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The intricate connection between depression and dementia as a major challenge for clinicians

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With the aging of the population over the world, clinicians are called to confront more and more with depression and dementia due to Alzheimer's disease/other neurodegenerative types and vascular dementia. Depression and dementia raise widespread concerns due to their negative consequences on physical functions, quality of life and mortality in the elderly, associated to undesirable effects on caregivers and society. Growing evidence from population studies indicates that late-life depression (LLD) often accompanies dementia through its stages of severity, but also it is a major risk factor for development of later dementia, or again it can be configured as prodromal manifestation of dementia. Although the nature of the relationship between the two mental disorders is unclear and results of research are heterogeneous, many scholars point out that currently depression is underdiagnosed and -treated by clinicians and speculate that an appropriate diagnosis, monitoring and treatment (using antidepressants and/or other pharmacological/non-pharmacological regimes) could be of benefit for elderly, regardless of the severity of cognitive decline or even in subjects with adequate cognitive abilities. The authors of this paper, describe and reflect about some problematic characteristics of the relationship between LLD and dementia, taking into consideration epidemiological, pathophysiological and clinical aspects. In their opinion, a conceptual organization of the think around the role plays by depression in dementia could be of some utility to optimize clinical practice.

Key words: aging, depression, dementia, risk factor, antidepressant agents

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INTRODUCTION

Population aging is a global phenomenon that is accompanied by a dramatic rise of persons suffering for two main disabling disorders, as depression (major depression and subsyndromal symptomatic depression) and dementia, especially due to Alzheimer's disease (AD) and that due to vascular causes (VaD) [1-5]. Prevalence of late-life depression (LLD), typically defined as depression or depressive symptoms after age 60 [6], varies among different studies and populations from 8.5 to 14.5% [7-9]. Prevalence of dementia currently ranges from 5 to 8% with an estimated growing trend, worldwide [10]. Each of the two illnesses, by itself, is associated with dangerous consequences due to serious adverse effects on health and well-being of the elderly, as disability and impairment of quality of

life (QOL) [11,12]. Both disorders are strongly implicated to contribute to development of physical illnesses as cardiovascular disease, and are burdened with an excess of mortality due to comorbidity [13-17]. The role of depression as independent risk factor for suicide in the elderly deserves particular interest between scholars due to its elevated prevalence and dramatic force [18,19]. In addition, LLD and dementia have often negative repercussions on psychological and functional abilities of caregivers [20,21]. Finally, they raise a number of problems for society and health policies, such as an excess of health care services utilization [15,22] and considerable costs for family informal care [23].

When LLD and dementia co-exist, a not rare occurrence [1], the entity of respective undesirable effects worsens, due to a set of factors as exacerbation of cognitive and functional impairment, increasing behavioural disturbances related to dementia, early increased mortality, early patient admission in care and assistance institutions, increased health costs in a context of limited resources, increased depression on families and caregivers [15,24-28]. Co-existence of depression and dementia make the differential diagnosis between the first and second a challenging, for clinicians [29]. Not only, but an emerging concern is that while the second seems to be more considered, the first is to be often overlooked in the clinical practice [2,15,30]. Currently, despite depressed elderly patients, regardless the cognitive status, can respond to anti-depressant medication [31], major depression and subsyndromal symptomatic depression continue to be still underdiagnosed and treated, above all in persons living with dementia (PWD), and a not negligible heterogeneity of management persists [2,32,33]. Likely, undertreatment of depression symptoms in older adults with dementia is due to lack of consistent diagnostic criteria to assess depression in the context of cognitive impairment that characterized dementia [32,34]. In this complex scenario, the purpose of authors of this paper is to describe and reflect about the entity and some problematic characteristics of the relationship between LLD and dementia. This, in the assumption that the current heterogeneity of practical approaches, with some degree of carelessness for depression can benefit from a conceptual organization that takes its cue from a series of key questions and possible answers.

