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Differential Diagnosis Findings Between Alzheimer's Disease and Major Depressive Disorder: A Review

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ABSTRACT

Background: Differentiating diagnosis between Alzheimer's disease and major depressive disorder in the elderly is a great clinical challenge. This study aimed to identify the establishment of differential diagnosis protocols between Alzheimer's disease and major depressive disorder.
Methods: We searched studies in the Ovid MEDLINE, EMBASE, PsycINFO, and Web of Science databases between 2009 and 2019. A total of 155 references were found for searching relevant articles using Boolean search. After exclusion of redundancies and assessing of title, abstract, and full text for eligibility, 11 articles were selected. The total sample size was 1077 distributed in 8 different countries.
Results: Significant results were found for differential diagnosis between Alzheimer's disease and major depressive disorder, such as overall mental status, episodic memory, visuospatial construction, delayed recognition task, semantic verbal fluency, visual task in short-term memory, atrophy of the hippocampus, cortical activation in specific tasks, and cerebrospinal fluid biomarkers.
Conclusion: These findings are good pathways for discriminating Alzheimer's disease from major depression in the elderly.

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INTRODUCTION

The differential diagnosis between Alzheimer's disease (AD) and major depressive disorder (MDD) in the elderly might be difficult and problematic when the cognitive profile of both conditions overlaps. Differentiating cognitive deficits secondary to depressive disorders from AD remains a great clinical challenge in neurology and psychiatry. It has been complicated because MDD in the elderly may be a risk factor or prodrome for neurodegenerative diseases and likely indicating subjacent vascular and/or degenerative process.[1,2]

Dementia and depression are also characterized by cognitive and behavioral changes. Several patients might present any cognitive, affective, and behavioral problem combinations in a clinical investigation, thus making it harder to differentiate whether the specific cognitive impairment is secondary to a depressive disorder or to an organic dementing process, for example.[1,3]

ALZHEIMER'S DISEASE

Alzheimer's disease is a neurodegenerative disease and also has been the principal cause of progressive decline in 2 or more cognitive domains, such as memory, language, executive and visuospatial function, personality, and behavior, which lead to loss of abilities to execute instrumental and/or basic daily activities.[4,5] Besides, late-onset AD may be modified by several genetic factors, cellular and molecular pathways, genes linked in the immune responses, and neuroinflammation and dysregulation of central nervous system.[6]

In 2010, 35.6 million people worldwide were diagnosed with dementia and will reach 75 million in 2030 and 131.5 million in 2050. There are over 9.9 million new cases of dementia each year worldwide.[7] Nowadays, approximately 47 million people have suffered from dementia around the world, and the highest prevalence has been in the elderly over 65 years old. About 60-80% of dementia cases are due to AD. People in this age range have increased around the world. It is likely that the prevalence of AD will increase to about 74.7 million people in 2030 and break 1.25 billion in 2050—22% of the global population.[5,8]

AD diagnosis requires post-mortem assessment of brain tissue, cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers combined with neuropsychological tests,

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and several relevant clinical criteria provide probable or possible dementia diagnosis.[2,5] According to Stephen et al.[4] it has been estimated that about one-third of AD cases may be connected to modifiable risk factors such as diabetes, midlife hypertension and obesity, physical inactivity, depression, smoking, and lower educational level.

In a systematic review and meta-analysis, Chi et al[9] showed that patients with severe AD tended to have a higher prevalence of major depression. The prevalence of depression was 12.7% (CI, 8.8-17.8) and 42% (CI, 38-45) according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria for MDD and specific criteria for dementia, respectively.

MAJOR DEPRESSIVE DISORDER

Major depressive disorder is a psychiatric disorder with significant morbidity, mortality, disability, and cognitive dysfunctions with a large economic impact worldwide. Several comorbidities have been studied, such as obesity, type 2 diabetes, heart conditions, autoimmune diseases, and neurodegenerative disorders.[10]

Cognitive impairment is a feature of depressive disorders according to the American Psychiatric Association[11] *DSM*-5 and World Health Organization[12] International Classification of Diseases-11 (ICD-11). Moreover, biological risk factors of major depression in old age may include endocrine, inflammatory, or immune, cardiovascular, and neuroanatomical factors. According to Fiske et al.[13] the older population is estimated to nearly double by 2050, being up to 2 billion people over the age of 60. Major depressive disorder has been one of the most common psychiatric disorders in the elderly.

