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Review Article

Evaluation and treatment of depression in dementia

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ABSTRACT

Depression in later life is common with depressive symptoms present in 15% of all older adults and is often associated with coexisting chronic medical conditions, cognitive dysfunction or both. Although the depressive in later life conduction frequently manifests subthreshold symptoms such as not to satisfy the diagnostic criteria of DSM V, depression in the course of dementia should not be underestimated. The clinical features of depression associated with dementia vary from dysthymia-type psychopathological conditions to major depressive forms. Scientific evidence leans towards depression, not only as a comorbidity occurring in the various forms of dementia but as a significant contributor to the dementia etiopathogenesis. Depression in later life can be a prodrome, risk factor, comorbidity or consequence of mild cognitive impairment and dementia. In clinical practice in patients with dementia it is necessary to distinguish depression from apathy which is very frequent and overlaps with depression. Treatment of the psychological behavioural symptoms of dementia (BPDS), including depression, should initially be addressed non-pharmacologically with integrated management, as indicated by several guidelines as a first-line treatment approach except in emergency situations or severity.

Keywords: Antidepressant, Apathy, Depression, Dementia

INTRODUCTION

Depression and dementia are highly prevalent conditions that are increasing exponentially with serious economic and resource burden on health services and on society in general in every nation. Major depression (MD) is the most frequent mood disorder in the world with a prevalence in the course of life ranging from 4% to 17%. In Italy, the estimate is about 10%. Depression is the fourth leading cause of disability and illness worldwide.[1,2] Mild cognitive impairment (MCI) is the intermediate stage between the cognitive changes of normal aging and dementia. The prevalence of MCI has been estimated to be 14-18% for individuals 70 years of age and older.[1] The World Health Organization in its report made dementia a global public health priority. An estimated 47 million people worldwide are living with Alzheimer's disease (AD) and other forms of dementia.[3] The prevalence of dementia is increasing in our aging population at a pressing rate and the risk of dementia is projected to quadruple by 2050.[4] In Italy, there are estimated to be over one million patients affected by dementia and of these around 600,000 with Alzheimer's dementia.[5]

DEPRESSION IN LATER LIFE

Geriatric depression is common and depressive symptoms are present in 15% of all older adults and are often associated with coexisting chronic medical illness, cognitive dysfunction or both. Drug treatment is usually required and many patients may not respond to initial therapy. Relapses and relapses are common among those who recover. Treatments include antidepressants or psychotherapy. The benefits of antidepressant treatment reduce the risk of relapse and or recurrence of symptoms for approximately two/ three years.[6-8] Many elderly patients present with subthreshold symptoms that do not meet the criteria for a depressive diagnosis according to

DSM V with typical symptoms, somatic complaints, anhedonia, lack of interest, cognitive impairments (IC) such as concentration and memory loss, altered psychological tests, executive function altered, tendency not to spontaneously report depressive symptoms or not to express them, psychotic symptoms, insomnia, weight loss.[9] One could speak of "masked depression" (a term, no longer present since the publication of the DSM-IV) in which the affective, cognitive symptoms of depression are less intense and are hidden behind a variety of somatic complaints and complaints, behavioral problems, a condition that was underdiagnosed or treated with little success.[10,11]

The criteria for the diagnosis of major depression DSM-V are summarized in (Table 1).[12] Risk factors can be of various types and are often common in the elderly (Table 2).[13,14]

COGNITIVE IMPAIRMENT IN OLD AGE DEPRESSION

Geriatric DM is accompanied by structural and functional abnormalities in the frontal lobes and their connections with the limbic and striatal systems. The interruption created by the lesions of the neural circuits responsible for cognitive functions (dorsolateral prefrontal cortex, anterior cingulate and parietal association regions) can lead to symptoms of executive dysfunction syndrome, reduced concentration, disorganization, difficulty in shifting attention, inability to disengage from previous behavioral responses, reduced interest in activities and instrumental activities of daily life, psychomotor slowdown. Approximately 30-40% of non-demented seniors with DM show signs of executive dysfunction on cognitive testing.[15,16]

