Late-life depression with cognitive impairment
– A review
Andreea Sopu

“Prof. Dr. Alexandru Obregia” Psychiatric Hospital, Bucharest, Romania
Psychiatry Department, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT
Late-life depression (LLD) is a heterogeneous disorder often associated with different forms of cognitive impairment. Within this pathology, cognitive impairment may represent a prodrome or risk factor for a later form of dementia. Currently, the treatment of the current depressive episode and the long-term follow-up of the evolution of the cognitive disorder is considered the most correct method of therapeutic approach in case these two disorders are associated. In this article, we analyzed different studies with the help of which we wanted to highlight the common risk factors between late-onset depression and cognitive impairment, predictive factors for further progression to dementia, neuropsychological and imaging changes, but also useful therapeutic interventions in patients with present both disorders.

Keywords: late life depression, cognitive impairment, dementia

BACKGROUND
Elderly-onset depression is now considered a distinct clinical entity, with the clinical picture of depression often presenting differently from the clinical picture of depression in young people [1]. The prevalence of depression varies between 10-20% among the elderly population (aged between 60 and 65 years) [2].

Depressive disorder is defined in DSM-V [3] and ICD-10 [4] by the presence of at least five of the following symptoms: sad mood, decreased interest or pleasure, restlessness or psychomotor slowness, asthenia or loss of energy almost daily, feelings of worthlessness or guilt, difficulty concentrating, recurrent thoughts of death, appetite or sleep disturbances, symptoms present for at least two weeks and interfere with daily activities.

Elderly patients present a poorer clinical picture than young patients, reporting less often symptoms such as sadness and dysphoria. Some of the more common depressive symptoms in the elderly are decreased energy, feelings of guilt, and suicidal thoughts. Whereas cognitive impairment and morning anxiety are more predictable symptoms for a poorer pharmacological response [2,5].

The Geriatric Depression Scale (GDS) is a specific validated scale to be used among the elderly population, it avoids the assessment of symptoms of a somatic or sexual nature, it evaluates the subjective experiences given by the cognitive impairment, it uses simple “Yes/No” answers that decreases cognitive burden. The scale contains 15 or 30 questions (GDS-15 and GDS-30) and has a sensitivity between 80% and 100% [6].

METHODS
The present work represents a literature review that has analyzed several scientific articles which had as the main theme LLD associated with cognitive impairment symptoms. The included studies were selected following systematic searches of the online database (PubMed), the search words being: LLD accompanied by cognitive impairment; common risk factors; progression to dementia; changes in neuropsychological tests; neuro-imaging changes; treatment. All included articles were written in English. The paper contains information from 52 articles published between 1986 and 2021, which are clinical trials, randomized clinical studies, systematic/unsystematized reviews, and meta-analyses.
Is LLD with cognitive impairment a prodrome or a risk factor for dementia?

Depressive symptoms are found in the variable form of dementia. Being associated with 20-30% of Alzheimer’s dementia (AD) cases, 20-50% of Parkinson’s dementia, and 50% of vascular, fronto-temporal, and Lewy body dementia [2]. The incidence of AD is doubled when associated with older age-onset depressive disorder (where the first episode appears after the age of 60) and increases up to fourfold when the depressive episode is severe [7].

While most neurodegenerative disorders present distinct symptoms, in Alzheimer’s dementia, the affective and cognitive symptoms are very similar to depression in the elderly, making it difficult to differentiate between the two pathologies [8]. In a study by Shdo et al., he wanted to identify the depressive symptoms that could distinguish Alzheimer’s dementia from other forms of dementia, thus he observed that a high level of depressive symptoms “worry about cognitive functioning”, accompanied by a low level of a tendency to social “withdrawal”, low “general worries” and low “helplessness”, allowed the identification of Alzheimer’s dementia in 76% of cases [9].

In a longitudinal study conducted over 12 years, it was observed how the presence of the depressive disorder is associated with a faster decline in memory function [10]. In another study, Whitehell II (2010), carried out over 18 years, the presence of depressive disorder was associated with a decline in episodic memory, language, and verbal fluency performance. The author also highlighted the impact of the depressive disorder from an interval of 1 to 9 years compared to one of 10 to 18 years difference. Thus, the presence of depressive disorder at the beginning of the study was associated with decline in episodic memory and semantic fluency, while at the end of the study they were associated with a broad cognitive decline [11].

