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Review Article

A common challenge in older adults: Classification, overlap, and therapy of depression and dementia

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Abstract Late-life depression is frequently associated with cognitive impairment. Depressive symptoms are often associated with or even precede a dementia syndrome. Moreover, depressive disorders increase the risk of persistence for mild cognitive impairment and dementia. Here, we present both the current state of evidence and future perspectives regarding the integration and value of clinical assessments, neuropsychological, neurochemical, and neuroimaging biomarkers for the etiological classification of the dementia versus the depression syndrome and for the prognosis of depression relating to dementia risk. Finally, we summarize the existing evidence for both pharmacotherapy and psychotherapy of depression in demented patients. There is an urgent need for large-scale collaborative research to elucidate the role and interplay of clinical and biological features in elderly individuals with depressive disorders who are at elevated risk for developing dementia. To overcome barriers for successful drug development, we propose the introduction of the precision medicine paradigm to this research field.

Keywords: Depression; Dementia; Differential diagnosis; Classification; Prognosis; Biomarkers; Neuroimaging; Pharmacotherapy; Psychological intervention; Precision medicine

1. Introduction

Dementia and depression are the most common psychiatric syndromes in older age. Although early identification of underlying causes and subsequent treatment are essential, the accurate differential diagnosis and discrimination (classification) remain clinically extremely challenging [1]. Late-life depression is frequently associated with cognitive impairment. In turn, dementia has been related to an increased risk of depressive symptoms. Moreover, due to their abundance, both syndromes often occur together in older age. As an association appears to exist, this common occurrence might be more frequent than by chance. Therefore, the diagnosis of one condition does not rule out the other one.

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Dementia, a major psychopathological syndrome, is traditionally diagnosed according to very slowly evolving operationalized criteria manuals, including the *International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)* [2] and the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V)* that have only been updated after decade long intervals [3]. Contrary to expectations, the recently published *DSM-V* did not yet integrate any biological information (biological markers) into the diagnostic armamentarium. The conservative primarily symptom-based, descriptive approach has been maintained for the neurocognitive disorders categories as well [4]. However, advanced expert consensus criteria have attempted classification approaches grounded on clinical, biological, and etiological factors.

The most common underlying causes of dementia in the elderly include Alzheimer's disease (AD) [5], vascular dementia [6], mixed dementia, dementia with Lewy bodies [7], dementia in Parkinson's disease [8], and frontotemporal dementia [9] Notably, depressive symptoms have been reported in 30%–50% of patients with AD dementia and are especially common at the prodromal stage [10]. Overt major depression can be diagnosed in >10% of AD patients, mostly during the early to moderately impaired stage [11] and in up to 50% of patients with vascular dementia [12–14]. Moreover, approximately 50% of patients with dementia with Lewy bodies show depressive symptoms [15].

Late-life depression is also generally diagnosed according to the *ICD-10* [2] or *DSM-V* criteria [3]. In addition to standard clinical assessment, psychometric indexes, such as the Geriatric Depression Scale [16], are frequently administered in the elderly. Late-life depression is common in patients with chronic physical illnesses. Age-related and disease-related changes, including arteriosclerosis, chronic inflammation, hormonal, and immune modifications, may affect the integrity of frontostriatal circuits as well as the amygdala and the hippocampus, ultimately increasing the vulnerability to depression [17]. In addition, age-related psychosocial stressors including poor socioeconomic status, disability, and social isolation are significant risk factors for depression [18]. Vegetative symptoms and impairments of executive functions, attention, information processing, psychomotor speed, and working memory are common. In particular, subcortical vascular changes play a major role in the pathophysiology of late-life depression [1] leading to the conceptualization of vascular depression, as defined by the results of magnetic resonance imaging (MRI) [19–22]. The risk of suicide is approximately 2-fold higher in the elderly, especially in older males, compared with the general population [23]. Overall, late-life depression has distinctive features that allow its differentiation from depressive disorders occurring at a younger age [24].

2. Increased dementia risk in depression

To date, most of the published studies have focused on late-life depression—that is depression in subjects aged 60 years and older—and the risk of dementia, as well as the link between depression and dementia; in contrast, relatively few studies have been conducted in patients with earlier-life depression, that is, in subjects younger than 60 years. Because (1) depression onset shows a high degree of variability, (2) both young adulthood and middle age are characterized by a high incidence of depression, and (3) dementia is characterized by a long asymptomatic preclinical phase, the examination of earlier-life depression might represent an opportunity to examine whether depression is a risk factor for dementia many years before the advent of clinical signs. It should be acknowledged, in any case, that the association between late-life depression and dementia might allow for a more in-depth analysis of depression as part of the prodromal stage of dementia. Therefore, a careful analysis of both earlier-life and late-life depression is necessary to attain complementary evidence [25].

