the scientific evidence on Major Depressive Disorder (MDD) in elderly individuals, highlighting the main clinical manifestations and management strategies of this comorbidity for greater clinical elucidation. Methodology: This is a systematic review guided by the question: "What are the main comorbidities associated with depression in geriatric patients, as well as the management used to treat the clinical practice?". The searches were performed in the PubMed Central (PMC) database using the descriptors: Depressive Disorder and Elderly, and Depressive Disorder and Health Care for the Elderly, combined with the Boolean term "AND". A total of 170 articles were identified, of which 13 met the inclusion criteria, resulting in the analysis of a total of relevant studies. Results: MDD in the elderly is a significant public health challenge, with a high prevalence of comorbidities, frailty, and the impact of neurocognitive dysfunctions. Screening tools, such as the Geriatric Depression Scale, are useful but have limitations in excluding somatic symptoms. Pharmacological treatment should be administered with caution due to polypharmacy and frequent drug interactions. Nonpharmacologic interventions, such as lifestyle modifications and reduced polypharmacy,

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can improve depressive symptoms and quality of life in older adults. Conclusion: An in-depth understanding of MDD in older adults is critical to improving clinical practices and patient outcomes, necessitating a holistic and ongoing approach. Future studies should prioritize specific therapeutic strategies that include a comprehensive assessment of the physical, mental, and functional health of this vulnerable population.

Keywords: Major Depressive Disorder. Elderly. Treatment. Comorbidities.

INTRODUCTION

Depression is a disabling condition in older adults. In the geriatric population, depression is related to a lower level of well-being and quality of life, functional decline, cognitive impairment, early hospitalization in nursing homes, and even premature death by suicide or as a result of chronic somatic diseases. These negative health repercussions are linked to a depressive disorder according to the criteria of diagnostic classification systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the International Classification of Diseases (ICD-11), as well as to clinically relevant depressive symptoms (CRDS) measured by self-reported rating scales.

Statistics indicate that the global population over 60 will double between 2015 and 2050, increasing from 12.0% to 22.0%. With the rapid growth of the elderly population, late-life depression (LLD) has gradually emerged as a major topic in the field of geriatric medical research. LLD refers to depressive disorders that occur in adults over the age of 60. The survey results indicate an overall LLD prevalence of 28.4%, which may potentially be higher among individuals with concomitant physical illnesses.

There are several risk factors for depression in old age. First, possibly relevant risk factors, such as bereavement, isolation, disability, and somatic diseases, are more prevalent in old age. Second, research shows that depression in old age can be a prodromal or risk factor for adulthood. Third, the prognosis of late-life depression appears to be worse than for younger age groups. In addition, late-life depression has been found to be severely underdiagnosed by primary care physicians, considering the presence and persistence of depression.

Depressive disorder is the leading cause of disability worldwide. It is also associated with psychosocial dysfunction, high societal costs, and premature mortality compared to the general population, largely due to medical comorbidities, including diabetes, metabolic syndrome, and cardiovascular disease. Many potential pathways contribute to poor physical health among patients with mood disorders, including genetic vulnerability, environmental risk factors such as economic disadvantage and loneliness, unhealthy lifestyle, and adverse effects of treatment. Individuals with mood disorders practice less physical activity and have a lower quality diet, with higher intake of sugar, fat, and carbohydrates. Smoking and other substance use disorders are highly comorbid in this population.

This systematic review article aims to compile and evaluate the existing scientific evidence on Major Depressive Disorder in elderly individuals. The intention is to provide a comprehensive and up-to-date view, which not only synthesizes current knowledge about the condition, but also identifies gaps in research and directs future investigations and

clinical practices. By offering an in-depth analysis of the evidence, this work aims to serve as a resource for health professionals, researchers, and academics, helping to optimize diagnostic and therapeutic approaches to depression in the elderly population.

METHODOLOGY

This is a systematic review that seeks to compile and evaluate the existing scientific evidence on Major Depressive Disorder in elderly individuals, in addition to demonstrating the main comorbidities and management strategies of this pathology, aiming to ensure a greater clinical elucidation of this pathology. For the development of this research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "What are the main comorbidities associated with depression in geriatric patients, as well as the management used to treat the clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Two descriptors were used in combination with the Boolean term "AND": Depressive Disorder and Aged, and Depressive Disorder and Health Care for the Elderly. The search strategy used in the PMC database was: Depressive Disorder AND Aged and Depressive Disorder AND Health Care for the Elderly. From this search, 170 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 170 articles were found. After applying the inclusion and exclusion criteria, 23 articles were selected from the PubMed database, and a total of 13 studies were used to compose the collection.