Therefore, LLD may represent a prodrome of cognitive decline, and the associated cognitive deficit may persist after the remission of depressive symptoms, representing the first sign of the beginning of a neurodegenerative process [12]. However, in other cases, cognitive impairment does not always progress to dementia, which may improve with the remission of depressive symptoms [13]. In this case, we talk about “pseudo dementia”, a cognitive impairment that can reach the severity of dementia, but which disappears after the remission of depressive symptoms. Compared with patients with depressed patients and AD, patients with depression and “reversible dementia” present more pronounced psychic and somatic anxiety, loss of libido, and more frequent early morning awakening [14].

Adler et al. conducted a study of 34 patients with LLD, 53% of them present mild cognitive impairment with a preponderance of impairments in short-term memory and visuospatial capabilities before the initiation of treatment. After a six months follow-up the entire group showed an increase in the HDRS score, but 44% from the patients who showed cognitive impairment at the beginning of the study were still fulfilling the criteria after six months. No link between cognitive impairment or functional level and severity of depressive symptoms could be highlighted [15]. In another study by Lee et al., 67 geriatric patients with LLD under antidepressant treatment were reassessed after a 12-months interval. At the time of inclusion in the study, 54% of the patients had mild cognitive impairment, after one year, only 44.8% of them continued to meet the criteria for mild cognitive impairment. At the end of the study, the author concluded that self-reported decline in functional activities may be a marker for persistent cognitive impairment, suggesting that assessments of both neuropsychological and functional status are important prognostic factors in the evaluation of geriatric depression [16].

Several studies suggest that adolescent-onset depression or chronic depression is a greater risk factor for the later development of dementia than older-onset depression [17]. These claims are based on the fact that recurrent and untreated depressive disorder is associated with reduced hippocampal volume (6), which ultimately contributes to hypothalamic-pituitary-adrenal axis dysfunction [18].

Do depressive disorder and cognitive impairment share the same risk factors?

According to some studies, regarding the etiology of old-onset depression and cognitive impairment, vascular risk factors represent a common risk factor for both disorders. Among them are listed: high blood pressure, cholesterol level, but also coronary diseases [19]. Therefore, the old-onset depressive disorder may be precipitated, predisposed, or perpetuated by cerebrovascular diseases, the so-called “vascular depression” hypothesis [20]. Patients with “vascular depression” show much more significant cognitive impairment than depressed patients without vascular comorbidities [21].

Another risk factor can be represented by the level of cortisol, which can cause degenerative lesions in the hippocampus through the glucocorticoid cascade [18]. According to one study, hippocampal atrophy accompanied by reduced memory capacity was observed among elderly patients with elevated cortisol levels over at least 5 years [22].

In other studies, it has been observed that the association of certain comorbidities can influence mood and cognitive symptoms. Cognitive impair-
ment in chronic renal failure (CRF) has been associated with both depression and impairment of various cognitive areas such as attention, memory, processing speed, and executive function. Also, in CRF patients on hemodialysis, the depressive disorder may further exacerbate cognitive deficits in terms of processing speed and executive function [23].

Neuropsychological test and imaging changes in LLD with cognitive impairment

Neuropsychological testing can provide additional information regarding the subsequent progression of cognitive impairment after the remission of depressive symptoms. Rushing and his colleagues evaluated the cognitive performance of the patients at the time of the onset of the depressive episode. They observed, in 15 of 120 patients, that only recall of narrative contextual information (i.e., short stories) predicted conversion to AD over 13 years [24]. This impairment in memory for verbal contextual information, which depends on intact hippocampal function, may predict conversion to AD in the geriatric population with depression whereas mild impairment in frontally mediated executive functions may not [25].

Patients diagnosed with LLD, even those with dysthymia, tend to display a “subcortical profile” on neuropsychological evaluations:

- Poor learning and recall, but good cued recall and recognition on memory testing
- Poor executive functions, processing speed, and verbal fluency
- Intact visuospatial skills and orientation [26, 27].

Approximately 30–40% of patients diagnosed with LLD have impaired executive function. Thus, geriatric patients during a depressive episode frequently perform poorly on word-list memory and recall, mediated by executive functioning while memory on recognition and cued recall conditions and narrative contextual memory, tasks that do not depend on executive functions, are often intact [13].

Low performance on executive function tests, such as impaired verbal fluency and cognitive inhibition, are predictive of slow and poor response to antidepressants, higher risk of relapse, and increased functional disability [13]. Impaired performance in semantic organization during verbal fluency in the Clinical Dementia Rating Scale (CDR), a global test of cognitive function, has also been observed to predict poor response to antidepressants among these patients [28].