PREVALENCE OF DEPRESSION AT THE STATE OF DEMENTIA

Prevalence studies of depression in PWD have provided heterogeneous results largely depending by different diagnostic criteria, methodology and the source of the sample. Depression occurs until 20-30% of PWD, and is even higher in patients with VaD and dementia with Lewy bodies [35]. In a recent meta-analysis, including 55 studies with a total of more than 13,000 older adults with dementia the prevalence of major depression was 15.9% in all causes of dementia, 14.8% in AD and 24.7% in subjects with VaD [36]. Scholars conclude their paper by stating that depression is common among PWD, and the estimated prevalence of depression in dementia varies with the types of dementia and dementia criteria (NINCDS-ADRDA, DSM III, DSM IV). They add that is likely that difference of prevalence of depression between AD and VaD is due to direct relationship between cerebrovascular disease pathology and the risk of developing depression. Rubin et al. (2001) [37] underlined that depression is common among patients with mild and moderate AD dementia type, but is less common in severe dementia. Depression is also often found in individuals with mild cognitive impairment (MCI), with an estimated prevalence of 32% [38]. A large prospective US cohort study presents robust evidence that MCI as well as dementia were both associated with significantly higher rates of depression compared with those with normal cognition [39].

DEMENTIA RISK IN PEOPLE WITH A HISTORY OF DEPRESSION

Growing evidence indicates that depression exposes individuals to subsequent dementia.

Meta-analysis studies and several reviews have suggested that the presence of depression increases to a two or more times the risk of later dementia [40-44]. In a nationwide cohort study carried out by Holmquist et al. (2020) [45] from 1964 to 2016 in Swedish inhabitants aged ≥ 50 years, the odds risk (OR) of dementia subsequent to depression was 10-20 times in the first 6 months after diagnosis of depression (adjusted OR 15.20, 95% CI 11.85-19.50; $p < 0.001$), and was higher for individuals with severe depression compared with those with mild depression, while a stronger association was seen with VaD; furthermore, the risk of dementia after the first year decreased more or less rapidly, but was still evident 20 years after the diagnosis of depression (aOR 1.58, 95% CI 1.27-1.98; $p < 0.001$). In a prospective study of over 5,500 subjects with normal cognition and 2,500 subjects with MCI at 30 US Alzheimer's Disease Centers, Steenland et al. (2012) [46] found that at base line depression was associated in normal individuals as well as in individuals with MCI; a diagnosis of depression within 2 years, but not past depression, was a strong relative risk (RR = 2.35; 95% CI 1.93-3.08) for progression for normal to MCI versus never depressed, and a borderline-significant risk for progression from MCI to

AD. More recently, Wang et al. (2021) [47] in a nationwide population-based cohort study (n = 939,099 individuals aged 66 years who participated in the South Korea-National Screening Program between 2009 and 2013) found that depressive symptoms, recent depressive disorder and subjective cognition decline (SCD) independently increased dementia incidence with adjusted hazard ratio (aHR) of 1.286 (95% CI: 1.255-1.318), 1.697 (95% CI: 1.621-1.776), and 1.748 (95% CI: 689-1.808) respectively. Results of this study well demonstrate that depressive symptoms and depressive disorder are relevant risk factors for dementia. In addition, scholars showed that co-occurrence of depression and SCD have an additive effect on the risk of dementia.

KEY QUESTIONS ON RELATIONSHIP BETWEEN DEPRESSION AND ALZHEIMER'S DISEASE DEMENTIA

The coexistence between AD dementia and depression is an intricate event that raises a number of problems, doubts or questions that directly or indirectly, passing through epidemiology and pathophysiology, involve clinical practice. In particular, some major questions emerge: what is the nature of the relationship between the two clinical entity, in other terms is LLD a risk factor or early sign or prodromal event or also a progression enhancer of dementia? What are major implications on clinical practice of relationship? Do antidepressant treatments in LLD have any effect on improving cognition, also?
The possible answers to these questions are considered in the following sub-paragraphs.