DISCUSSION

Major depressive disorder (MDD) is a heterogeneous neuropsychiatric condition that affects individuals throughout their lives. Depression is the second leading cause of disability in the United States and worldwide, and results in significant morbidity and mortality. Depressive symptoms vary throughout life and include changes in mood (i.e., sadness, irritability), anergy, changes in appetite or weight, and changes in neurocognitive functions. For the latter, TDM was found to predominantly affect neurocognitive functions

governed by fronto-subcortical networks, including processing speed, attention, and executive functions. Depression in the elderly is associated with several negative consequences, such as decreased quality of life, difficulties with activities of daily living, physical comorbidities, cognitive impairment, and premature mortality (DOTSON et al., 2020) (CORPAS; GILBODY; MCMILLAN, 2022).

In older adults, accurately diagnosing depression can be challenging due to the high prevalence of medical comorbidities whose symptoms overlap with those of a depressive disorder. In addition, as individuals age, polypharmacy and adverse drug reactions become more common and may overlap with symptoms of depression. The Geriatric Depression Scale (GDS) is used as a screening tool to identify possible depression in older adults, including those with a medical condition or with mild to moderate cognitive impairment. To avoid overlap with symptoms of physical illness, GDS does not include somatic symptoms such as insomnia, loss of appetite, or fatigue; This may, however, exclude key features of depressive disorders that could be assessed in a diagnostic interview to determine the source. The GDS included 30- and 15-item versions, as well as shorter 10-, 5-, and 4-item versions. For GDS-30, cut-off points of 11 are used for at least mild depression and 21 for moderate to severe depression. For GDS-15, cut-off points of 5 for at least mild depression and above 10 for moderate to severe depression are used for screening purposes (PARSONS et al., 2024).

Evidence suggests that older adults with chronic illnesses are more likely to be affected by depressive symptoms than those without chronic conditions. Seniors with chronic conditions are more likely to seek medical attention and follow treatment. Therefore, by actively treating chronic conditions, there may be a degree of relief in depressive symptoms among older adults (WU et al., 2024).

Frailty is a condition of loss of homeostasis due to dysregulation of multiple systems, resulting in a lower biological reserve against different forms of stressors. Frailty predicts future adverse health outcomes such as falls and fractures, physical disability, restricted activities of daily living, hospitalization, and, in particular, mortality. Although operational definitions of frailty are still a matter of debate, geriatric societies generally agree that biomedical frailty is clinically characterized by decreased strength, endurance, and a reduced physiological function of various organ systems. Although there is heterogeneity among frail patients, frailty is generally progressive and strongly correlated with increased mortality and dependence (APRAHAMIAN et al., 2023) (MALLERY et al., 2019) The seven longitudinal studies with the highest methodological quality found that depressed older adults were approximately 2 to 3 times more likely to develop frailty than their non-

depressed counterparts over a 3- to 5-year follow-up. After these initial studies, meta-analyses of cross-sectional comorbidity rates showed that among frail older adults, the pooled prevalence of depression was 38.6%, while conversely among depressed older adults the prevalence of frailty was 40.4% (APRAHAMIAN et al., 2023)

Among depressed patients, frailty has predictive validity, being associated with higher mortality rates and an exponentially higher risk of falls due to antidepressants. However, guidelines on the treatment of depression do not consider frailty for risk stratification or treatment selection. We argue that assessing frailty allows clinicians to better target pharmacological and psychological treatment of depression, as well as the need for interventions that primarily target frailty, e.g., lifestyle interventions and reduction of polypharmacy (APRAHAMIAN et al., 2023).

According to the International Continence Society (ICS) definition, urinary incontinence (UI) refers to a condition in which urine involuntarily flows out of the urethra. This is usually due to bladder sphincter injury or neurological dysfunction and loss of urinary control function. Although it is a non-life-threatening condition, UI is accompanied by high levels of stress and embarrassment due to the odor and discomfort that comes from urine leakage. In addition, UI can occur rapidly and in large volumes, which seriously affects normal social interaction and leisure activities among affected individuals. This effect is not only physiological, but also has a great impact on the patient's psychological health. For too long, a lack of knowledge about UI has resulted in a low rate of medical treatment, poor patient adherence to behavioral training, and low psychological status among those with UI. Studies have shown that the incidence of depression was 11% in people with UI and 7% in those without UI. Among patients who did not receive hospital medical care for UI, the prevalence of depression and anxiety is higher than that reported in the general population (CHENG et al., 2020).

