CLINICAL PARTICULARITIES OF DEPRESSION IN GERIATRIC PATIENTS

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Abstract. The major depressive disorder (MDD) is the most common affliction of the elderly persons. Its presence, reduces the life quality, adds disability to the other comorbidities, decrease response to treatment for the somatic diseases, it complicates the course of dementia and it becomes a risk factor for them. Having just a few persistent symptoms with low functionality and low life quality can be by itself a risk factor for MDD or mild cognitive impairment (MCI). Subsyndromal MDD or dysthymia is more frequent in older persons. Typical presentation of the elderly with MDD also can contain insomnia, late onset of alcohol abuse, memory deficits, unexplained pain, deliberately minor self-harm, loneliness, exacerbated anxiety with somatizations, accentuation of the abnormal personality traits or behavioral disorders. So MDD with no sadness and other atypical features can obscure the diagnosis. From the clinical subtypes of MDD, the psychotic depression is likely more present. The classical delusions are worthlessness, poverty, guilt or hypochondriacal delusions. Elderly rarely fake suicide in order to attract attention or by accident. 25% of the people with MCI have significant depressive symptoms and 50% of the people with Alzheimer have depressive symptoms. MDD may appear after stroke that affect certain areas like those closer to the anterior pole of the left hemisphere, but not all agree to that. We suggest that using a scale like Stroke Aphasic Depression Questioner Hospital Version may be helpful in these cases. When we choose a treatment for MDD elderly we must consider the comorbidities, the current medication, clinical form, patient needs and to start with lower doses. In all these cases, only a multidisciplinary approach can lead to the best course of treatment.
Key words: depression, elderly, comorbidities, clinical particularities, treatment

Rezumat. Tulburarea depresivă majoră (TDM) este de departe cea mai frecventă afecțiune a vârstnicilor. Reduce calitatea vieții, adaugă dizabilitate celorlalte comorbidități și un răspuns mai slab la tratamentul bolilor somatice, complică cursul demenței și devine un factor de risc pentru acestea. Prezența doar a câtorva simptome persistente cu funcționalitate scăzută sau calitatea vieții scăzută poate fi de la sine un factor de risc pentru TDM sau deficitul cognitiv (MCI). Depresia sub-sindromală sau distimia este mai frecventă în prezentare geriatrică. Caracteristicile clinice tipice la vârstnicii cu MDD pot include și: insomnie, debut tardiv al abuzului de alcool, deficite de memorie, durere inexplicabilă, auto-vătămare deliberată, singurătate, exacerbarea anxietății cu somatizări, accentuarea anormală, trăsături de personalitate accentuate sau tulburări comportamentale. Deci, MDD fără tristețe cât și alte caracteristici atipice pot ascunde diagnosticul. Dintre subtipurile clinice ale MDD, depresia psihotică este probabil mai prezentă. Ideile delirante ale vârstnicilor pot include lipsa de valoare, sărăcia sau vina, dar în principal ei au ideație hipocondriacă. Tentativa de suicid a pacientului geriatric rar are ca scop atragerea atenției. 25% din persoanele cu MCI au simptome depresive semnificative, iar 50% dintre persoanele cu demență Alzheimer au unele simptome depresive. MDD poate apărea după accident vascular cerebral care afectează anumite zone precum cele mai apropiate de polul anterior al emisferei stângi, dar nu toți medicii sunt de acord cu aceasta. În aceste cazuri vă sugerăm să utilizați o scală similară cu Stroke Aphasic Depression Questioner Hospital Version. Atunci când alegem un tratament pentru vârstnicii cu MDD, trebuie să luăm în considerare comorbiditățile, medicația curentă, forma clinică, nevoile pacienților și să începem cu doze mai mici. În toate aceste cazuri, numai abordarea multidisciplinară poate duce la cel mai bună evoluție a pacientului.
Cuvinte cheie: depresie, vârstnic, comorbidități, particularități clinice, tratament