APATHY IN DEMENTIA

Apathy is a very common symptom in psychiatric and neurological disorders. In cortical and subcortical dementias such as Lewy body dementia (DLB), progressive supranuclear palsy, affects about 20 to 70% of patients with AD. Apathy is evident in the FDT variant and can be mistaken for a depressive state or underestimated, especially by the patient's family members.[17]

Apathy is primarily a lack of internal motivation with poor rehabilitation outcomes, as well as rapid cognitive decline.[18] Functional imaging studies report decreased blood flow in areas comprised in the subcortical network of the frontal cingulate lobe and the ventromedial frontal gyrus. in subjects with apathy and AD. Brain area is also compromised in depression. In FTD, the comorbidity between apathy and depression may be related to the fact that they share common neural circuits.[19,20]

The Neuropsychiatric Inventory (NPI) was used as a screening for the evaluation of symptoms table 3.[21] There are no drugs approved by the Food Drug Administration for the treatment of apathy. Several studies have shown that methylphenidate, olanzapine, choline, alfoscerate, citalopram are useful in apathy related to AD.[22]

DEPRESSION AS A BEHAVIORAL PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Depression is one of the manifestations of Behavioral Psychological Symptoms of dementia (BPSD) as a consequence of dementia. These reduce the quality of life, also increasing the possibility of institutionalization of the patient. More than 90% of patients with dementia develop at least one of these symptoms The treatment of BPDS in general should be initially addressed by modifying the scavenger's behavior or reducing environmental stimuli, involving family members in support or psychoeducational programs offered by the various associations for dementia and by clinical care pathways, with integrated management.[5] A very recent meta-analysis shows that the female sex was associated with a greater prevalence and severity of specific depressive symptoms, psychosis, delusions and aberrant motor behavior, while the male sex was more associated with a more severe state of apathy than the sex female.[23] Depression and dementia have a strong impact on the cargiver creating a strong stress with worse results on the patient's care path.[24] Furthermore, family cargivers of demented patients are exposed, after a long time, to physical and mental health risk (depression and high suicide risk).[25]

DEPRESSION IN THE ETIOPATHOGENENSIS OF DEMENTIA

Primary dementia as, such as AD, have multifactorial etiopathogenesis, contributing unchangeable risk factors such as old age, female sex, genetic factors and modifiable factors such as environmental ones, low level of education, vascular pathologies, traumatic events, etc.[26] Scholars Barnes and Yaffe found that one-third of Alzheimer's cases are attributable to depression, but in the scientific literature it was unclear whether they had any real causal effect on the development of dementia.[27] Subsequently, substantial evidence appears to consider depression both cause and consequence of AD. It is estimated that the prevalence of depression and comorbidity is 30-50%.[28] There is a significant prevalence of depression in patients with MCI or dementia and vice versa, especially in AD. Depression in old age can be a prodrome, risk factor, comorbidity or consequence of MCI and dementia. Conditions constitute one of the most confusing aspects of psychogeriatric practice, leading to under-detection and mismanagement of depression.[29]

Some North American scholars (Emery and Oxman 1992, Folstein and Mc Hugh 1978) have instead stated that in the third age there is a continuum between depression and dementia and 5 different categories can be classified. Major depression without dementia, depressive dementia, degenerative dementia without depression, initial depression from degenerative dementia, association of depression and degenerative dementia.[30] DM can have negative effects on the cognitive aspect of the individual,

especially if elderly and if the depressive state is severe, it can mimic a dementia-like psychopathological picture and therefore be confused with AD and other neurodegenerative diseases. Historically, this phenomenon, in general, has been known as "pseudo-dementia" (a term no longer used), in other words, a psychiatric condition disguised as a neurodegenerative disease, but largely reversible.[31] The percentage of patients with dementia meet the diagnostic criteria for a depressive episode was reported as 33.2% and 43.7% for AD and DLB, 60% for vascular dementia (VaD) and 33%, respectively for FTD.[32] Depression with sleep disturbances increases the risk of AD by about three times.[29] It would seem that there is a relationship between sleep and the neuropathological characteristics of AD disturbed sleep and increased wakefulness lead to an acute increase in Aβ production and a decrease in Aβ clearance. Acute sleep deprivation would lead to increased levels of Tau in the human cerebrospinal fluid.[33] Mild DM can compromise cognitive function and the severity of psychopathological and neurological impairments increases with increasing severity of depression.[34]