The risk of developing dementia later in life increases 2-fold in presence of a positive history of depression at younger age. In presence of recurrent depressive disorders, a monotonic rise in the risk of dementia can be observed with an estimated 14% increase with each episode [26]. Although the available findings remain partly inconsistent, it can be assumed that late-life depression leads to a substantially increased risk of dementia. In this setting, depression can be a risk factor, a prodrome, or a consequence of dementia [25]. A recent study suggested that chronic depression during life may be etiologically associated with an increased risk for developing dementia, particularly vascular dementia, whereas depression occurring for the first time in late life may reflect a prodromal stage of dementia, in particular AD [27].

Currently, various mechanisms have been proposed to explicate the association between depression and dementia. First, there is significant evidence indicating that vascular disease is the primary link between depression and dementia, which is substantiated by the "vascular depression hypothesis" [28,29]. This pathophysiological theory states that cerebrovascular disease is a risk factor, a trigger, or a perpetuating factor for depressive syndromes in the elderly [18,30]. In particular, vascular changes in the frontostriatal brain regions have been linked to both depressive symptoms and cognitive impairment [31–33].

In addition, increased cortisone levels, a biochemical alteration frequently observed in depressive disorders [34], can lead to worsening hippocampal atrophy associated with cognitive deficits [31,35]. Notably, atrophy of the hippocampus is a well-characterized brain alteration detected both in AD [36] and in patients with depression [37,38].

In the conceptual framework of protein-misfolding disorders, the presence of accumulating brain amyloid beta (Aβ) plaques represents a key pathologic hallmark of AD. It is well-known that both Aβ peptides and hyperphosphorylated tau proteins accumulate significantly in AD brains, leading to the formation of neuritic plaques and neurofibrillary tangles, respectively [39,40]. Interestingly, evidence indicates that depression might lead to an increased disequilibrium in terms of Aβ production and/or clearance. This effect is mediated by the depression-related stress response and the resulting hypercortisolemia, as well as the direct impact on Aβ processing, probably due to alterations at the level of the serotonergic system [41–44]. Notably, depressed AD patients have a higher burden of Aβ plaques and neurofibrillary tangles in the hippocampus than AD patients without depression [45–48].

During the last decade, chronic inflammatory processes have been also implicated in both depression and dementia [49–51]. On the one hand, a subtle and chronic brain inflammatory state, inducing cellular dysbalance, the activation of microglia and reactive astrocytes, resulting into increased concentrations of brain cytokines detected in depression and dementia, may result in a reduced modulation of anti-inflammatory and immunosuppressive mechanisms, increased acute-phase, and proinflammatory regionally spreading alterations in the central nervous system, and, ultimately, in a non-linear progressive fashion inducing neural network dysbalance, decompensation and breakdown, cognitive deficits, and subsequent dementia [52]. Moreover, proinflammatory cytokines overexpression is supposed to interfere with the serotonin metabolism, thereby decreasing both synaptic plasticity and hippocampal neurogenesis [42,49].

Another mechanism that may link depression with dementia is represented by decreased levels of circulating neurotrophic factors, mainly the brain-derived neurotrophic factor (BDNF). BDNF modulates neuronal structure and function and plays an important role in synapse development and plasticity [53]. Reduced plasma BDNF levels have been observed both in animal models of depression [54] as well as in patients with depression [55,56] and AD [57,58].

Recent data have revealed that depressed patients face an accelerated cellular aging. In particular, those with the most severe and chronic major depressive disorder displayed the shortest telomere length, and participants with remitted major depressive disorders had shorter telomere length than controls [59].

A more comprehensive systems-based neurobiological approach—larger genetic and epigenetic studies, analyses of gene and biomarker expression pattern, as well as innovative multimodal structural, functional, and metabolic neuroimaging—is needed to shed more light on the pathophysiology of late-life depression. To this aim, much can be learned both conceptually and methodologically from recent discoveries in the field of AD [60–62].

3. Common occurrence of depression and mild cognitive impairment as a risk condition

A recent large cohort study conducted in Northern Manhattan (New York, NY), including more than 2000 individuals aged 65 years or older, has shown that late-life depression is associated with both an increased risk of prevalent mild cognitive impairment (MCI), an established risk factor for the progression and occurrence of dementia, as well as overt dementia itself. Depression was also associated with an increased risk of incident dementia but not incident MCI. Notably, individuals presenting a concomitant depressive disorder and MCI showed a significantly increased risk of developing dementia, in particular vascular dementia, compared to those with MCI without depression [63].

