ELSEVIER

Alzheimer's & Dementia ■ (2016) 1-13

Alzheimer's & Dementia

Review Article

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

Thomas Leyhe[a,*], Charles F. Reynolds, III[b], Tobias Melcher[a], Christoph Linnemann[a], Stefan Klöppel[c], Kaj Blennow[d], Henrik Zetterberg[d,e], Bruno Dubois[f], Simone Lista[g,h], Harald Hampel[f,h]

[a]*Center of Old Age Psychiatry, Psychiatric University Hospital, Basel, Switzerland*
[b]*Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[c]*Department of Psychiatry and Psychotherapy, Center for Geriatric Medicine and Gerontology, Department of Neurology, University Medical Center Freiburg, Germany*
[d]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*
[e]*University College London Institute of Neurology, London, UK*
[f]*Sorbonne Universités, Université Pierre et Marie Curie, Paris 06, Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A) & Institut du Cerveau et de la Moelle épinière (ICM), Département de Neurologie, Hôpital de la Pitié-Salpêtrière, Paris, France*
[g]*IHU-A-ICM—Paris Institute of Translational Neurosciences, Pitié-Salpêtrière University Hospital, Paris, France*
[h]*AXA Research Fund & UPMC Chair, Paris, France*

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.

*Corresponding author. Tel.: +41(0)61-325-53-53; Fax: +41(0)61-0325-55-85.
E-mail address: thomas.leyhe@upkbs.ch

http://dx.doi.org/10.1016/j.jalz.2016.08.007
1552-5260/

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-5) that have only been updated after decade long intervals [3]. Contrary to expectations, the recently published DSM-5 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-5 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].