Dementia patients with DM have greater impairment in daily activities such as feeding, dressing and bathing, compared to demented patients without depression.[16] It is common to find in the elderly a mixed dementia AD and VaD, the comparison between the two dementias is given by a greater prevalence, severity and duration of depression and anxiety in the VaD.[35] Depression such as obesity, diabetes, arterial hypertension (AI), cigarette smoking, etc. is a modifiable risk factors for AD, so action is essential.[36]

THE BIOLOGICAL MECHANISMS BETWEEN DEPRESSION AND DEMENTIA

Depression has been linked to different types of dementia. Likely biological mechanisms linking both diseases include. Chronic inflammation plays a role in AD and RV, increasing the risk of vascular events and the development of AI. Pro-inflammatory cytokines contribute to a smaller Hc, increasing the risk of AD.[1,37] In recent decades, light has been shed on inflammatory processes confirming that pro-inflammatory cytokines play a role in SERT regulation and synaptic plasticity of neurons.[38]

Dysfunction of the cerebral microcirculation and AI are risk factors for the development of depression secondary to vascular disease (vascular depression). There are deficits in working memory and attention, psychomotor slowdown and poor insight. There is a subcortical hyperintensity typical of a vascular lesion at the level of the impaired cortical-striated-pale-cortical thalamus circuit.[16] Magnetic resonance imaging (MRI) studies have shown that white matter (WM) hypertensity in depressed subjects is an expression of Cerebro vasculopathy, the presence of ischemic brain lesions (subcortical WM) is an expression of frequent depression in the elderly.[39] Vascular lesions as well as structural changes in the brain can contribute to depression in old age.[37,40,41] The two hypotheses of vascular depression relate cerebrovascular disease to the etiopathogenesis of depression in the elderly. Subcortical WM ischemic lesions (lacunar infarcts) in the basal ganglia and WM could be the direct cause of vascular depression in subgroups of stroke patients. The accumulated presence of small vascular lesions could eventually reach a threshold that could lead to the onset of depression. Threshold theory.[40]

HPA disorders that cause prolonged hypercortisolaemia can promote Hc atrophy (rich in glucocorticoid receptors) and functional decline. Glucocorticoids can promote Hc cell damage and death if chronically exposed, so even long-term exposure to stress or depression contributes to a smaller Hc, leading to the later development of AD, assuming that a long history of depression contributes more to AD than to RV.[1] Repeated episodes of depression may further contribute to the loss of HC volume and thus increase the risk of AD.[42]

BDNF, an endogenous neurotrophic protein that has greater expression in the brain of the adult mammal and is involved in the activation of the (R) tyrosine kinase receptors of neurons and has a neurotrophic function, on synapses, on neurogenesis, on neuroplasticity, also in response to stress.[43,44] In the conditions of depression and dementia there is a decrease in the levels and activities of neurotrophic factors, such as BDNF which modulates synaptic plasticity also in HC where the deficiency of BDNF can complement the Hc cell apoptosis.[42] Brain deposition of Aβ peptide is associated with both cognitive and neuropsychiatric symptoms, which can be interpreted as a biological compensatory mechanism.[45] Decreased BDNF and decreased 5-HT leads to high Aβ toxicity, which first causes Hc atrophy with progression from depression to AD is facilitated.[32]

Barnes, et al, in a retrospective cohort study examined depressive symptoms assessed at a middle and late age and the different types of dementia. Subjects with depressive symptoms in old age had a double increase in the risk of AD while subjects with symptoms of middle age and old age had a more than threefold increase in RV.[46] Depression in later life may be a prodrome symptom of AD while recurrent depression may be associated with RV.[37] The accumulation of Aβ in the brains of patients with AD begins more than 20 years before the first manifestations of dementia changes pathologies in the brain caused by the early dementia process can influence the onset of depression.[47]