INTRODUCTION

The need for this article appeared after discussions with various caregivers in our institute, due to the fact that a geriatric patient has in general more comorbidities and we tend to consider its depression as a result of the ageing process or a consequence of his psycho-traumas or physical diseases. Sometimes it is the case, but it was proved that the late life depression is not just a mental disorder that affects an undifferentiated group or subgroup of age arising from senility or just getting old. It seems that besides the

different disorder prognoses, comorbidities, particularities and clinical aspects the depression at old age needs special attentions and approaches. Although dementia and mild cognitive impairment (MCI) are regarded as the main psychiatric afflictions at old age, major depressive disorder (MDD) is by far the most common [1]. Regarding the MDD clinical aspects the findings have been inconsistent, but majority opinion holds that depression (especially 'subsyndromal') is more common in old age. There may be two peaks in the prevalence rate of major depression, one in late old age and the other in middle age or earlier [1]. Consistent with the international published data, a study on Romanian patients, confirms the peaks of depression are in the middle age and at old age. Also, more women than men are affected by depression (ratio of 2:1.2) [2].

MDD in old patient is often overlooked but it is a serious disorder because it reduces the life quality, adds disability to the other comorbidities, decreased response to treatment for the somatic diseases, it complicates the course of dementia or MCI and it becomes a risk factor for them [3]. A study on Romanian patients showed that the recently diagnosed (<3 months) and treated have presented a significant improvement after ten weeks of treatment compared with the patients diagnosed with depression more than one year ago. Also, the patients above 65 years, diagnosed with depression for more than one year, had a slow improvement during all the visits. These two observations sustain the importance of recognizing depression and the initiation of the treatment from the beginning, which allow a good improvement of the functionality [4]. Many healthcare providers are tempted to presume that older people are more susceptible to MDD because of their end of life is approaching or because of their somatic chronic illnesses. So, it is a trap to 'normalize' MDD in older people with chronic illnesses because you can overlook it. The fact is that many older people are living content with their quality life, and this is improving constantly with age [3]. In the group that became depressed, the medical and psychological intervention may help significantly [3].

The objective of this article is to provide a resource to the healthcare providers that are involved in the geriatric patients care by summarizing the core knowledge from the most relevant evidence-based literature.

DIAGNOSIS CRITERIA

Depression can be a symptom or a syndrome. If we refer it as a symptom, the key in order to distinguish from a transitory low mood is a qualitative and persistent (most days, most of the time) change of the mood. Also, in depression the mood is worst during mornings, it improves during noon and afternoon and again it became worst in the evenings. In the recent years, we significantly change the way we conceptualized depression. In the Diagnostic and Statistical Manual of Mental Disorders the fifth edition (DSM 5), depression is seen on a continuum rather than fixed categories of disorder into which the patient must be forced. Moreover, the evidences suggest that depression is on a continuum from normal sadness to severe MDD. But the DSM 5 is beginning to be used in research. DSM IV is widely used by clinicians. Interestingly the US Centers for Medicare and Medicaid Services has recently called for providers to bill for services using the International Statistical Classification of Diseases and Related Health Problems 10^{th} edition (ICD-10) designations.

In Europe, the healthcare providers use for now, in order to diagnose the MDD, the ICD-10 criteria. In ICD-10, the depression diagnostic criteria are used as an agreed list of ten depressive symptoms divided into key symptoms and associated symptoms. The key symptoms must be present most days, most of the time for at least 2 weeks (persistent sadness or low mood *and/or* loss of interests or pleasure

and/or fatigue or low energy). If any of above present, ask about associated symptoms like - disturbed sleep, poor concentration or indecisiveness, low self-confidence, poor or increased appetite, suicidal thoughts or acts, agitation or slowing of movements, guilt or self-blame. The 10 symptoms then define the degree of depression and management is based on the degree: not depressed (fewer than four symptoms), mild depression (two or three of the above symptoms are usually present and the patient is usually distressed by these but will probably be able to continue with most activities), moderate depression (four or more of the above symptoms are usually present and the patient is likely to have great difficulty in continuing with ordinary activities.), severe depression (an episode of depression in which several of the above symptoms are marked and distressing, typically loss of self-esteem and ideas of worthlessness or guilt; suicidal thoughts and acts are common and a number of "somatic" symptoms are usually present). These symptoms should be present for a month or more and every symptom should be present for most of every day [5].