A concomitant diagnosis of MCI has been reported in 25% to 50% of patients with late-life depression [64–66], compared to a 3% to 6% prevalence of MCI in community-based samples [11,67]. In addition, cognitive impairments emerging during a depressive episode can persist even after the remission of depressive symptoms [64,68]. The extent of cognitive impairment identified in elderly depressed patients before treatment seems to predict cognitive outcome after therapy [65,69–71].

Another recent study has demonstrated that cognitive impairment in late life depression might be related to greater cerebrovascular disease along with abnormalities in the immune–inflammatory control, cell survival, intracellular signaling, protein and lipid homeostasis, and clotting processes. As a result, individuals with late life depression and cognitive impairment seem to be more susceptible to accelerated brain aging processes at the cellular and molecular levels [72].

4. Classification—differential diagnosis—of dementia and depression

The concomitant occurrence of a depressive disorder and cognitive impairment should always be carefully investigated from a diagnostic viewpoint. Olin et al. [73,74] have proposed criteria to discriminate major depression and depression in AD. Accordingly, depression due to AD can be diagnosed when all criteria of dementia of Alzheimer type are fulfilled, and three (or more) typical depressive symptoms have been detected during the same 2-week period and represent a perturbation from previous physiological activity. At least one of the symptoms consists of either depressed mood or decreased positive affect or pleasure. Symptoms that are clearly due to a medical condition other than AD or are the direct result of nonmood-related dementia symptoms (e.g., loss of weight due to difficulties with food intake) should not be included. Clinical signs are often less severe and pervasive than in major depression. They often do not persist over a time period of 6 months [75]. Age of onset, rate and course of

cognitive change, subjective memory complaints, and typical sleep-wake cycle disturbances can aid in differential diagnosis.

4.1. The emerging role of specific memory testing for the differential diagnosis

AD is currently designated as a clinical entity typically characterized by a progressive amnestic syndrome with appearance of other cognitive, behavioral, and neuropsychiatric changes [76]. The episodic memory disorder, in the typical form of AD, shows a specific pattern which is the expression of hippocampal dysfunction and can be identified by tests including word list learning. This amnestic syndrome of the hippocampal type [77] is defined by (1) low free recall as for any brain-related memory disorder and (2) a low total recall performance, despite retrieval facilitation with cueing, due to hippocampal damage which affects the ability to store new information. Therefore, information cannot be retrieved even after facilitation procedures. Such a pattern demonstrates excellent specificity for AD [78].

In case of a pure depressive disorder, there is no genuine storage deficit; rather, attention difficulties that impair encoding or retrieval strategies can be observed [79]. Therefore, the differential diagnosis between AD and a pure depressive disorder can be improved by using a test paradigm that provides encoding specificity (with semantic cues) [80] and a retrieval facilitation (with the same cues), such as the free and cued selective reminding test [81]. Regarding the memory domain, an improvement with repeated exposure and a normal recall with both control of encoding and retrieval cues are typically found in major depression, whereas a flat learning curve despite repeated exposure, a rapid forgetting, the inefficacy of cueing for recall, and intrusions are typical for AD.

4.2. The role of biomarkers for the differential diagnosis

Although there are no specifically established fluid biomarkers for depression, three relevant biomarkers have been detected in the cerebrospinal fluid (CSF) for the key neuropathologic alterations in AD. Actually, owing to its contiguity to the brain parenchyma and the free exchange with the brain extracellular space, the biochemical composition of CSF is able to provide information on the brain chemistry. The "core", feasible biomarkers are (1) total tau (T-tau, a marker reflecting cortical axonal degeneration), (2) phospho-tau (P-tau, a marker reflecting tau phosphorylation and AD-type neurofibrillary tangle pathology), both tau-related markers are the best indicators for disease progression, and (3) the 42 amino acid long form of Aβ ($A\beta_{1-42}$, a marker of senile plaque pathology) [82]. This biomarker "triad" can be used to examine if patients with dementia-like depressive symptoms have AD pathologic changes. Depression *per se* does not result in an AD-like CSF biomarker pattern, that is, increased T-tau and P-tau concentrations, and reduced levels of $A\beta_{1-42}$ [83] although marginally decreased CSF $A\beta_{1-42}$ concentrations have been reported [84]. A positive AD biomarker pattern is around 90% specific for AD neuropathology but does not exclude comorbidity in AD and depression. As demonstrated by Ewers et al. [85] in a large-scale multi-centric study, CSF $A\beta_{1-42}$ best discriminates AD dementia from frontotemporal dementia, non-neurodegenerative neurological diseases and depression but shows significant overlap with other non-AD forms of dementia, possibly reflecting the underlying mixed pathologies. The combination of the three gold-standard markers provides added diagnostic value; in particular, at a fixed sensitivity of 85%, the specificity was >85% [85].