Several cross-sectional and longitudinal studies have shown that older age is associated with increased vulnerability to depression-related cognitive deficits and decline. This vulnerability may be due, at least in part, to age-related changes in some of the neurobiological mechanisms related to depression, such as structural and functional changes in frontolimbic brain networks, vascular changes such as increased white matter lesions in the brain, decreased brain-derived neurotrophic factor, and increased inflammation. It is possible that the cumulative effect of age-related neurobiological changes and depression-related changes on similar mechanisms creates a "double jeopardy" for cognitive dysfunction, including cognitive control deficits. It is also possible that factors such as medical comorbidities, depression severity, and the type of tests used

varied between studies of different age groups and contributed to the age difference observed in the meta-analysis (DOTSON et al., 2020).

Approximately 15% to 20% of adults aged 65 and older have depression. The American Psychiatric Association recommends antidepressants as an initial treatment option. SSRIs, SNRIs, mirtazapine, and bupropion are suggested as first-line agents for the general adult population and for older adults. Meta-analyses of randomised controlled trials (RCTs) have shown that among adults aged 60 years and older, antidepressants are more effective than placebo in treating depression, although the effect size is modest. However, the 2019 Beers Criteria for Potentially Inappropriate Use of Medications in the Elderly recommend that SSRIs, SNRIs, and tricyclic antidepressants be avoided in older adults with a history of falls or fractures.5 The Agency for Healthcare Research and Quality (AHRQ) review aims to synthesize research on adverse event profiles of antidepressants in older adults. In trials comparing SSRIs (paroxetine, citalopram, or sertraline) face-to-face with tricyclic antidepressants (amitriptyline or nortriptyline) during the acute phase of treatment, patients taking SSRIs were less likely to withdraw from trials due to adverse events. A large cohort study of people aged 65 and older who had depression found that SSRIs were associated with an increased risk of falls, fractures, and mortality (SALISBURY-AFSHAR, 2020).

Depression and dementia profoundly affect older adults (those aged 65), leading to decreased quality of life and independence. Approximately 22.1% of older adults with mild dementia and 11.6% of those with moderate dementia also have major depressive disorder. Depression is associated with a higher risk of developing dementia, in addition to being considered a neuropsychiatric disease that is a symptom of dementia (LENOUVEL et al., 2024). Studies have shown that the use of vortioxetine in older adults showed statistically significant improvements in cognitive function. However, it is important to consider the clinical significance of these individual findings. Vortioxetine is an antidepressant with a multimodal mechanism of action. Similar to SSRIs and SNRIs, vortioxetine binds to the serotonin transporter protein to inhibit serotonin reuptake in the central nervous system. However, vortioxetine is also thought to directly deliver 5-HT1A receptor agonism, 5-HT1B receptor partial agonism, and 5-HT3, 5-HT1D, and 5-HT7 receptor antagonism.11,12 These effects on serotonergic receptors may enhance the antidepressant effects resulting from serotonin transporter protein inhibition. In addition, some of these serotonergic receptor interactions are thought to facilitate the release of other neurotransmitters. These indirect interactions may regulate the release of norepinephrine, dopamine, acetylcholine (ACh), histamine, gamma-aminobutyric acid (GABA), and glutamato.Com the cognitive

improvements seen among other antidepressants and with long-term use of SSRIs showing reduction in conversion from mild cognitive impairment, it is possible that antidepressants as a class may improve cognitive function in older adults, or the treatment of depression may be the main reason for cognitive improvement. However, these positive cognitive effects have not been found in all studies of antidepressants (GUTSMIEDL et al., 2020).

In 2015, a study was conducted that was considered the first randomized placebo-controlled trial designed to test the efficacy and tolerability of methylphenidate and citalopram in geriatric depression as a combination strategy compared to citalopram or methylphenidate as monotherapy or placebo. There was a significant improvement in depression severity and cognitive performance in the three treatment groups compared to placebo. Improvements in depression severity and Clinical Global Impression score were more prominent in the citalopram plus methylphenidate group compared to the other two treatment groups (i.e., citalopram plus placebo or methylphenidate plus placebo) (SASSI et al., 2020).