Epidemiology

From an epidemiological perspective, currently is unclear if depression is a risk factor for dementia or a prodromal symptom of cognitive decline or an early manifestation of dementia or also a component that accelerates and worsens the clinical course of dementia [32,40]. Results of quantitative population studies illustrated in "Dementia risk in people with a history of depression" paragraph support the hypothesis of depression as a risk factor or symptom predicting the onset of AD dementia. In addition to these studies the role of depression as possible risk factor for subsequent dementia and cognitive decline found sufficient evidence in a review of case-control and prospected studies carried out by Jorm (2000) [48]. Jorm reviewed the literature in relation to six hypotheses that might explain an association: (1) depression treatments are a risk factor for dementia; (2) dementia and depression share common risk factors; (3) depression is a prodrome of dementia; (4) depression is an early reaction to cognitive decline; (5) depression affects the threshold for manifesting dementia, and (6) depression is a causal factor in dementia. In its paper author affirms that while the first hypothesis is the most probable, further research is needed to examine the others. In a review and meta-analysis, and meta-regression analysis including case-control studies and cohort studies, Ownby et al. (2006) [41] – with the aim to determine the relationship between the interval length between diagnosis of depression and AD, and the risk for developing AD – found that the length of the interval between the diagnoses of depression and AD was positively associated with an increased risk of developing AD in later life. Authors conclude claiming that this finding is in accordance with the hypothesis that depression is a risk factor for AD rather than a prodrome. It is also in accordance with the results of Green et al. (THE MIRAGE study, 2003) [49]. This study, including 1,953 subjects with AD and 2,093 subjects without AD, showed existence of an association between depression symptoms and AD with adjusted odds ratio of 2.13 (95% CI 1.71-2.67) [49]. A noteworthy point is that a divergence of results emerges: if develop of AD symptoms is within a year of the depression symptoms, thus depression represent an early symptom of AD; if instead depression symptoms occur decades before the onset of AD, this fact suggest that depression is a risk factor for later development of AD. Finally, Li G. et al. (2011) [50], in a community-based prospective research of 3,410 participants initially without dementia aged ≥ 65 years, confirmed previous observations of an association between LLD and increased risk of developing dementia, and supplied evidence that LLD may be an early manifestation of dementia rather than increasing risk for dementia.

Pathophysiology

Common pathophysiological process and neurobiological mechanisms contributing to an increased risk of depression and dementia could explain the association between the two [51,52]. This interpretation suggests the existence of a relationship between depression and neurodegenerative changes of AD mediated by brain vascular-ischemic lesions. There is a growing evidence to support existence of a common primary etiological mechanism between depression and neurodegenerative brain lesions [53], including hippocampal atrophy, hypothalamic-pituitary-adrenal axis dysregulation, inflammation and activation of microglia, decrease of nerve growth factors, modifications in the serotoninergic and noradrenergic system, and cerebrovascular changes [54]. For their part, Aznar and Knudsen (2011) [55] explain the co-morbidity suggesting the existence of

common neurodegenerative cascade behind depression and AD. In addition, recently Monereo-Sánchez et al. (2021) [56] provide evidence of a genetic overlap between dementia and depression. Common etiological mechanisms between depression and neurodegenerative pathologies make plausible the hypothesis of an accelerating effect of depressive symptoms in progression of symptoms of AD. Figure 1 illustrates predominant pathways linking depression as a risk factor for the onset of dementia [40].

Main implications on clinical practice

As already mentioned, clinicians have to deal with a series of problems arising from the complex and debated link between the two mental disorders. Below are the main critical aspects.