Also, we can have the situation when a patient does not meet the diagnosis threshold, but it has an impaired functionality and a significant degree of distress in its life. Having just a few persistent symptoms with low functionality and low life quality can be by itself a risk factor for MDD or MCI [6]. Subsyndromal depression or dysthymia are more common and have a negative impact on health of the older persons [6]. Interestingly, the incidence and prevalence of the sub-threshold depression (STD) is bigger than the incidence and prevalence of the MDD (between 8.6% and 14.1% for STD and from 1% to 4% for MDD) [7]. These rates were then lower than those of the peoples under 65 years old. This fact can be partially explained by the ICD/DSM strict criteria used to diagnose MDD that may not be suited to older population. This was underlined also by the 'EUORO-D' study results because it used an aged specific rating scale to compare symptoms of depression among European elderly. Also, a large cohort study proved that healthy older people were not at a greater risk of depression than the younger ones, so the increased MDD prevalence with age may be explained by the greater prevalence of the chronical somatic illnesses in the older people not by their age [8].

CLINICAL FEATURES IN GERIATRIC PATIENTS

It seems that no matter what the aetiologia of the MDD could be, the phenomenology is the same and the different clinical particularities are constant and specific [9]. The typical clinical features like sadness is minimize in older patient, but other clinical features like guilt, marked withdrawal, hypochondriasis somatization or psychomotor retardation/agitation are more common, and they are associated more with age than with the age at onset [9]. Moreover, they are more pronounced in females. Also, another feature of the later life depression is that these patients became excessively concerned about their physical health [9]. So, typical presentation of the elderly with MDD also can contain in addition to the features already discussed: insomnia, late onset of alcohol abuse, memory deficits, unexplained pain, deliberately minor self-harm, loneliness, exacerbated anxiety with somatizations, accentuation of the abnormal personality traits or behavioral disorders [9]. So MDD with no sadness and together with these other features can obscure the diagnosis of depression.

Also, typical for elderly is the apathy (it can be a symptom or a syndrome), which is a disorder of motivation rather than mood and it is different from depression. From the behavioral point of view the syndromic aspect consist in indifference, impoverished thoughts and indolence. From neurological point of view, it is associated with stroke, frontal lobe trauma

or degeneration, other traumatic brain injuries, multiple sclerosis, vascular or mixt dementias or depression [10]. From the biological psychiatry point of view apathy appears when there are imbalances in the subcortical-frontal connection (front-striatal circuits) like in the diseases of the basal ganglia, anterior cingulate and/or dorsolateral prefrontal cortex [10]. So, the front-striatal circuits are important in later life because if happens any disruption here, it will cause a dysexecutive syndrome [10]. Although there are overlaps between MDD and apathy, we can distinguish them. MDD is a mood disorder that can cause effects on apathy which are felt by the patient as distressing and it respond to the medication. On the other hand, apathy does not cause distress on the patient and is most of the time notices by the care givers and requires behavioral interventions.

From the clinical subtypes of depression (some other author considers it a form more severe form of MDD rather than a specific subtype), the psychotic depression is likely more present in later life than in the young adults. The classical delusions may include worthlessness, poverty or guilt but in older patients it mainly includes hypochondriacal delusions [11]. Also, in old age is far more present the Cowards syndrome in which the patients negate their own existence or physical body [11]. The most common abnormal perception in old age is auditory hallucination, which content is congruent with the mood [11].