The variability of the clinical presentation of cognitive impairment may suggest the pathophysiological process underlying the depressive episode. Thus, in a study conducted by Yeh et al., on 230 patients (130 patients diagnosed with LLD, but in remission at the time of the study and 100 control patients), they observed that 52.3% of the patients who were diagnosed with a depressive disorder, presented MCI at the time conducting the study. Of these, 28.5% met the criteria for amnestic mild cognitive impairment and 23.8% for non-amnestic mild cognitive impairment. Later, they observed that patients with the amnestic cognitive disorder had an older age of onset of the depressive episode, also associated with ventricular atrophy on neuroimaging investigations, while those with non-amnestic cognitive disorder presented higher risk factors for cerebrovascular disease [29].

There are numerous studies regarding the impact of LLD on brain structure changes in the clinical presentation of depressive disorder and neurocognitive outcomes respectively. Some studies point that the volume changes in the gray matter in the prefrontal region (orbitofrontal, dorsolateral), medial-temporal, and in the subcortical structures (hippocampus, anterior cingulate cortex, striatum, and brain-stem) as having different involvements in the presentation depressive disorder [30]. Deterioration to these structures may explain poor performance on episodic recall tasks. Moreover, the prefrontal structures are involved in encoding processes, while the hippocampus contributes to the consolidation of information but also to the error control occurring during response, and the anterior cingulate cortex has a role in organizing strategies during learning [30]. In the case of patients with LLD, an association was observed between changes in prefrontal structures and low performance in word recognition tasks. In this context, memory disorders are attributed to subjective difficulties in organizing the information, but also to the impairment of executive function [31]. Likewise, prefrontal structures facilitate the use of contextual associations during encoding, which strengthens the memory by creating cues for retrieval [32].

However, in a study conducted by Kohler et al., they did not find an association between cognitive deficit and volume reduction at the cortical level, including the level of the pre-frontal lobe, the hippocampus, or the entire brain structure. Instead, they associated the hyperintensity appearing in the white matter with disturbances in executive function, memory, and processing speed [33]. In another study by Kim and Han, they highlighted research linking white matter hyperintensity to emotion regulation processes and cognitive function among patients with depressive disorder. The studied literature suggests that the intensity of the white matter is correlated with “vascular depression”, causing different disconnections between neural pathways, and therefore disturbances in numerous cognitive areas, especially executive functions, and processing speed [34].
Treatment

Antidepressant medication

LLD is a heterogeneous condition with an increased rate of treatment resistance [12]. Antidepressants, the most used drugs for the treatment of this condition, also have different effects on cognitive impairment. Current literature focusing on the combination of the 2 conditions reports mixed cognitive effects of both SSRI and SNRI antidepressants. The results of recent studies focusing on the benefit of SSRIs and SNRIs in late-onset depression are variable. Antidepressants with anticholinergic action can have unwanted effects on the cognitive side [35]. On the other side, antidepressants act differently in AD than in MCI, therefore antidepressants (including sertraline and citalopram) may have some beneficial effects on agitation in AD, but their long-term use has been correlated in some cases with cognitive decline [36-38].

Pharmacological treatment combined with psycho-social intervention are the first choice in the case of these patients [39]. Tricyclic antidepressants have not been shown to improve cognitive function in elderly patients with depression [40]. Also, the use of tricyclic antidepressants can cause significant cognitive impairment secondary to anticholinergic effects. Amitriptyline, imipramine, and doxepin have the highest anticholinergic effect among tricyclic antidepressants [41].

In contrast, some SSRI can improve cognitive impairment in patients whose depressive symptoms subside after treatment [42]. Specifically, sertraline has been shown to be effective in improving performance on tests of attention, episodic memory, and executive function in patients with treatment response [42]. Similarly, elderly patients responding to citalopram therapy showed an improvement in psychomotor speed and visuospatial function. However, in patients without an adequate response, citalopram appears to have worsened verbal learning and processing speed in patients who remained depressed despite treatment [43]. Paroxetine is usually avoided among geriatric patients with cognitive impairment because of its anticholinergic effect [23].

Duloxetine, a dual-acting antidepressant, has demonstrated efficacy in elderly patients with depressive disorder and cognitive impairment, as serotonin and/or norepinephrine imbalance or deficiency in these patients may be responsible for cognitive impairment [44,45]. Joel Raskin and his colleagues conducted a study, carried out for 8 weeks, on 311 patients out of which 207 were under treatment with duloxetine 60 mg/day and 104 were under treatment with placebos. At the end of the study, the following benefits of duloxetine over placebo were observed: improvement in verbal learning and memory function, but no benefits in attention or executive function [46]. In another study, patients treated with levomilnacipran showed benefits in terms of the ability to focus attention and attention as well as reaction time [47].