CLINICAL EVALUATION OF DEPRESSION IN DEMENTIA

The clinical features of depression associated with dementia range from psychopathological conditions such as dysthymia to major depressive forms. Other mood disorders may also be present with dysphoric manifestations usually associated with frontal dysfunction or DFT, emotional liability with pseudobulbar signs (dysphagia, creeping gait present in subcortical or vascular

neurodegenerations,) euphoria and mania associated with focal lesions of the limbic region.[30] The assessment of the depressive state in dementia is an aspect that should not be underestimated and must include personalized medical history, social and family status, neurological/psychiatric examination, laboratory investigations and neuroimaging to exclude contributing factors. Depression must be adequately treated with longitudinal neuropsychological reviews to assess the patient's cognitive status.[29] Although there are numerous screening tools useful for identifying depressive symptoms in the elderly (Table 3) depending on the dementia state, whether intermediate or advanced, the problem is caused by the patient's IC who cannot understand the questions or does not remember. Therefore, the test psychometric assessments are unusable, perhaps with the exception of the Cornell scale of depression in dementia (CSDD).

The mini-mental state exam and the short-blessed test are tools for cognitive screening, to monitor IC during and after the treatment of depression. If the IC persists despite the improvement in depressive symptoms, further investigations such as brain imaging (TC or MRI) should be carried out to rule out coexisting dementia or other concomitant causes. Useful laboratory tests to recognize and rule out reversible types of dementia or other secondary causes.[51]

TREATMENT OF DEPRESSION IN THE COURSE OF DEMENTIA

Non-drug treatments are the initial approach to the management of BPDS, as indicated by numerous guidelines as a first-line therapeutic approach with the exception of emergency situations, but the data to support these is scarce. Treatment options are antidepressants (SSRIs) of the first choice for clinically significant depression in the general population, but the evidence supporting their use in dementia is conflicting and efficacy is uncertain.

Potential side effects in the elderly are always to be considered. In dementia, pain can have significant effects on behavior and mood, especially the coexistence between depression and chronic pain can make treatment and the initial recognition of depression more complicated.[11,52]

NO PHARMACOLOGICAL TREATMENTS

Studies have shown improvement in depressive symptoms using structured sleep hygiene programs, exercise, artistic interventions and music therapy. At the moment, the best evidence of art-based approaches is in music therapy. Dementia with severe depressive symptoms responds well to electroconvulsive therapy. Transcranial magnetic stimulation is not currently widely used.[53] The expert consensus guideline recommends drug antidepressant therapy combined with psychosocial intervention as the treatment of choice in geriatric depression. Several randomized studies show that physical activity and pleasant events reduce depression in demented patients who live alone or music therapy has had positive effects on aggression and wandering. A study of 23 studies involving 3,300 community-resident patients examined interventions targeting family caregivers and confirmed the significant reduction in BPDS.[54,55]

Pharmacological treatments

Although no drug is currently approved for the treatment of BPSD in the United States and also in Italy, antidepressants and neuroleptics, except some with clear indications, are commonly used off-label in patients with AD. In general, the use of antidepressants selective serotonin reuptake inhibitors (SSRIs) is recommended for the treatment of depressive symptoms associated with dementia, although the available evidence is conflicting.[3] Classes of antidepressants used in geriatric depression

The classical monoamine hypothesis proposes that depression is caused by the reduced availability of neurotransmitters 5-HT, noradrenaline (NA) and dopamine (DA) in the central nervous system. Antidepressants act selectively on R-5-HT and NA to block their reuptake and increase their concentrations in the neuronal synaptic space, thereby improving neurotransmission and having an antidepressant effect.[36,56] The antidepressants most used in geriatric depression are summarized in Table 4.[57]

It is still unclear whether SSRIs have beneficial effects on cognition in AD patients.[28] A 2011 Cochrane review studying the efficacy and safety of antidepressants concludes that although there are relatively few studies available, there is some evidence to support the use of some antidepressants for agitation and psychosis in dementia. SSRIs sertraline and citalopram have been associated with a reduction in agitation symptoms.[28,58]

