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Treatment of depression comorbid with dementia among the elderly patients

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ABSTRACT

Depression is a frequently encountered comorbidity in individuals with dementia, posing significant diagnostic and therapeutic challenges. Among older adult population, clinical manifestations often do not represent a typical phenotype of depressive symptoms, which poses a challenging issue in the differential diagnosing process and requires engaging additional clinical assessment tools for guiding patient management. Conjunction of multimorbidity and polypharmacy in these individuals, creates obstacles in the pharmacological treatment of depression, because of higher risk of adverse drug reactions and interactions. In this review we present a comprehensive summary of the clinical approach to depression in the context of dementia. We discuss development of those two diseases, while identifying senior patients at increased risk of depression, and latest treatment strategies. Further, we draw attention to the fact that according to mildly cognitively impaired individuals' consideration of efficacy and safety profiles of particular classes of antidepressants is extremely significant. Obtaining sufficient treatment requires a holistic approach to our patients, therefore we included in this review non-pharmacological interventions, which may enhance medication.

Key words: depression, dementia, antidepressants in elderly, geriatrics, comorbidity

1. INTRODUCTION

The incidence of dementia increases with length of life of older adult population, along with depression those two are the most common disorders among seniors. In both cases, they have a significant impact on the quality of life of patients and their relatives. These conditions pose substantial medical and social problems as they increase mortality and contribute to considerable deterioration of health (Bennett and Thomas, 2014; Zwyrtek and Rymaszewska, 2016). Some recent

meta-analyses determined that the prevalence of major depression was 15.9% among patients with all-cause dementia and 14.8% among those with Alzheimer's disease, respectively. Moreover, 32% of those with dementia may experience symptoms of depression (as part of neuropsychiatric symptoms of dementia) without a formal diagnosis of major depressive disorder (Agüera-Ortiz et al., 2021; Watt et al., 2021). Aging-related and disease-related processes, such as arteriosclerosis and changes in endocrine function, immune response, and chronic generalized inflammation, disrupt the integrity of frontostriatal pathways, the amygdala, and the hippocampus, making individuals more susceptible to depression (Alexopoulos, 2005).

According to World Health Organization (WHO) untreated depression is a primary reason of global disability. Further, it is a major contributor to the overall worldwide burden of disease, is associated with decreased life expectancy, and at its worst can also lead to suicide (Guo et al., 2023). Therefore, the appropriate treatment of depression in elderly patients is crucial, and clinicians play a key role in distinguishing between depressive disorders and dementia to best approach the patient's condition amelioration. Some studies suggest that up to 32% of geriatric patients with mild cognitive impairment (MCI) may experience depression, and 37% of those with depression report MCI symptoms. Mood disturbances in older people often do not fully meet diagnostic criteria for specific disorders but rather present as broad affective symptoms, underscoring the need for precise assessment and treatment as well as posing a big challenge for clinicians (Bidzan, 2011; Bilikiewicz and Matkowska-Białko, 2004; Guo et al., 2023).

In our review, we focus on summarizing the key aspects of identifying older adults at high risk of depression, diagnosing and distinguishing depression from dementia, highlighting essential considerations in the treatment of depression in elderly and/or cognitively impaired patients, recommending preferred classes of antidepressants, and presenting non-pharmacological strategies to complement pharmacological treatment.

2. MATERIALS AND METHODS

For this review, we searched databases such as PubMed and Google Scholar using terms: depression comorbid with dementia, depression in elderly, dementia, depression and dementia differential diagnosis, depression in Alzheimer's disease, and risk factors of depression in elderly. We cited 47 articles in this publication. This review covers studies from 2012 to 2024. However, we included several older articles to provide background on basic definitions and epidemiology. We excluded case reports, case series, editorials, perspective papers, studies with weak methodologies, and publications in languages other than English and Polish.

3. RESULTS AND DISCUSSION

3.1. Differentiating Depressive and Dementia-Related Disorders in the Elderly

According to clinical practice guidelines, the hallmark to diagnose dementia is a documented progressive decline in at least two cognitive domains over six months. There are few subtypes of dementia, and it is crucial to identify them, as it may determine different treatment decisions and prognosis (Connor and Baytree, 2024). Most reviews classify dementia into subtypes based on a variety of symptoms and pathophysiology. Two broad categories of the disease that we can conceptualize are those that are 'neurodegenerative' (originally called 'irreversible') and 'non-neurodegenerative' (potentially 'reversible') (Barczak and Gabryelewicz, 2021; Baruch et al., 2019). The evaluation and diagnosis should include the following four steps:

- thorough clinical history;
- neurological examination, with an emphasis on the assessment of mental status;
- selective labs to screen for selected metabolic/physiologic abnormalities (e.g., basic chemistries, thyroid panel, B12, Vitamin D);
- A structural brain scan, preferably magnetic resonance imaging (MRI), should be performed rather than computed tomography (CT) (Gale et al., 2018).