In the case of vortioxetine, an antidepressant approved in 2013 for the treatment of depressive disorder, it has been observed to have a benefit in terms of the remission of depressive symptoms, and benefits in improving information processing speed, learning ability, and memory [48].

A substantial number of elderly patients continue to have residual depressive symptoms and neuropsychological deficits after antidepressant treatment. Some patients persist with impaired executive function, working memory, and reduced information processing speed, even after mood symptoms resolved [49].

Cholinesterase inhibitors, NMDA antagonists and stimulants

Studies regarding the use of cholinesterase inhibitors in depressive disorder accompanied by cognitive impairment are contradictory [14,50,51]. In a study conducted by Reynolds, he noted that while Donepezil may have potential cognitive benefits, it may also worsen depressive symptoms [14]. Interestingly, Lu et al. (2009) observed that donepezil administration can delay the progression of MCI patients with depression to AD, but not in MCI patients without depressive symptoms [52].

Ketamine shows a rapid antidepressant effect among young adults with refractory depressive disorder. However, use in elderly patients with late-onset depression has not shown any benefits. Similarly, memantine, another FDA-approved N-methyl-D-aspartate antagonist for the treatment of moderate to severe dementia, is not effective as adjunctive treatment in the elderly population with the major depressive disorder [53].

Stimulants, such as Methylphenidate, are also used off-label for depression, they may have benefits on the apathy of AD in the absence of depressive elements. However, stimulants have not been shown to improve cognitive function in randomized control trials in patients with MCI and major depressive disorder [54].

Psychotherapy for LLD patients with cognitive impairment

There are specific therapies aimed at ameliorating the behavioral deficits present in patients with LLD and cognitive impairment associated who have a poor response to antidepressants. For example, problem-solving therapy (PST) addresses the behavioral deficits of patients with late-life depression and executive dysfunction, it is a specific therapy for this kind of patient. It is effective in reducing depressive symptoms and disability, both in elderly patients.
without LLD and cognitive impairment and in patients with LLD without cognitive impairment. PST is based on the idea that teaching patients how to carry out their daily activities can reduce stress and thereby ameliorate depression. Patients are trained to identify their problems, find different ways to solve them, form action plans, perform cost-benefit analysis, and evaluate the effectiveness of potential solutions. PST improves the skills needed in interpersonal relationships and remediate communication difficulties [13].

CONCLUSION

Late-onset depression with cognitive impairment may represent a prodrome, or risk factor, for a later form of dementia. Among the population aged over 60, the prevalence of depression is between 10-20% [2].

The presence of a first depressive episode after the age of 70 doubles the incidence of AD, and the severity of the depressive episode can increase up to four times [7]. Among the most common risk factors between the two pathologies, we can list the vascular risk factors (hypothesis of “vascular depression”), cortisol level but also the presence of various general comorbidities.

Regarding the neuro-psychological assessment, the cognitive impairment in LLD presents a “subcortical” profile characterized by the following: Poor learning and recall, but good cued recall and recognition on memory testing; Poor executive functions, processing speed, and verbal fluency; Intact visuospatial skills and orientation [26,27].

According to some studies, among the signs and symptoms that can be predictive of a poor therapeutic response, we can list the presence of symptoms of cognitive impairment and morning anxiety; (2) the presence of impaired verbal fluency and cognitive inhibition in neuropsychological tests [13].

In terms of neuro-imaging changes, some studies have demonstrated how the volume changes in the gray matter in the prefrontal (orbitofrontal, dorsolateral) area, medial temporal, but also in the subcortical structures (hippocampus, anterior cingulate cortex, striatum, and brainstem) as having different implications in the presentation of depressive disorder. In contrast, other studies have observed how white matter hyperintensity is correlated with memory disorders, executive function, and processing speed [33], but also with emotion regulation processes [34].

In terms of treatment, the most used psychotropic drugs are SSRI- antidepressants (most studies being conducted on sertraline and citalopram) and SNRIs (most studies being conducted on the use of duloxetine), the rest of the antidepressants having very few studies, and those with anticholinergic effects should be avoided in the case of elderly patients. The use of cholinesterase inhibitors shows conflicting results. In addition to the pharmacological intervention, the psychotherapy brings an additional benefit in the case of these patients, PST (problem-focused therapy) is mainly addressed to this class of patients.

Conflict of interest: none declared

Financial support: none declared

REFERENCES