Regarding the attempted suicide in older patients, they resemble successful suicide in its clinical characteristics. In older patients it can be a fatal mistake not to take seriously any deliberate act of self-harm, because elderly rarely fake suicide in order to attract attention or by accident. Even a sub-intentional suicide or a passive suicide must be very carefully assessed because these patients that show profound withdrawn, refuse food, reject help or suffer huge weight losses represent a heterogenous and hard to asses group. So, if we are unsure of the risk of suicide, we must prescribe with caution benzodiazepines, tranquilizes, sedatives, non-opiate analgesics or other drugs that have an overdose that can be reached easily with the prescribed quantity [6]. There are many suicide risk factors (male, living alone, no social support, chronic stressor or conditions, alcohol abuse, cultural or family history of suicide), behaviors (suicide plan expressed, altering wills, hoarding drugs, self-neglect, accidental overdoses or leaving notes behind) and illness factors (Psychosis, agitations, substances misuse, insomnia, guilt, hopelessness), in older patients, but the most important one is the history of self-harm [6]. In contrast to earlier research, recent studies have found relationship problems are the most prominent factor. However, in the past decade there has been inadequate examination of psychosocial precipitants, motivations and psychopathology and the way these factors interact. The possibilities of the psychological trait of hopelessness and the biological trait of low central serotonergic activity being linked with suicide attempts in the elderly require further research. Future studies should be prospective, longitudinal, use standardized measures, matched control groups and include evaluations of post suicide attempt interventions, hopelessness and central serotonergic activity [12].

The suicide prevention in elderly has received little attention, despite suicide rates being highest in older men, in the context in which almost 90% of older people who attempt, or complete suicide have a mental disorder (mostly MDD), which often has been inadequately treated [13]. Other treatable contributing factors include pain, grief, loneliness or alcoholism. Few suicides in older people occur in the context of terminal illness or can be regarded as "rational". Educational programs are required to improve the recognition and treatment of depression in primary care [13].

MDD AND THE DIFFERENTIAL DIAGNOSIS OF PSEUDODEMENTIA

Another important clinical aspect that we need to mention is the so called pseudodementia (a term invented in 1980, that probably it outlives its usefulness), which in most of the cases appear in older patients that accuses huge memory loses with fast onset. They also appeared to be amnestic, the attention is poor, but they do not present any deficit of the higher cognitive functions (aphasia, apraxia, acalculia) [14]. Pseudodementia term suffered in time few other modifications: Pearlson called it dementia of the depression and in 2002 Alexopulos called it Depression-Executive Dysfunction Syndrome (DEDS), term used until today [14]. This also implies different etiological pathways like vascular injuries to the FSC that causes executive disfunctions and amnesia from neurodegeneration of the limbic regions. Patients with DEDS seems to have higher risk of dementia, but it is no clear correlation to which type (speculation on the subject we can assume that DEDS patient are at risk for vascular dementia and the amnestic type are at risk for Alzheimer dementia, but there are no data to confirm this) [14]. What we know for sure is that MDD is a risk factor for later cognitive impairment or dementia [15]. This may be because of the depression action on the cortisol level, HPA axis or because of the commune inflammatory mechanism [16].

Around 25% of the people with MCI have significant depressive symptoms and 50% of the people with Alzheimer dementia have some depressive symptoms of clinical significance [17]. On these categories of patient, we can use Cornell scale in order to detect depressive disorder in dementia. Also, it is important to mention that dementia usually have a slow and insidious onset and the relatives, or the caregiver are the one that notice the memory disturbances and, on the memory, tests the patient may just guess. On the memory impairment from MDD, the patient is the one who is complaining and, on the memory, test struggles to give an answer or just give up. In dementia the high cortical function is compromised also. We must consider also that MDD often is a prodrome for dementia with a cut off around 10 years and beyond that is a risk factor for it. In this context a proper treatment and patient follow-up is required [17].

INTERRELATIONS BETWEEN MDD AND CARDIOVASCULAR DISEASES

An important association is between the coronary heart disease (CHD) and MDD. 20% of the peoples after a coronary event develop MDD [18]. 7.1% of the CHD patient has MDD and 5.3% have generalized anxiety disorder (GAD) [18]. American Heart Association recommends screening for depression all cardiac patients because the presence of MDD in old cardiac patient is an independent factor for vascular events. There are many biological possible explanations for the relationship between MDD and cardiovascular diseases:

- Endovascular low-grade inflammation, present in cardiovascular diseases (CVD) but also in MDD, proves that this is a two-way street for both pathologies [16].
- At the vascular endothelial level, the balance between the nitric oxide (NO) which has a vasodilator effect and endothelin (a peptide with vasoconstrictor action) is affected. So, the endothelial disfunction is considered to predict the atheromatous process [19].
- Autonomic system imbalance (HPA axis hyperreactivity leads to sympathetic overactivity and parasympathetic under-activity) from MDD is well known for decreasing the heart rate variability, decreasing the baroreceptors sensitivity and down regulating the beta-receptors. All these leads in the end in making the heart more susceptible for arrhythmias [19].
- The pallets seem more active in the depressed patients with CVD [19].