Another aspect of the diagnostic process is the objective assessment of reported complaints through cognitive function evaluation using screening tests. Commonly used and recommended screening assessment methods are: Questionnaire on Cognitive Decline in the Elderly (IQCODE), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) or Clock Drawing Test (CDT) (Barczak and Gabryelewicz, 2021; Park et al., 2018; Quinn et al., 2021; Siqueira et al., 2019). It is also crucial that we identify the warning signs observed in patients, including memory loss, difficulty performing activities of daily living, problems with verbal communication, disorientation to time and place, poor or decreased judgment, issues with abstract thinking, misplacing things, changes in mood or behavior, personality changes, and loss of initiative. Dementia patients often present with increased muscle tone and episodes of sudden falls.

Researchers have observed that altered circadian sleep rhythm, prolonged daytime sleepiness, and excessive activity at night are also associated with dementia. As dementia progresses, behavioral and mood disorders, along with aggression and agitation, may develop, particularly in its later stages (Agüera-Ortiz et al., 2021; Galvin and Sadowsky, 2012; Zwyrtek and Rymaszewska, 2016).

Clinicians diagnose a depressive episode when a patient experiences a persistently low mood, loss of interest, or anhedonia for a minimum of two weeks (Alexopoulos, 2005). A depressive syndrome may precede or complicate neurodegenerative diseases (Alzheimer's and Parkinson's disease) as well as cerebrovascular diseases (vascular and post-stroke depression). In older adults, mood disorders often do not fully align with the established diagnostic criteria for this category of illnesses. Rather than presenting as a distinct clinical entity, mood disturbances in late life manifest as a broad spectrum of symptoms that may not fit neatly within conventional diagnostic frameworks.

Characteristic clinical manifestations include emotional lability, irritability, anxiety, psychomotor agitation, pervasive guilt, suicidal ideation and intent, and somatization disorder. Additionally, various delusional symptoms may be present, particularly hypochondriacal and nihilistic delusions (Cotard's syndrome), as well as delusions of guilt, moral transgression, self-condemnation, worthlessness, persecution, and referential ideation. It is essential to recognize that somatic complaints and cognitive impairments often conceal the core symptoms of depression (Bidzan, 2011; Bilikiewicz and Matkowska-Białko, 2004).

To summarize, it is essential to take into consideration information provided by the relatives regarding the patient's condition, as it might facilitate diagnosing depression in dementia patients. In contrast, sadness, depressive cognitions, and early-morning awakening distinguish depression from apathy in dementia. Furthermore, one of the most valuable tools for assessing dementia in patients in daily clinical practice is Cornell Scale for depression in dementia (CSDD). This clinician-rated scale consists of 19 items and integrates information from the patient and a caregiver or nursing staff member, making it well-suited for use in cognitively impaired individuals. (Agüera-Ortiz et al., 2021; Alexopoulos et al., 1988)

It is worth noting that, according to the 2021 Delphi Consensus, an Alzheimer's disease diagnosis should be deferred in patients with co-occurring depression and cognitive impairment until the effects of antidepressant therapy have been assessed (Agüera-Ortiz et al., 2021).

3.2. Risk factors of depression in older people

A recent systematic review by Maier et al., (2021) indicates that risk factors for depression in later life are multifactorial, with genetic factors being one of the contributing elements. One of the mentioned studies identified an increased risk of incident depression associated with the GPR50 polymorphism rs561077. Moreover, while a decline in financial status alone did not appear as a crucial risk factor for the onset of depression, lower income, indicative of economic stress, was found to be a notable risk factor. Evidence indicates that physical activity—whether mild, moderate, or vigorous—is a protective lifestyle factor against depression.

A history of depression may serve as a marker of increased vulnerability, potentially exacerbated by neurodegenerative changes or the psychosocial stressors associated with dementia, which intensify as the disease progresses. Unlike in the general population, existing research suggests that the risk of depression in dementia is comparable across genders and educational levels (Steck et al., 2018).