Notably, several other molecular changes have been examined in CSF in relation to depression and dementia disorders; nevertheless, none of them has yet shown potential clinical utility for differential diagnosis and classification. However, depression is characterized by slightly increased CSF concentrations of several pro-inflammatory cytokines, which are most often disregarded in dementia-causing diseases [86]. Pro-inflammatory cytokines enhance the activity of the indoleamine 2,3-dioxygenase enzyme that is the first rate-limiting enzyme of the tryptophan degradation pathway, the kynurenine pathway. Increased tryptophan degradation may induce serotonin depletion and depression, which is reflected by low CSF concentrations of kynurenic acid [87]. This alteration is not found in AD or dementia with Lewy bodies [88], which suggests that CSF kynurenic acid may be a promising biomarker to explore further for differential diagnosis.

At present, there are no established blood (plasma/serum)-based biomarkers for AD or other dementia-causing diseases. However, mounting evidence suggests that depression is associated with a proinflammatory cytokine response in serum. Studies have shown elevated serum concentrations of interleukins (ILs) such as IL-1 and IL-6, the tumor necrosis factors alpha, the C-reactive protein, and the monocyte chemoattractant protein-1 in depressed patients with mixed results for IL-8 [89]. There is no study so far assessing the potential diagnostic and prognostic utility of this molecular pattern. It is important to note that altered immune function is by no means specific to depression; any inflammatory biomarker evaluated as a potential tool to differentiate depression from dementia disorders has to be carefully examined in relation to diabetes, obesity, and a range of other disorders.

4.3. The role of imaging for the differential diagnosis

To some extent, CSF biomarkers listed in the previous section can also be quantified using positron emission

tomography (PET) of the brain. The use of tracers for tau is still restricted to research studies, but amyloid PET is now an established diagnostic tool in many specialized memory clinics. Cross-sectional studies report increased amyloid depositions in cognitively normal depressed older individuals [90]. It seems most likely that these are individuals with very early stage AD which manifests with depression as first symptom. Longitudinal studies or studies focusing on individuals with early onset depression could provide further insights. A recent study did not find any significant difference in terms of brain β-amyloid deposition (and gray matter volume) between elderly patients with remitted major depression and persistent MCI compared with elderly patients with remitted major depression and normal cognitive function [72].

Although patients with major depression may also show an altered regional brain glucose metabolism as measured using [^{18}F] Fluorodeoxyglucose–PET [91], this is far less consistent and pronounced and affects different regions than hypometabolism observed in overt clinical dementia or MCI.

Besides PET, quantifying hippocampus atrophy and brain white-matter lesion load are relevant to distinguish late-life depression from mild dementia. Although both can be assessed using computed tomography, MRI is substantially more sensitive. Recurrent depressive episodes lead to hippocampus atrophy, whereas a high number of white matter lesions is a common risk factor for late-onset depression and dementia, particularly of vascular origin [28,29].

Studies comparing the extent of hippocampus atrophy in late-onset depression and AD typically report substantially more pronounced atrophy in AD [92]. This result is not surprising given the extent of neurodegeneration observed in manifest dementia. A current large meta-analyses indicate areas such as cingulate cortex and precuneus may serve best to separate AD from late-life depression [93]. The degree of hippocampal atrophy may be similar between subjects with MCI and those with a high number of depressive episodes; however, such studies are missing.

On the other hand, the first appearance of depression in late life is often associated with increased white-matter hyperintensities and clinically with lack of initiative and cognitive slowing. Consequently, global brain atrophy and white-matter hyperintensities contribute to a diagnostic separation between late-life depression and healthy aging [94]. However, separating patients with late-onset depression from those in the initial stages of vascular dementia can be difficult, particularly since both can manifest in the same individual, with accelerated cognitive decline and poorer response to antidepressants.

5. Pharmacotherapy of depression in dementia

The design and evaluation of pharmacological interventions of depression in dementia is challenging for several methodical reasons. The large range of published prevalence rates from under 5% to nearly 50% for major depression in AD [95,96] foreshadows the problems of the correct detection and diagnosis of depression in dementia. It is a well-known fact that cognitive decline and dementia can progressively limit language skills and self-awareness of depressive symptoms. The difficult differential diagnosis of apathy and depression contributes to the complexity.

Clinical trials assessing the effects of pharmacotherapy of depression in dementia rest on rating scales. The Montgomery–Asberg Depression Rating Scale (MADRS) [97] is not validated for demented patients [98,99]. The Hamilton Depression Rating Scale (HAM-D) [100] is another widely used scale that has not been validated in patients with severe dementia [101]. However, the Cornell Scale for Depression in Dementia (CSDD) [102] and the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (ADCS-CGIC) [103] are validated in demented patients [103,104].