- MDD presence is also liked with the physical change in arteries: intima-media thickness (measurement for atheroma) is affected by depression presence at baseline in a 3 years study, after adjusting for confounding factors [20].
- To complicate the things even more, the MDD patients is reducing the like hood of taking the medication as prescribed and so these patients will have reduced treatment adherence, poorer life quality and more comorbidities.

MDD AND NEUROLOGICAL DISEASES

Also, the ***stroke*** is an important comorbidity with the MDD, because around 20% of the patients within develop depression in the first year after it. The peak prevalence of the MDD after stroke is between the 3rd and the 6th month, tailing off after 3 years [21]. Between the 1st and the 3rd year after the stoke 10 to 15% of the survivors remain affected [21]. It is an important comorbidity because post stroke MDD is one of the most important predictors for impaired quality of life, poorer functional recovery and a risk factor for cognitive decline [18]. Also, around 25% of the stroke survivors in the first 6 month after it begin to cry or laugh in inappropriate social situation (like laughing at a funeral) with little control of it [21]. There are theories that the MDD may appear after stroke that affect certain areas like closer to the anterior pole of the left hemisphere (by disruption of the routes connecting the cortex with the brain stem) but not all agree to that [18]. But to make a diagnosis can be difficult after a stroke and therefore we recommend using a scale like Stroke Aphasic Depression Questioner Hospital Version may help.

Moreover, MDD is a heterogeneous disorder from the clinical point of view, common in ***Parkinson Disease (PD)*** elderly patients. In some studies, almost 28% of the PD patient met DSM-IV criteria for a current depressive episode [22]. The best-fitting confirmatory factor analysis model had 3 factors (negative affect, apathy, and anhedonia). All factors are uniquely associated with depression status. Negative affect exhibited the strongest relationship. Psychological disturbance in PD is heterogeneous and can produce symptoms of apathy, anhedonia, and negative affect [22]. Apathy appears to be the core neuropsychiatric feature of PD, whereas negative affect (like dysphoria) seems to be most pathognomonic of depression. Future studies should examine the specific neural correlates and treatment response patterns unique to these 3 components [22]. In another study, the mentation, behavior and mood functions were studied, and the lack of motivation/initiative was most frequently observed in 83.6%of the patients, followed by depression – in 68.2% of the cases and memory disorders in 67.9% [23]. Thought the MDD diagnostic after the ICD criteria was the less frequent (26.9%). As result, all patients had a considerably reduced quality of life mainly due to the development of significant cognitive impairment [23]. From neurobiological point of view, L-DOPA administration does not seem to improve the mood in PD patients, and therefore SSRIs are administered because tricyclic agents (TCA) aggravate the constipation and the postural hypotension [24]. However, in a study with nortriptyline (a TCA), in PD patients with a mean age of 62 years old, was more effective than paroxetine [24]. Some authors concern that SSRIs can cause extrapyramidal effect is contro-versial. The combination of SSRIs and selegiline/rasagiline (MAO-B inhibitors) can lead to serotoninergic syndrome and ca be lethal (the cases are very rare) but the combination of an SSRI and a dopamine agonist was not more effective than either agent alone, or did not produce a more rapid onset of antidepressant action [25]. Combination therapy with escitalopram and pramipexole may not be well-tolerated [25]. The combination of tianeptine and moclobemide (a reversible and selective

inhibitor of monoamine oxidase) has been used to treat MDD in PD patients but the proof is mostly empirical. The electroconvulsive therapy may be effective in severe depression treatment and in improving the motor symptoms of the PD patient, but the results are temporary. Also, deep brain stimulation is can be a treatment for both MDD and PD, but paradoxically may cause MDD in PD patients.