According to the Delphi Consensus (2021), caregiver stress and depression exacerbate depressive symptoms in patients with dementia, while social environment plays a crucial role in the onset of depression. Additionally, more significant vascular damage is associated with a higher risk of depression in dementia. Importantly, treating depression in individuals with dementia has a positive impact on disease progression, as depression itself accelerates cognitive decline (Agüera-Ortiz et al., 2021). Summary key points are included in Table 1.

Table 1. Risk factors of depression in elderly

Risk factors of depression in elderly
- genetic factors (GPR50 polymorphism rs651077),
- significant vascular damage,
- economic stress,
- physical inactivity,
- depression in the past,
- isolation.

3.3. Treatment of depression comorbid with dementia.

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are considered primary therapy due to tolerability (Agüera-Ortiz et al., 2021; Baruch et al., 2019; Hughes et al., 2019). One of the studies indicated that prolonged SSRI treatment for over four years has been associated with a delayed progression to Alzheimer's disease by approximately three years in patients with mild cognitive impairment and a history of depression, compared to those receiving short-term SSRI therapy or no treatment, despite no observed differences in Cerebrospinal Fluid (CSF) biomarker levels (Bartels et al., 2018). The majority of studies support that SSRIs aid in the prevention of dementia (Huang et al., 2024; Yang et al., 2023), though some of them may present different outlooks on the matter (Chan et al., 2019; Heath et al., 2018).

Evidence suggests that citalopram may lower amyloid-β levels and decrease the formation of amyloid plaques (Bartels et al., 2018). Moreover, serotonergic dysfunction associates with agitation among patients with dementia, and treatment with citalopram reduced that symptom in individuals with Alzheimer's disease (Cirrito et al., 2020; Porsteinsson et al., 2014). Besides, escitalopram-treated mouse models of Alzheimer's disease showed an overall 9.4% greater reduction in CSF Aβ42 concentration than the placebo groups (Cirrito et al., 2020). Citalopram or escitalopram may be effective; however, it is essential to recognize that these drugs increase the risk of QTc prolongation in older adults. Therefore, sertraline is usually the treatment of choice due to its favorable cardiovascular safety profile (Baruch et al., 2019; Hsu et al., 2021).

Clinicians typically avoid fluoxetine due to its long half-life and extended side effects duration. At the same time, paroxetine is not recommended as a first-line option because it has the highest anticholinergic burden among selective serotonin reuptake inhibitors, which increases the risk of dementia, impaired cognitive and physical outcomes, and has a short half-life, which complicates withdrawal (Heath et al., 2018; Hughes et al., 2019).

Studies have linked SSRIs to a higher risk of intracranial hemorrhage and gastrointestinal bleeding. Therefore, clinicians should consider prescribing gastroprotective medication. Furthermore, when considering the use of this group of drugs in therapy, their association with hyponatremia should be taken into account, which is particularly perilous for elderly patients. The Maudsley Prescribing Guidelines recommended measuring serum sodium levels in high-risk patients at baseline, at 2 and 4 weeks, and subsequently every 3 months. Mild hyponatremia (>125mmol/L) can be managed with fluid restriction and daily monitoring of sodium levels, whereas severe hyponatremia (<125mmol/L) is life-threatening, requiring immediate drug discontinuation and hospital admission for treatment (Baruch et al., 2019; Taylor et al., 2018).

In several observational studies, SSRIs also occurred with an increased risk of falls and higher prevalence of postural hypotension. Still, the reviews marks that it is not known if it may be confounding by indications (i.e., falls due to disorders that lead clinicians to prescribe SSRIs) or by contraindications (i.e., preferential use of SSRIs in patients at higher risk for falls) (Baruch et al., 2019; Mulsant, 2014).

Serotonin antagonists and reuptake inhibitors (SARIs)

In a prospective cohort study in 2018, researchers demonstrated that using low-dose SARIs was associated with lower dementia risk than nonuse (Heath et al., 2018). On the other hand, a different study found that the prevalence of dementia was higher among patients treated with trazodone compared to those using other antidepressants; however, the study did not identify any causal relationship. The results indicated a potential case of reverse causation, where individuals in the early, prodromal phase of dementia were more likely to receive trazodone, as reflected by a shorter time to dementia diagnosis in these patients (1.8 vs. 4.1 years).