As reviewed recently by Leong [105], several randomized placebo-controlled interventions reported negative outcomes for antidepressant efficacy in dementia: with sertraline (95 mg daily) and mirtazapine (30 mg daily) for 13 weeks, assessed by CSDD in 326 patients [106]; sertraline (93 mg daily) for 24 weeks, assessed by CSDD and a modified ADCS-CGIC in 117 patients [107]; venlafaxine (75 mg daily) for 6 weeks, assessed by MADRS in 31 patients [108]; fluoxetine (maximum 40 mg daily) for 6 weeks, assessed by HAM-D in 41 patients [109]; sertraline (maximum 100 mg daily) for 8 weeks, assessed by CSDD in 31 patients [110]; and imipramine (83 mg daily) for 8 weeks, assessed by HAM-D in 61 patients [111]. In contrast, positive outcomes were reported for the following randomized placebo controlled trials with sertraline (95 mg daily) for 12 weeks, assessed by CSDD and HAM-D in 44 patients [112]; moclobemide (maximum 400 mg daily) for 6 weeks, assessed by HAM-D in 511 demented patients [113]; clomipramine (maximum 100 mg daily) for 6 weeks, assessed by HAM-D in 21 patients [114]; and citalopram (maximum 30 mg daily) for 4 weeks in 98 patients [115].

In summary, well-controlled studies, systematic reviews, and meta-analyses [105,106,116,117] have shown no reliable and convincing efficacy of antidepressants in patients with dementia and co-occurring depressive disorders. Even the addition of a cholinesterase inhibitor in depressed patients showed only a small effect on concurrent cognitive impairment and on the conversion rate to dementia syndrome but with increased risk of recurrence of depression [118].

Given the fact that pharmacological interventions based on serotonergic and noradrenergic abnormalities have shown disappointing results, the discussion of novel strategies becomes pertinent. The role of glutamatergic signaling, especially the dysfunction of N-methyl-D-aspartate

(NMDA) receptor complex signaling, might be a promising overlap in the pathology of AD and major depression in late life. NMDA receptor antagonists have been demonstrated to feature antidementia as well as antidepressant potential (for review see [119]). These joint NMDA receptor-regulated signaling pathways in depression and dementia might represent a point of action in—so far treatment-resistant—depression in dementia.

The sobering results of pharmacological trials also highlight the need to consider alternative non-pharmacological treatments; for instance, psychological and behavioral interventions as well as supportive clinical management.

6. Psychological intervention for depression in dementia

Systematic reviews provide a substantial evidence base for psychotherapy as an effective treatment in older depressive patients, with mainly modest effect sizes which compare quite well to those of antidepressant pharmacotherapy in this patient group [120–124]. Moreover, the level of efficacy of psychotherapy in geriatric depression appears to be similar to that in younger patients (e.g., [120,125–127]). Evidence-based recommendations have been made especially for the cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and problem solving therapy (PST), whereas the literature provides no profound evidence that psychodynamic therapies were less efficient compared to other types of psychotherapy in the treatment of geriatric depression (c.f. [122,128–130]). On the whole, psychotherapy in late-life could evidently use all approaches established in younger patients, which, however, always needs to be reviewed before application for necessary modifications to accommodate age-related mental changes and relevant contextual characteristics in the life of elderly people [131].

A necessity for technical or procedural adaptations is particularly appropriate in older depressed patients with dementia, who are easily overstrained by standard psychotherapeutic procedures. The progressive course of disease inevitably requires permanent adaptation of therapeutic actions to accommodate the advancing loss of mental resources. Concrete modifications of psychotherapeutic procedures for elderly patients have been described in the literature (e.g., [132–134]) and essentially comprise an increase of structure and redundancy, that is, rehearsal of important issues or messages, combined with a slowing of the conversational flow (to accommodate slowed cognitive processing) and a flexible organization of session lengths, which together should preserve the patients' involvement and comprehension in the therapeutic process. Moreover, and partially evident from the former issues, psychotherapy in the elderly needs an especially active and supportive (i.e., not neutral) therapeutic stance combined with a limited changing intent, that is, to adaptively shift the emphasis of therapeutic interventions from changing (cognition or behavior) to insight and/or acceptance, at least in some domains (cf. [135]). More specific modifications concern the therapeutic content and include a stronger interdisciplinary focus, that is, an intensified collaboration between the psychotherapist on the one hand and physicians, social workers, and ambulatory services on the other, as well as a strengthened therapeutic focus and goal orientation such as an emphasized selection, prioritization, and pursuit of therapeutic goals (cf. [134–136]).