OTHER MDD COMORBIDITIES

Maybe the most common psychiatric comorbidity of the MDD is represented by ***anxiety***. If comparing this association of comorbidities between different age classes, it was proven that a statistically significant higher percent from the very old compared to the old people experienced depression: OR=1.309, CI=1.066-1.609, p=.005. From the total number of the old patients, almost 70% presented anxiety compared to 58% from the very old age group, without statistically significant differences between the two groups: OR=.686, CI=.319-1.474, p=.498. So, we can conclude that MDD and anxiety are present with high rates of prevalence in the old age patients in geriatric presentation. Still, there is an increase in risk for depression in the very old age group. More research for identifying risk and protective factors in different segments of the old age people are necessary for both depression and anxiety [26].

Diabetes is also an important comorbidity for depression. Simultaneous occurrence of chronic diseases like diabetes, cancer, chronic obstructive pulmonary disease, and cardiovascular disease has been at the center of attention of specialists in highly developed countries [27]. A series of epidemiological studies demonstrated that depression is more likely to occur in people with diabetes regardless of whether the individuals are aware of their diabetes. In addition to depressive disorders, people with diabetes are also registering significant levels of diabetes-specific distress, which is clearly distinguishable from depressive disorders but can act as a risk factor for MDD. Epidemiological studies of depression and diabetes and their comorbidity have been carried out in the United States of America (USA), the United Kingdom, and some other high-income countries [27]. An important study of 30 022 adults in the USA showed that the risk of functional disability in people with diabetes was 2.42 times higher than in people who did not have diabetes; that in people with depression alone, it was 3 times higher than in people without depression; and that the risk for those who had MDD and diabetes, the risk was 7.15 times higher than in people who did not have depression or diabetes [27]. It was proven that it was a direct link between MDD presence and the onset of the diabetic complications and poorer glycemia control. The other way around, the level of the HbA1c was a predictor of the recurrent depression or the relapses of the MDD [28].

Chronic obstructive pulmonary disease (COPD) presence in a patient is linked with a high prevalence of depression ranging from 19.4% to 50% [29]. Majority of COPD patients have severe symptoms related to depression with increasing severity of COPD [29]. For example, in one recent study, out of the total COPD patient showed depressive symptoms in 51.76% [29]. Moreover, a higher depression scores 12.35 ± 9.18 was present in moderate to severe COPD. Depression was found to be higher among patients with higher CAT Score, SGRQ_S Score, SGRQ_I Score and SF-36-MCS scale (HRQoL) Score. Activity components of SGRQ (SGRQ_A Score) were found to be potential predictors of depression in COPD patients and a proportion mild moderate to very severe 43% 57% [29]. So, the clinicians and the patients both should be focused on adequate and timely management of both these comorbidities. There is no clear guideline regarding the pharmacological treatment but because of the

association of COPD with depression and anxiety symptoms SSRIs, mirtazapine, bupropion or tianeptine can be administrated. Benzodiazepines should be avoided because they depress the respiratory center. Cognitive behavioral therapy, peer groups and other psychological interventions have been found to alleviate the symptoms and improve the quality of live [30]. In mild and moderate MDD it seems that the psychotherapy is as effective as psychopharmacological treatments, in elderly peoples [30]. For the moment, it seems that CBT, behavioral therapy, interpersonal therapy, dynamic therapy has the most evidences in elderly peoples with depression [30]. Problem solving therapy seems to have a proven efficacy in younger adults with mild and moderate MDD [30]. The best therapeutically course of action and the best results were obtained when psychopharmacology was combined with psychotherapy, even in patient with severe MDD.