When researchers excluded early dementia diagnoses, they did not observe any significant link between trazodone use and dementia risk after more than three years of treatment. Furthermore, no evidence supported a neuroprotective effect of trazodone in dementia, aligning with findings from previous clinical studies (Brauer et al., 2019).

In summary, trazodone might be the right choice in a specific group of patients who suffer from symptoms such as insomnia, agitation, anxiety, or irritability. That drug is generally well-tolerated in the treatment of major depressive disorder. However, its use in older adults and individuals with dementia requires caution due to the potential risk of orthostatic hypotension linked to α1-adrenergic receptor blockade and in those with pre-existing heart disease.

Tricyclic antidepressants (TCAs)

Classic anticholinergic drugs, such as TCAs among antidepressant medications, are recognized to increase the risk of cognitive decline. Another case-control study demonstrated a relationship between dementia incidence and antidepressants with strong anticholinergic characteristics, such as amitriptyline and dosulepin (Chan et al., 2019; Heser et al., 2018; Huang et al., 2024). However, researchers reached disparate conclusions in one of the longitudinal studies of older adults, where they did not find associations between the use of TCAs or SSRIs (excluding paroxetine) and the risk of dementia (Heath et al., 2018).

According to Delpfi 2021 Consensus, nortriptyline is not a proper therapeutic option for depression in Alzheimer's disease, and the same statement can be found in other recommendations (Agüera-Ortiz et al., 2021; American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; O'Mahony et al., 2023; Seppala et al., 2021).

Other aspects of treatment

Other antidepressants that have a positive impact on cognitive functions are those with multiple mechanisms of action: tianeptine, vortioxetine, duloxetine, and mirtazapine. The latter is often considered when insomnia constitutes a significant concern in the clinical presentation (Baruch et al., 2019). When it comes to patients with anxiety, tianeptine is the preferred medication due to its anxiolytic properties, which can improve somatic symptoms. Moreover, its tolerability is of great use because of higher patient's compliance (Agüera-Ortiz et al., 2021). Studies have demonstrated that patients over the age of 55 with multimorbidity and polypharmacy tolerate vortioxetine well. Nevertheless, clinicians need to take into consideration the fact that vortioxetine may increase blood pressure, particularly during the initial phase of treatment (Nomikos et al., 2017; Staniec-Kutera and Waszkiewicz, 2024).

Clinicians often prescribe medications such as cholinesterase inhibitors (ChEIs) or memantine to elderly patients with dementia. Studies have shown that their use in individuals with coexisting depression exerts a beneficial effect on depressive symptoms through a synergistic mechanism (Lu et al., 2009; Mulsant, 2014). However, researchers have not yet established the optimal sequencing of these treatments. When making treatment decisions, healthcare providers should consider that anticholinergic antidepressants (such as TCAs or paroxetine) may counteract the therapeutic effects of ChEIs, rendering their simultaneous administration potentially inefficacious and unsafe, particularly in dementias associated with cholinergic deficits, such as Alzheimer's disease or Lewy body disease (Agüera-Ortiz et al., 2021; Seppala et al., 2020).

Limited studies have examined the effectiveness of mood stabilizers in treating depressive symptoms in dementia. Lithium, in particular, has been proposed as a potential therapeutic or preventive agent in Alzheimer's disease due to its role in tau protein phosphorylation (Kessing et al., 2010; Terao et al., 2006). However, older adults often experience reduced tolerability and an increased risk of neurotoxicity when using this medication, which can occur even at plasma concentrations considered therapeutic in the general adult population. Moreover, popular medications taken by older adults —such as thiazide diuretics, ACE inhibitors, and nonsteroidal anti-inflammatory drugs—can further elevate serum lithium levels, potentially exacerbating these risks (Sproule et al., 2000).

The National Institute for Health and Care Excellence (NICE) guidelines on dementia advise against the use of antidepressant medication for individuals with newly diagnosed mild to moderate depression coexisting with mild to moderate dementia, recommending psychological therapies as the first-line treatment in this population. An exception to this recommendation applies in cases where there is substantial concern regarding a pre-existing severe mental health condition; in such instances, pharmacological treatment should be initiated (*Dementia*, 2018)

While earlier literature recommended starting antidepressants at the lowest effective doses with careful monitoring in Alzheimer's disease patients (Ford and Almeida, 2017), the Delphi 2021 consensus adjusted this approach. Experts advised against lower dosing and shorter treatment durations to avoid subtherapeutic effects and treatment pseudoresistance despite the frequent comorbidities and polypharmacy in this population (Agüera-Ortiz et al., 2021).