How to manage the clinical complexity

Research on depression and risk of develop dementia have led to results such as to emphasize the importance of strategy of closely monitoring early-life depression and LLD for subsequent dementia [40]. The key concept being this recommendation is that depression, considered as a main risk factor for dementia, can be captured and successfully treated before dementia develops. The elimination of depression is estimated to produce a 4% reduction in dementia incidence on the population level, exceeding the estimated effects of other disorders as hypertension (2%), diabetes (1.2%), obesity (0.8%), and physical inactivity (2.6%) [54,57]. Currently, the treatment and management of depression in the elderly at risk of- or with cognitive decline goes through two strategies in order to improve depressive symptoms and to prevent cognitive impairment. The first approach is the use of antidepressant drugs (ADDs), the second is an integration of ADDs with other types of pharmacological and non-pharmacological interventions, all in any case with procognitive intent.

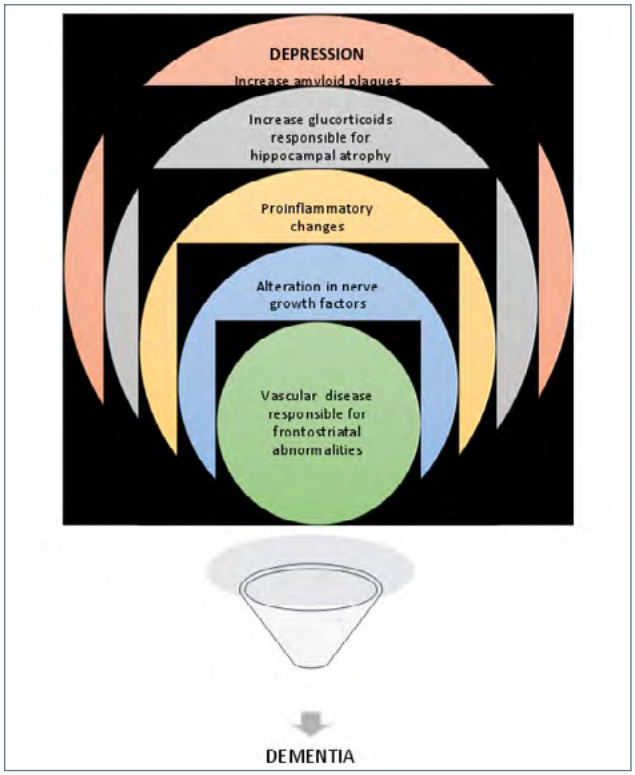

Figure 1. Pathways through which depression can promote the onset of dementia. Each of the pathways, indicated in different colors, can contribute to cognitive decline (from Byers, Yaffe, 2012, mod.) [40].

A problem that precedes the treatment is the diagnostic difficulty of depression in the elderly with neurocognitive symptoms. There is agreement among many experts on two point [32] : (i) that the existence of depression in patients undermines the neuropsychological assessment (Fig. 2, box 1), and (ii) that in early dementia depression symptoms can be masked by a prevalent somatic symptomatology, such as anorexia, weight loss, psychomotor retardation and daily mood fluctuation, while in advanced dementia it is masked by behavioral symptoms, such as agitation and aggression and sleep-wake cycle reversal (Fig. 2, box 2). If this "masking" is an obstacle for clinicians, it must be emphasized that help can come by using of appropriate rating scales, such as Cornell Scale for Depression in Dementia (CSDD) and information provided by the relatives (Fig. 2, box 2).

The procognitive role of antidepressant drugs

ADDs that are more frequently prescribed to treat LLD in subjects with or without cognitive impairment are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), drugs that tend to be better tolerated than others. Due to pro-cognitive and synergistic effects when utilized with cholinesterase inhibitors (ChEIs) a preference is reserved by some scholars to drugs having dual/multimodal effects (venlafaxine/desvenlafaxine, duloxetine, mirtazapine, vortioxetine and tianeptine [32] (Fig. 2, box 3). Potential mechanisms of antidepressant treatment on AD pathology includes molecular effects on neurogenesis, amyloid-ß burden, tau pathology and inflammation [54,58-61] (Fig. 3). These procognitive effects of ADDs would justify treatment of depressed patients also to prevent or mitigate the development of later dementia.