Another clinical and therapeutically challenge in geriatric patients is represented by the patients that have ***cancer and MDD***. The prevalence of depressive symptoms in patients with cancer exceeds those observed in the general population and depression is associated with a poorer prognosis in cancer patients [31]. The increased prevalence is not solely explained by the psychosocial stress associated with the diagnosis [31]. Pro-inflammatory cyto-kines, which induce sickness behavior with symptoms overlapping those of clinical depression, are validated biomarkers of increased inflammation in patients with cancer. A growing literature reveals that chronic inflammatory processes associated with stress may also underlie depression symptoms in general, and in patients with cancer. Therapeutic modalities, which are frequently poorly tolerated, are used in the treatment of cancer. These interventions are associated with inflammatory reactions, which may help to explain their toxicity [31]. There is evidence that antidepressants can effectively treat symptoms of depression in cancer patients though the database is meager. Novel agents with anti-inflammatory properties may be effective alternatives for patients with treatment-resistant depression who exhibit evidence of increased inflammation [31]. Antidepressant drugs should be considered for the treatment of moderate-to-severe major depression in cancer patients. Current evidence does not support the relative superiority of one pharmacologic treatment over another, neither the superiority of pharmacologic treatment over psychosocial interventions. The two main classes of medication for depression in cancer are tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). The choice of an antidepressant (AD) should be informed by individual medication and patient factors: the side effect profiles of the medication, tolerability of treatment (including the potential of interaction with other current medications), response to prior treatment, and patient preference [32]. TCAs have more adverse effects and a higher risk of overdose compared with SSRIs. However, a meta-analysis found no recommendation for one antidepressant type over another in cancer due to a lack of research [33]. The prescription of SSRIs must be carefully considered in patients receiving chemotherapy or radiotherapy, as SSRIs can often worsen emesis and nausea [34], whilst the anticholinergic effects of TCAs may worsen delirium associated with chemotherapy [34]. The use of AD in patients with terminal cancer may be unwise due to the delayed mode of action of these drugs [34]. An observational study supported this notion, concluding that currently prescribed antidepressants have little effect on improving depression in terminally ill depressed cancer patients, as measured by depression scores [33]. In one trial, methylphenidate provided moderate to marked improvement in depression symptoms in 73% of depressed oncology

patients within two days; this AD may be an effective alternative to conventional antidepressants [33]. But, the trials of methylphenidate have been promising, physiological tolerance develops quickly, and doses must be increased [33]. Also, Ketamine that has recently been studied for its rapid and effective antidepressant effects, due to its antagonism of NMDA receptors [33]. Ketamine has been suggested as a treatment of depression in terminally ill cancer patients where rapid reversal of depression is vital. A trial in a single patient with advanced cancer, however, exerted initially positive but unsustainable effects; larger randomized trials are necessary to assess the role of ketamine in treating depression in terminal patients [33]. We must consider that chemotherapy drugs may interact with antidepressants and cause nervous system toxicity, by reducing the metabolism of the antidepressants or by additive effects of the cancer drugs themselves [33]. Some antidepressants may reduce the efficacy of chemotherapeutic drugs (for example SSRIs prescribed together with tamoxifen, may reduce the metabolism of tamoxifen to its active metabolite - endoxifen, by inhibiting the hepatic CYP2D6 enzyme and this means the decreasing of the effectiveness of the drug and increases the risk of breast cancer relapse).

CONCLUSION

So, besides different clinical particularities, patient's fragility and comorbidities, when we face MDD in an elderly we must also, look at his medication, because certain chronic drug treatments can induce depression. So, we must look for drugs like non-selective beta-blockers, methyldopa, reserpine, clonidine, digoxin, nifedipine, steroids, analgesic drugs (opioids, indomethacin), antiparkinsonian drugs (levodopa, amantadine, tetrabenazine), interferon, sulfonamides, neuroleptics or benzodiazepines. MDD can appear also in some medical conditions like - diabetes, hypothyroidism, Cushing disease, hypercalcemia, pernicious anemia, sub-nutrition, cerebrovascular disease, stroke, CNS tumor, Parkinson's disease, multiple sclerosis, systemic lupus erythematosus, Alzheimer's disease, carcinoma, neurosyphilis, brucellosis, neurocysticer-cosis, myalgia or AIDS. In all these cases only and multidisciplinary approach can lead to the best course of treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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