Non- pharmacology interventions

The network meta-analysis conducted by Watt et al., (2021) demonstrated that non-pharmacological interventions were equally or more effective than pharmacological treatments in alleviating depressive symptoms in people living with dementia.

Evidence suggests that successful depression management through psychological therapies is related to lower risk of developing dementia, so it is the best choice as a first-line treatment. Specifically, approaches such as enhancing social engagement, reminiscence therapy, and cognitive rehabilitation have demonstrated efficacy in alleviating depressive symptoms in individuals with dementia (Huang et al., 2024; John et al., 2023; McHugh et al., 2013).

Expert opinions on physical activity remain divided. Some studies suggest that physical exercise can alleviate depressive symptoms in individuals with dementia, with evidence that supports its plausible effects on dysphoria and even major depression, particularly in nursing home settings (Agüera-Ortiz et al., 2021; Hughes et al., 2019). Others, however, express skepticism regarding the methodological quality of existing research. Nonetheless, it is essential to note that there is no evidence indicating that physical activity causes harm to participants (Baruch et al., 2019; Forbes et al., 2015).

Another commonly used strategy to manage depression in the elderly is art therapy, which is often implemented in the care of individuals with dementia and encompasses a variety of modalities, including music, movement, visual arts, and visits to galleries or museums (Baruch et al., 2019).

In a scoping review, Vaartio-Rajalin et al., (2020) found that art-making activities within nursing care were associated with various positive outcomes for individuals with dementia. These included reduced wandering, enhancement of cognitive abilities, lower levels of anxiety, decreased physiological stress, increased positive emotions, and improvements in mental health and overall well-being.

Bleibel et al., (2023) provided an interesting approach to the topic by researching music therapy as a supplementary treatment option for depression. They demonstrated that music therapy increases social interaction and modulates emotional states. Moreover, it induces neuroplastic changes in specific brain networks and expedites brain recovery, making it a promising rehabilitation strategy. However, the positive emotional effects observed in patients dissipated within three weeks post-intervention. The duration of the therapeutic effects varied across studies, with follow-up periods ranging from one to six months. These results state that further inquiry is necessary to establish the most beneficial and optimal duration of therapy.

4. CONCLUSIONS

Depression is a common issue among patients with dementia. Its management presents a significant clinical challenge due to the high prevalence of multimorbidity and polypharmacy in this population, which increases their susceptibility to adverse effects of antidepressants often resulting in iatrogenic hospital admissions and increased healthcare utilization.

Therefore, pharmacological strategies should prioritize agents that emphasize cognitive function amelioration. Additionally, researchers suggest that clinicians should also consider medications such as mirtazapine, vortioxetine, and tianeptine for the elderly patients. Most studies recommend using memantine and cholinesterase inhibitors, as they may offer additional cognitive benefits in patients with dementia. Selective serotonin reuptake inhibitors (SSRIs) are generally well-supported by the literature; however, clinicians must remain vigilant for the risk of hyponatremia and should avoid paroxetine due to its unfavorable side effect profile in older adults. Recommendations do not endorse tricyclic antidepressants (TCAs) in elderly populations, and health providers should avoid this group of drugs.

Creating a treatment plan draft, we need to consider psychotherapy, music therapy, and systematic physical activity. Those non-pharmacological strategies demonstrated efficiency in ameliorating mood and cognitive function. In patients with mild to moderate depression coexisting with mild to moderate dementia, healthcare providers should initially withhold pharmacotherapy. Instead, the treatment plan should focus on interventions such as promoting social engagement, reminiscence therapy, and cognitive rehabilitation.

Authors' Contributions

Adrianna Witkowska: Conceptualization, coordinating, writing – main draft and finishing

Julia Piotrowska, Antonina Teresa Witkowska, Barbara Anna Zapalska, Aleksandra Łubińska- Kowalska, Adrianna Domańska, Agata Żak- Gontarz, Aleksandra Minda, Justyna Janikowska, Monika Wendland: writing – data selection, rough preparation

Krzysztof Julian Długosz: writing – review, editing

All authors contributed in the preparation of the final manuscript.

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Data and materials availability
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