The authors concluded that stimulants can be used as a safe alternative when other medications fail to treat resistant late-life depression. It is worth mentioning that major depressive disorder occurs in up to 5% of community-dwelling older adults, while 8 to 16% of older adults have clinically significant depressive symptoms. Depressive disorders are frequent in this population group, and resistance to treatment is not uncommon. In addition to representing an augmentation strategy, additional methylphenidate therapy appears to accelerate the improvement of depression compared to citalopram alone (SASSI et al., 2020).

Due to differences in pharmacokinetics, the effect of antidepressants may be peculiar in this population. Various metabolic changes in the body of the elderly can influence the concentration of active substance in the body, altering metabolism and elimination. For example, liver mass and blood flow decrease, and creatinine clearance from the kidney decreases continuously with increasing age. In addition, frequent polypharmacy in elderly patients increases the risk of drug interactions. Therefore, concentrations of antidepressants should be chosen carefully to avoid overdose, which can cause serious side effects. Pharmacodynamics may also change with age, as increased pharmacodynamic sensitivity has been reported in the elderly, due to neuronal and neurotransmission changes (GUTSMIEDL et al., 2020). In adults with depression, compared with placebo, more adverse events were observed with dextroamphetamine, amitriptyline, aripiprazole, brexpiprazole, bupropion, fluoxetine, lisdexamfetamine, paroxetine, venlafaxine, vortioxetine, but not with mirtazapine. In direct comparisons,

fluvoxamine and paroxetine had fewer adverse events than TCAs, and agomelatine had fewer adverse events than SSRIs and paroxetine (CROATTO et al., 2023) (SALISBURY-AFSHAR, 2020).

In direct drug comparisons, SSRIs had a lower hypertensive effect than SNRIs (small) and imipramine (moderate). For overall cardiovascular health, in elderly patients, fluoxetine showed a very large worsening effect compared to sertraline and escitalopram. A small effect on weight gain emerged for the increase in antidepressants with brexpiprazole, while in direct comparisons paroxetine was worse than reboxetine, but better than maprotiline and mirtazapine, with a moderate to large effect. A moderate effect for weight gain emerged for mirtazapine also compared to SSRI. Considering tolerability, in the deposition, in general, all pharmacological classes were less tolerated than placebo; SSRIs were better tolerated than PCIs, while no significant difference emerged comparing SSRIs-SSRIs and SSRIs-SNRIs, with the exception of duloxetine for higher intolerability-related discontinuation rates (CROATTO et al., 2023).

The longitudinal effects of religion on depressive symptoms have been studied in six studies. A study was carried out, where they investigated two waves (1984–1985 and 1989–1990) of older Finns and noted that low religious participation increased the risk of depression in women, but not in men. These results were expanded, and observed that older adults with higher church attendance had a reduced risk of developing depression and depressive symptoms in a short period of time. Religious and spiritual beliefs (SR) are far from just cultural traditions. In fact, they involve numerous organizational, non-organizational, introspective, and community practices that can potentially influence human behavior. Regarding mental health, a growing number of studies have observed improved mental health status in people involved in SR activities. These results were confirmed by descriptive and systematic reviews. However, a specific pooled analysis based on a systematic search focused on the elderly population and incorporating a variety of religious and spiritual approaches is still needed (COELHO-JÚNIOR et al., 2022).

CONCLUSION

Based on the reviewed findings, it can be concluded that Major Depressive Disorder (MDD) in older adults is a significant public health challenge, with important implications for clinical management and quality of life. The high prevalence of comorbidities, frailty, and the impact of neurocognitive dysfunctions associated with MDD underscore the need for a careful and differentiated diagnostic approach, considering both depressive manifestations and symptoms of chronic conditions. Screening tools, such as the Geriatric Depression

Scale, are useful but have limitations in excluding somatic symptoms, which may compromise the complete diagnosis in some cases.

Pharmacological treatment, although effective, should be managed with caution, mainly due to polypharmacy and frequent drug interactions in the elderly. Frailty should be incorporated into risk stratification when selecting therapeutic interventions, including antidepressants. In addition, the potential impact of antidepressant therapies on cognitive decline, falls, and mortality requires special attention. The data also suggest that non-pharmacological interventions, such as lifestyle modifications and the reduction of polypharmacy, may play a key role in improving depressive symptoms and quality of life in older adults. Thus, future research and clinical guidelines should prioritize personalized therapeutic strategies that include a comprehensive assessment of the physical, mental, and functional health of this vulnerable population.

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