The necessity for major adaptations to therapeutic procedures contradicts, at least in part, the assumption that psychotherapy in late life has similar outcomes, that is, produces an equal amount of "positive change" as in younger patients. This claim arguably does not apply to the "older old" and dementia patients (cf. [127,137]). Moreover, the adaptability of specific psychotherapies could be outpaced by a level of mental decline. Accordingly, different psychotherapies can be construed to have different indication areas depending on their individual adaptive flexibility. Concretely, modified psychodynamic therapy has been described to be restricted to early stages of dementia or to MCI, whereas modified behavioral therapy may be still practicable and effective even in severely demented patients [138,139].

Despite the evident limitations and barriers, there is a constantly growing evidence-base for psychotherapy in dementia patients, data which evidently provide a valuable alternative or complementary treatment option to the pharmacotherapy of neuropsychiatric and particularly depressive symptoms. More specifically, a series of studies show that the adapted application of standard psychotherapies like CBT, PST, and IPT (compared to usual community or residential care) has a moderate effect on the level of depression in dementia and, hence, the potential to significantly improve the patients' psychological well-being ([140,141]; for review, see [137,142]).

Of note, these results compare quite favorably with the limited effects of psychopharmacological interventions on depression in dementia patients, who in addition are more susceptible to adverse side-effects and interaction effects than younger patients (cf. [143]). As a restriction, however, participants of such studies mostly have mild dementia so that it remains unclear as to whether similar positive effects of nonpharmacological interventions can be achieved in more severe forms, too. Moreover, efficacy measures of psychotherapeutic interventions to reduce depression in older patients appear to largely depend on the type of control condition, with the prevalent waitlists or attention control conditions yielding stronger effects as with control groups receiving, for example, supportive therapy (cf. [124]). This suggests that nonspecific effects of psychotherapy which emanate, for example, from the experience of attention and reassurance in the therapeutic alliance are

especially important (i.e., potent) in the treatment of depressive elderly patients, particularly when they are cognitively impaired. Hence, to adequately estimate the efficacy of more specific psychotherapeutic strategies in this patient group requires to accurately control for the nonspecific elements of psychotherapy which appear to be best represented in supportive therapy as baseline control condition (cf. [124]). Problem adaptation therapy (PATH) [144] is a relative novel psychotherapeutic intervention specifically designed for the treatment of depression in dementia. This therapy, which can be applied from mild cognitive deficits to moderate dementia, specifically aims to strengthen the patient's emotional regulation, and for this purpose, integrates a problem solving approach with environmental adaptation, compensatory strategies, and caregiver participation. In a recent efficacy evaluation study [145], PATH has been compared to supportive therapy for cognitively impaired patients and, thereby, has been shown to be superior in the reduction of depressive symptoms. The authors conclude that PATH may provide a valuable relief to a large group of dementia patients.

Other psychological interventions which have been evaluated in dementia patients are not specifically or uniquely aimed at the reduction of depressive symptoms but follow more general or nonspecific goals like, for example, to increase social interaction, to stimulate memory, and/or to stabilize the sense of identity. These therapies have been developed specifically for the treatment of dementia patients, so-called "dementia-specific therapies" and, therefore, can be generally applied without adaptation, even in advanced disease stages. Although dementia-specific therapies are not specifically aimed at the reduction of depressive symptoms, they still may improve the patients' mood and reduce the emotional stress related to dementia. Reminiscence therapy and validation therapy, for instance, are "emotion-oriented" psychological interventions, which can be applied to treatment for MCI and all stages of dementia. Reminiscence therapy [146] consists of different techniques to stimulate memories of personal history and thereby to reactivate life experiences, particularly positive ones and their related mood states. Techniques to make these memories more meaningful are, for example, asking deepening questions, which suggest the importance of the life event or the allocation of historical materials like vintage photographs, documents, or auditory records. Validation therapy (e.g., [147]) was originated and further developed by gerontologist Naomi Feil. This therapy focuses on the comprehension of emotional messages, which are assumed to lie behind the partly confused speech and behavior of the dementia patient. According to the therapy rationale, dementia patients actively retreat to an inner reality, which is based on feelings rather than intellect, because they cannot tolerate their present reality. Based on this assumption, validation therapists prioritize the emotional content over the person's orientation to the present, so to speak, and accordingly validate (i.e., mirror and confirm) the communicative efforts of the patients rather to correct them in their confused expressions. This procedure is expected to reduce negative affect and consequent behavioral disturbances.

Unfortunately, dementia-specific therapies still have a rather weak or inconclusive evidence base (e.g., [148–150]), whereas, however, a lack of evidence can and should not be interpreted as proof of inefficacy. Validation therapy and reminiscence therapy, among other dementia-specific psychotherapies, are clinically relevant and an inherent part of the dementia care practice (e.g., [148]).