ADDs when correctly prescribed – taking in account some factors, including the type and daily dose of drug, the length of the treatment, side effects and potential interactions with other drugs – may to be of benefit for depressed patients improving depressive symptoms

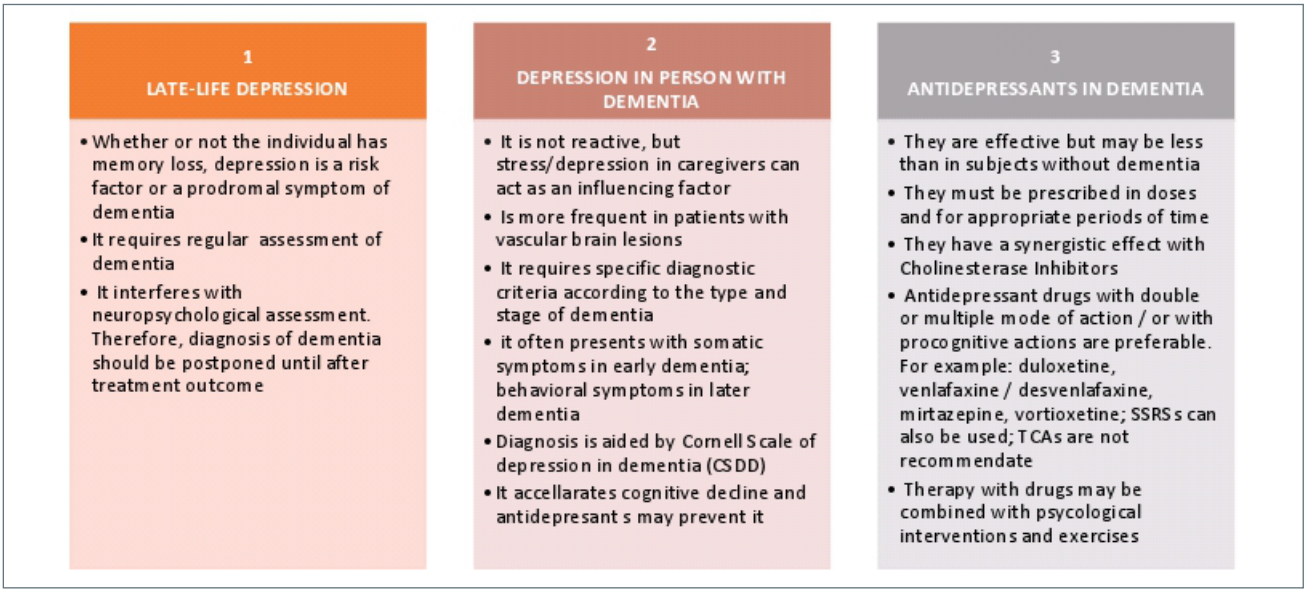

Figure 2. Key messages from expert physicians in neurodegenerative disease (from Agüera-Ortiz et al., 2021 [Delphi consensus], mod.) [32].

in conjunction with QOL and physical functional status – two dimensions notoriously compromised during clinical course of depressive disorder [11]. In addition, depression requires an adequate treatment when co-exists with AD/VaD to improve functional status and QOL already compromised by neurodegenerative and/