There are a limited number of studies that include SSRIs for the treatment of agitation in BPSD. SSRIs such as citalopram were associated with the treatment of agitation symptoms and with a lower risk of adverse effects than antipsychotics.[59] Both SSRIs and trazodone appear to be reasonably well tolerated compared to placebo. Trazodone is used although the evidence is limited to reduce irritability and agitation, most likely due to its sedative effects and with citalopram considering the potential prolongation of the QTc interval.[57-60]

SSRIs can exacerbate apathy, as demonstrated by a recent retrospective study of 119 outpatients with psychiatric disorders, which reported that the proportion of patients with apathy was significantly higher in the SSRI-treated group than in the control group.

In a prospective cohort study, he reported that the use of non-cholinergic type antidepressants more commonly prescribed in later life did not appear to be associated with the risk of dementia. Paroxetine and other anticholinergic

antidepressants should exceptionally be used in older individuals. The combination of antidepressants and hypnotics does not increase the risk of dementia in patients with depression. In 2019, an Italian open label observational study by Cumbo et al, on 108 AD patients with depression for 12 months, has shown that the use of vortioxetine on these patients has positive effects on cognitive functions. Vortioxetine is an antidepressant that has a multimodal mechanism of action, binds to SERT, has an agonist action of R-5-HT1A, partial agonism on R 5-HT1B and antagonism on R-5-HT3, 5- HT1D and 5-HT7, indirectly regulate NA, DA, acetylcholine (ACh), gamma-aminobutyric acid (GABA) and glutamate (GLU). According to studies by Spanish researchers, the antidepressants that improve cognitive function are those with dual or multimodal function: duloxetine, venlafaxine, desvelafaxine, tianeptine, mirtazapine and vortioxetine by Ortiz et al. There is not much evidence to date to support the efficacy of antidepressants and therefore they should be used with caution.[28]

Table 1: DSM V diagnostic criteria for major depression.

S. no.	Symptoms
1	Depressed mood or
2	Loss of interest or pleasure
3	Significant weight loss
4	Insomnia or hyper insomnia
5	Agitation or psychomotor slowing
6	Lack of energy
7	Feelings of guilt or self-depreciation
8	Reduced ability to concentrate or think
9	Recurring thoughts of death Symptoms cause significant impairment or discomfort; symptoms are not caused by substance use or other medical condition or other mental illness (except bipolar or mood disorder).
Specifiers: with anxiety, mixed characteristics, melancholic, atific, psychotic, with catatonia, onset in the peripartum, seasonal trend.	

Table 2: Risk factors for late-life depression.

S.no	Physiological factors	Psychosocial factors	Pathological factors
1	Old age	Being a widower or single	Physical illness (loss of function/disability)
2	Being a woman	Low level of education	Use of drugs
3	Presence of altered white matter	Existence of psychosocial stressors, bereavement, caregiver stress, lack of social support, changes in social/work roles	—

Table 3: Evaluation scales for depression in the elderly.

S. no	Evaluations
1	The CSDD serves to evaluate the signs and symptoms of depression. 19 item instruments administered by a physician interviewing the patient, and utilizing information from a member of the nursing staff/caregiver. Attention is focused on the depressive signs and symptoms that occur during the week preceding the interview (first the informant is interviewed followed by the patient).[16-50]
2	The fifteen-element version of the geriatric depression scale (GDS) demonstrated good delivery characteristics. Five or more depressive symptoms suggest the diagnosis of depression by distinguishing the symptoms of depression and dementia.[50]
3	The patient health questionnaire-9 (PHQ-9) was developed for use in primary care settings and has demonstrated validity and reliability. It includes all nine DSM-IV criteria for major depression. The PHQ-9 is a tool that can also be used to assess response to treatment.[16]
4	The center for epidemiologic studies depression scale (CES-D) is commonly used in primary care settings for the assessment of depressive symptoms. It was developed for research not for the clinical context, so individual scores must be interpreted with caution.[16] The neuropsychiatric Inventory (NPI) used as a screening for the evaluation of 10 behavioral dists occurring in dementia: delusions, hallucinations, dysphoria, disinhibition, anxiety, agitation/aggression, aberrant motor activity, lability/irritability and apathy

Table 4: Antidepressant.