7. Conclusions and future directions

Both depression and cognitive decline impose a significant burden on public health. It has been shown that depressive syndromes have distinct features in the elderly. Close monitoring of cognitive disorders in elderly people showing depressive symptoms is of paramount importance, and the presence of dementia should be excluded through extensive neuropsychological investigations. At present, although core, feasible AD neuroimaging modalities, and neurochemical CSF biomarkers show evolving evidence, they have not yet been generalized world-wide and implemented in guidelines for clinical practice and are not routinely used in patients with late-life depression for differential diagnosis/classification and progression/prognosis.

Whereas psychological interventions have shown promising beneficial results, the clinical utility of approved antidepressant pharmacotherapies in patients with dementia and depression remains questionable. Actually, the understanding of the biological mechanisms underlying both dementia and depressive disorders as well as their genetically biologically determined endophenotypes deserve further scrutiny and may pave the way for the development of novel diagnostic strategies and primary therapeutic targets for both dementia and depression. In this scenario, future studies should investigate clinical and biological features that may predict the development of persistent cognitive impairment in both earlier-life and late-life depression.

Preventive strategies against cognitive decline should take into account the patients' affective vulnerability. Moreover, much research effort should be devoted to the understanding of the neurobiology of depression with concomitant cognitive decline, with special reference to the involvement of networks and neurotransmitter systems that may differ from those affected in depression without cognitive decline.

It appears that there is an urgent need for large-scale collaborative research to shed more light on the role of

clinical, neuroimaging, neuropsychological, genetic, neurochemical, and environmental characteristics of patients with late-life depression. In addition, studies on their significance for the prediction of cognitive decline and dementia development need to be performed.

In general, depressive syndromes present a highly heterogeneous spectrum of clinical phenotypes and are characterized by a still largely unclarified, intricate genetics and biology reflecting a partly overlapping variety of underlying etiologies. In addition, pathological findings in different brain areas show a high degree of interindividual variability. In order to take these factors into adequate account, further research is needed into the phenomenology and neurobiology of depression in different ages of life, in patients with neurodegenerative and vascular diseases as well as in those showing pathologically mixed forms. To achieve this goal, a large amount of demographic, psychopathological, genetic, biomarker, and imaging data should be gathered in a standardized fashion. All these variables need to be analyzed both cross-sectionally and longitudinally. These results would be invaluable for refining research hypotheses and designing further studies aimed at developing novel interventional strategies in preclinical models and, subsequently, in clinical cohorts.

However, despite decade-long research in the fields of neurobiology and neuropsychology of depression and dementia translated clinical progress seems still very limited. A more progressive conceptual paradigm shift inspired by other more advanced fields in health care—such as oncology—should transfertilize research in neuroscience providing better solutions also for these complex neuropsychiatric disorders. As a consequence of the prevailing conceptual traditionalism and stagnation in Neuropsychiatry, both dementia and depression are still considered, since approximately a century, as clinically descriptive categorical entities and continue to be classified according to descriptive operationalized criteria catalogs. The assumption that a few drug classes will fit all genetic and biological heterogeneous clinically defined target populations (syndromes and "disease" entities) is treacherous and unlikely to lead to success.

The precision medicine paradigm [151,152] adopted from oncology (e.g., in patients with adenocarcinomas and lung cancer) may offer a way out. To this aim, we need to accept the notion that patients can indeed be stratified by complex genetic, epigenetic, and genomic patterns, by subsequent molecular and cellular pathways that can be tracked and that serve as targets for intervention. These biological conditions emerge (often) long before first clinical symptoms arise, which suggests the exploration of "silent" preclinical stages before symptoms and syndromes emerge as late stage signs of underlying disease. Biological markers reflecting specific biochemistry and mechanisms of action as well as pathophysiology need to systematically be discovered and validated. In this regard, the systems biology paradigm [61,153]—representing an integrated investigation of interacting biomolecules within cells and organisms and allowing comprehensive exploratory biomarker studies—offers the adequate toolset for supporting precision medicine.

Actually, the evolving hypothesis-free exploratory paradigm of systems biology also referred to as integrative biology or network biology [154,155] is an integrative interdisciplinary strategy exploiting advances in multimodal high-throughput technological platforms enabling the investigation of networks of biological pathways where elevated amounts of structurally/functionally different molecules are simultaneously explored over time at a system level (i.e., at the level of cells, tissues, organs, apparatuses, or even whole organism). This approach requires the comprehensive enumeration and quantification of biological processes, followed by efficient data analysis and integration, to allow the generation of hypotheses that need to be validated at a system level [153].