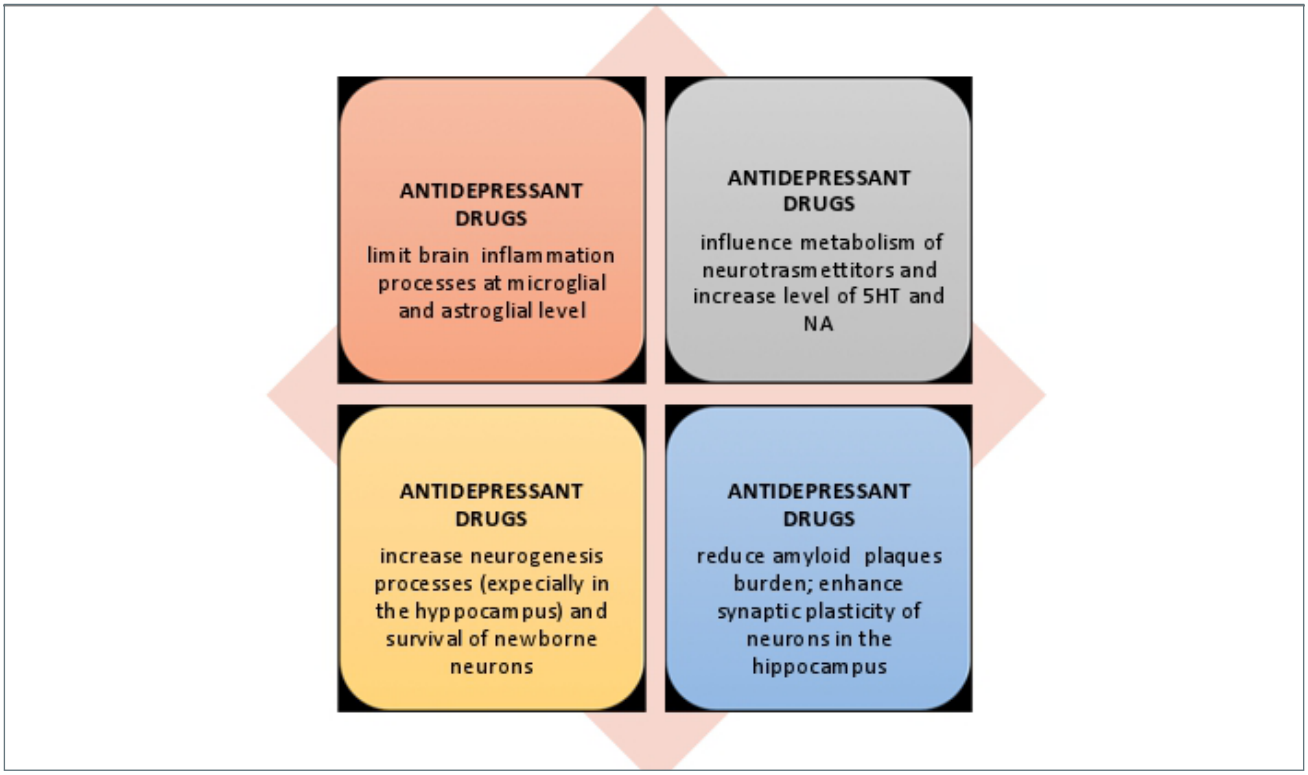

Figure 3. Molecular mechanisms and neuroprotective effects of antidepressant drugs (from Byer, Yaffe, 2012; Dafsari, Jessen, 2020; Banasr, Duman, 2007; Malberg, Schechter, 2005; Sheline et al., 2014, mod.) [40,54,58-60].

or vascular lesions [62]. Finally, ADDs act mitigating the conversion of MCI to dementia and the subsequent progression through the stages of severity of dementia [63-65].

The neuro-pathophysiological substrate linking LLD and dementia as described in subparagraph "Pathophysiology" supports the hypothesis that the benefit of ADDs in cognition is due to their action on pathophysiological processes and molecular circuits related to dementia [53,55,56,66,67].

This hypothetical link does not always seem to be confirmed by population studies. If there is evidence of substantial positive effects of ADDs on cognition (see above) [63-65], conversely there are studies founding that cognitive symptoms persisted after depression treatment [68,69] or this treatment have modest positive effects on some cognitive functions, such as divided attention, executive function, immediate memory, processing speed, recent memory [70].