Class of antidepressant	Mechanism of action (MOA)	Significant side effects
Selective serotonin reuptake inhibitors (SSRIs)	Inhibit serotonin transporter (SERT), increasing serotonin (5-HT) levels in the synaptic cleft	Gastrointestinal symptoms (nausea, vomiting, constipation, diarrhoea), sexual dysfunction, insomnia, tremor
Sertraline, Citalopram, Paroxetine, Escitalopram, Fluoxetine, Fluvoxamine		
Selective noradrenaline-serotonin reuptake inhibitors (SNRIs)	Inhibit norepinephrine transporter (NET) and serotonin transporter (SERT)	Gastrointestinal symptoms, tremor, sexual dysfunction, headache, hyperhidrosis
Duloxetine, Venlafaxine		
Serotonin antagonist and reuptake inhibitor (SARI)	Inhibit SERT and antagonize 5-HT_2A/2C receptors	Gastrointestinal symptoms, headache, hypotension, dizziness, sedation
Trazodone		
Multimodal antidepressants	Inhibit SERT, antagonize 5-HT_3, 5-HT_7, 5-HT_1D; partial agonist at 5-HT_1B; agonist at 5-HT_1A; modulates glutamate/GABA neurotransmission	Nausea
Vortioxetine		
Tricyclic antidepressants (TCAs) tertiary amines	Inhibit NET and SERT	Sexual dysfunction
Amitriptyline, Imipramine, Clomipramine		
Tricyclic antidepressants (TCAs) secondary amines	Inhibit NET	Constipation, blurred vision
Desipramine, Nortriptyline		

DISCUSSION

Although treatment with antidepressants for the treatment of depression in dementia still requires more in-depth studies, there is still some scientific evidence that favors a safe and partially effective use of antidepressants. While the association between mortality risk and the use of antidepressants in people with dementia is not known, the use of antidepressants has shown increased BDNF levels in various areas in post-mortem studies of patients with depression cerebral (dentate gyrus, insula, Hc region).[28] On the other hand, the Cochrane 2018 meta-analysis which summarizes the studies from 6 studies for a total of 194 patients, the available data did not finally show a favorable effect of antidepressants in improving the cognitive/functional profile in patients with dementia and depression. Despite the lack of strong scientific evidence, a 2015 study reports that geriatric-aged patients with dementia are three times more likely to receive an antidepressant prescription than their peers without dementia. The evidence and clinical experience achieved show that non-pharmacological approaches and watchful waiting to be attempted for the first 8-12 weeks in a patient who has both depression and mild to moderate dementia are first choices. In the case of severe depression or depression not treated pharmacologically, administration of an antidepressant may be initiated by Laitinen et al study.

CONCLUSION

Scientific evidence leans towards depression, not only as a comorbidity present in the various forms of dementia, but as a significant contribution to the etiopathogenesis of dementia. Depression in old age should not only be considered a prodrome, but also a risk factor. Therefore, it is necessary to treat depression as a risk factor. The treatment of BPDS should initially be addressed non-pharmacologically with integrated management. Good clinical practice and experience suggest non-pharmacological approaches and watchful waiting to be attempted for the first 8-12 weeks in patients with mild to moderate depression and dementia. In case of severe depression or depression not managed by non-pharmacological means, therapy with an antidepressant is started. Tricyclic antidepressants due to anticholinergic adverse effects and due to the risk of cardiac arrhythmia and orthostatic hypotension with risk of falls, are to be avoided. In the elderly, increased dehydration and decreased liver and kidney function and demethylation activity, are condictiones that increase plasma concentrations of tricyclic drugs and elimination half-life with greater susceptibly to side effects and iatrogenic toxicity.

SSRIs should be avoided particularly in the elderly with kidney disease due to the risk of hyponatremia. Although the scientific evidence is weak, the use of SSRIs is warranted in people with dementia who have clear symptoms of moderate or severe depression, especially if previous use of psychotropic drugs has been ineffective.

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