Technologies used in systems biology are the high-throughput screening methods typical of the omic sciences, namely genomics/epigenomics, transcriptomics, proteomics/peptidomics, and metabolomics/lipidomics. Omics-based data provide a comprehensive picture on complex systems at molecular level, which can be used to systematically elucidate molecular mechanisms of living organisms. Thus, omics sciences can inform a more definite prediction of the risk of developing the disease, its progression, the severity of symptoms, personalized to a specific individual [61,62]. This information is necessary to tailor precisely both prevention strategies and therapeutic approaches to that subject as well as to provide suitable decisions regarding lifestyle and preventative treatments.

To develop targeted therapeutic strategies in the field of depression, depression in dementia, and dementia in depression, it is mandatory to integrate cutting-edge multimodal biomarker technologies and transfertilization from more matured translational research fields, such as the previously mentioned area of oncology. These progresses will lead to a radical paradigm shift: from the traditional reductionistic "one-drug-fits-all" approach to the concept of precision medicine enabling the identification of patients who would likely benefit the most from a treatment and suffer the least side-effects [156]. For instance, the genetic makeup most likely associated with the molecular mechanisms of action of a drug can be revealed, thus increasing the probability of a patient's response to the therapy. This helps to identify better matches for existing and novel drugs, with the aim of ensuring that the "right drug" is delivered to the "right patient" at the "right time", with the highest possible success at lowest risk [157].

A precision medicine and, consequently, more comprehensive systems-based neurobiological approach—requiring larger genetic/genomic (e.g., whole genome and exome sequencing) and epigenomic studies, analyses of gene and biomarker expression patterns, as well as with innovative multimodal structural, functional, and metabolic neuroimaging—is therefore needed to gain more insights into late-life depression. To this aim, much can be learned both conceptually and methodologically from recent discoveries in the field of AD [61,62].

Many precision medicine projects are in motion around the globe and are gaining real momentum. The objectives are varied but they all share one central theme—to be able to predict and diagnose diseases more precisely, matching the right therapeutic more efficiently and more cost effectively. The real challenge we face is in the implementation, given the fragmented nature of health care systems globally, how are we able to adjust to this paradigm shift to ensure collective benefit for all participants.

In summary, the aim of precision medicine is specifically targeting the molecular and clinical heterogeneity by identifying an individual's comprehensive and specific pattern of risk factors, by defining the precise underlying molecular pathophysiological processes, and, finally, by aiming to administer a preventive or therapeutic intervention specifically "customized", that is, adapted, to the identified molecular pattern of risk and disease processes.

Finally, in the context of the precision medicine paradigm, the putative application of a multimodal model that may integrate into the pathophysiology of depression both imaging and biomarker data, which are well established for dementia, can ultimately reduce the burden of late-life depression on health care systems. Similarly, the burden would be decreased on the patients and their families, as a result of most appropriate prevention and clinical management. The availability of risk information assessed and specified for individuals with depression would facilitate clinicians' informed decision-making on cognitive outcomes, basically targeting a modifiable risk factor (i.e., depressed mood) for dementia.

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RESEARCH IN CONTEXT

1. Systematic review: References for this review were identified through PubMed searches using the terms "Depression", "dementia", "differential diagnosis", "classification", "prognosis", "biomarkers", "neuroimaging", "pharmacotherapy", "psychological intervention", and "precision medicine". Articles resulting from these searches and relevant references cited in those articles were reviewed.
2. Interpretation: The current article represents a comprehensive overview and perspective on the state-of-the-art concerning the integration and value of clinical assessments as well as of neuropsychological, neurochemical, and neuroimaging biomarkers for the classification of dementia versus late-life depression. Moreover, we assessed the prognosis of depression in relation to the risk of dementia. Finally, the evidence for pharmacotherapy and psychotherapy of depression in demented patients was summarized. To overcome current clinical challenges and obstacles in this field, we conclude that a research paradigm-shift toward precision medicine is needed; this paradigm represents a successful approach spearheaded by other more matured biomedical fields, such as oncology.
3. Future directions: There is an urgent need for large-scale collaborative research to introduce and establish the precision medicine paradigm using the comprehensive systems biology toolset to define biological mechanism and gene-based subgroups of patients. Based on these mechanisms, novel biologically tailored drugs can be developed that expand and overcome the traditional "one-fit-all" drug discovery and development approach into a more personalized approach, with more effective and safer compounds for individuals or groups of patients. Toward this end, comprehensive biomarker panels need to be discovered and developed to elucidate the role and interplay of clinical, neuroimaging, neuropsychological, genetic, neurochemical, and environmental characteristic of patients with late-life depression. In addition, studies on their significance for the prediction of cognitive decline and dementia development are warranted.

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