Clinical practice guidelines and recommedations

Pharmacological therapy for depression in PWD is recommended by guidelines with some variations. For example, NICE-guidelines (2018) [71] suggest of not offer ADDs to manage mild to moderate depression in people living with mild to moderate dementia, unless these drugs are indicated for a pre-existing severe mental health problem. The World Health Organization emphasizes that in PWD with moderate or severe depression, use of SSRIs may be considered. In case of non-response after at least 3 weeks, they should preferably be referred to a mental health specialist for further assessment and management [72].

In summary, the overall picture resulting by scientific literature is heterogenous and inconclusive with respect to this specific aspect. More recently a panel of 37 expert physicians in neurodegenerative diseases formulated key messages for clinicians with indications for antidepressant treatment in patients with depression and with or without associated cognitive impairment [32] (Fig. 2). Byers and Yaffe (2011) [40], already a decade earlier, had point out that it is critically important to determine if treatment of depression alone or combined with other regimes would delay or prevent dementia.

Effects of antidepressants on mortality in persons with cognitive decline

About effects of antidepressants on mortality, Enache et al. (2016) [73] in a population study including more that 20,000 memory clinic patients showed that use of antidepressants during prodromal dementia stages may reduce mortality in dementia and specifically in AD. Su et al. (2019) [74] in a population-based cohort study (25,890 cases between antidepressant users and non-users) found that antidepressant treatment showed significant protective effects in all-cause mortality, by reducing it by 4%. Most classes of antidepressants were effective, especially with longer treatment duration or higher dosage.

Alternative strategies

An alternative strategy to improving the course of cognitive decline in older adults using antidepressants is an approach that combines these drugs with other regimes of pharmacological and non-pharmacological interventions as physical activity and psychological interventions [40], including cognitive behavioural therapy, reminiscence therapy, multi-sensory stimulation, animal-assisted therapy, exercise, stimulation-oriented treatment (recreational or pleasurable activities), or improvements to a living situation [75,76]. A pilot study carried out by Pelton et al. (2008) [77] suggest that addition of a ChEI (donezepil) following antidepressant treatment in elderly with depression and cognitive impairment may improve cognition, but further studies with larger randomized placebo-controlled trial are needed. Finally, scholars shown that the use of antidepressants (such as sertraline, citalopram, venlafaxine) combined with multivitamins, vitamin E, alpha-lipoic acid, omega-3 and coenzyme Q in association to diet and physical exercise not only protracted cognitive decline for 24 months but even improved cognition, especially memory and frontal lobe functions [78].

CONCLUSIONS

Even if the nature of the association between depression and AD dementia is unclear and the link is complex to interpret, there is evidence that antidepressant treatment (pharmacological, behavioral or other regimes) is a rational approach in elderly subjects with a diagnosis of depression and different degrees of severity of cognitive decline, from a normal condition to MCI to dementia state [32,40]. Of particular relevance is that LLD is recognized a major risk factor for subsequent dementia [79] or prodromal symptom of dementia and it is plausible that antidepressant therapy, due to its neuroprotective effects could delay or mitigate the cognitive decline [32,40]. In this way, *a considerable fraction of dementia cases could be prevented.*

However, to date the discussion between scholars is open with studies leading to heterogenous results and conclusions. In other terms, the evidence regarding the efficacy of these agents in PWD or at risk of dementia remains conflicting. The obvious consequence is that a halo of uncertainty revolves around this topic. In clinical practice, there is a hesitation of the clinicians

to recognize symptomatic depression as a target for prevention and treatment of AD dementia [54].
In conclusion, net of the above difficulties, it emerges that undertreatment of depression in dementia currently persists, also if UK scholars shown that prescribing of appropriate antidepressant drugs in PWD appears to be increasing over the years [80]. In any case, the intricate relationship between the two late-life disorders requires further studies.

Conflict of interest statement
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Author contributions
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