Major depression has a significant social impact and accounts for 5.7% of years of living with disability among people older than 60 years. In these cases, MDD is often marked by apathy, psychomotor and behavior changes, and cognitive impairment.[1,11] In MDD, cognitive deficits involve executive functions, problem-solving and planning, flexibility, decision-making, inhibitory control, selective and sustained attention deficits, and semantic and phonemic fluency. Interestingly, cognitive impairments seem to be mediated by apathy in the elderly with MDD and AD.

MAIN POINTS

- Differentiating cognitive deficits secondary to depressive disorders from Alzheimer's disease remains a great clinical challenge in neurology and psychiatry.
- Major depressive disorder and Alzheimer's disease (AD) may be linked to normal effects of aging and are often identified as comorbidities.
- Cognitive variables and brain structural or functional changes are good pathways for discriminating AD from major depression in the elderly.

The differential diagnosis requires careful clinical follow-up with neuropsychological assessment, CSF, and PET neuroimaging tests. Understanding the biological interaction between MDD and AD and identifying putative biomarkers may improve the diagnosis process and may help develop specific interventions in the elderly.[1,9,11] Major depressive disorder and AD may be linked to normal effects of aging and are often identified as comorbidities. In clinical practice, differential diagnosis of MDD from AD remains difficult and may lead to misdiagnosis. Thus, the objective of this review was to identify the establishment of differential diagnosis protocols between AD and MDD.

METHODS

This review has been recorded in the international prospective register of systematic reviews, PROSPERO (https://www.crd.york.ac.uk/prospero/) with registration number CRD42020183472.

Search Strategy

We conducted this review for describing differential diagnosis between AD and MDD through Ovid MEDLINE, EMBASE, Web of Science, and PsycINFO databases search between January 2009 and December 2019. Thus, we searched for relevant articles using Boolean search for "*Alzheimer Disease*" OR "*Alzheimer's Disease*" OR *Dementia* AND "*Major Depressive Disorder*" OR *Depression* OR *Depressi** AND *Diagnosis* OR "*Differential diagnosis*" OR *diagnos** in published literature in English [...] language only. The authors added a supplementary file with the search strategy (Supplementary Table S1). Searches were filtered to human and clinical trial studies. A total of 155 references were found.

After exclusion of redundancies, assessing of title and abstract, and full text for eligibility, 11 articles were selected through consensus among the authors, according to relevance and contribution to the subject. All of them have been analyzed critically and were guided by preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria (further description following). The data extraction process of the current review was carried out independently and double-blindly by 2 reviewers allocated randomly.

Inclusion Criteria

Studies included following article screening had to be retrospective, prospective, longitudinal with population-based studies follow-up, and cross-sectional. Only patients over 60 years old with AD (not early onset) and/or major depression diagnosis were included. Studies in which at least 10% of the sample involved another comorbid diagnosis were excluded.

Patients in whom MDD and AD were measured using a standardized assessment tool were included as participants. Self-report of MDD and AD diagnosis (without any other objective measure) was excluded from the analysis. We included studies that used brain imaging tests, such as computerized tomography and magnetic resonance imaging (MRI) or PET scan; neuropsychological testing; biomarkers; physical and neurological exams.

Quality Assessment

The search strategy, selection, and the reporting of review results were aligned with the guidelines of the PRISMA[14] (www.prisma-statement.org). Two independent reviewers (RD and JY) evaluated all identified documents.

First, 2 reviewers extracted the data, and a third reviewer (FS or AS) checked the studies and then both reviewers discussed the process. Divergences and discrepancies were resolved through discussions that included the participation of a fourth reviewer (CR). The evaluation was guided by the PRISMA checklist, assessing the clarity of the research.

In addition, the PICOS tool (for participants, interventions, comparisons, results, and study design) was used to identify relevant articles. This was designed to reduce the risk of bias in included articles, evaluating the evidence and the applicability of the results in a separate manner. The entire process of study selection is further detailed in Figure 1.

Studies were required to have patients with MDD and/or AD in the sample aged ≥60 years. Studies with a sample size <20 and those not reporting specific sample age and not obtaining comparison group on original published peer-reviewed studies were excluded. We identified articles eligible for further review by realizing an initial screening through titles and abstracts and then by a full-text review.

Citations were imported into the EndNote citation management software, and duplicates were removed. The risk of bias was evaluated using the Risk of Bias in Systematic Reviews (ROBIS) tool in 3 phases: (a) assess relevance, (b) identify concerns with the review process, and (c) judge risk of bias. The ROBIS assessment was completed by 2 reviewers (RD and JY). One reviewer (FS) completed the assessment independently and a second one (CR or AS) checked the assessment.

RESULTS

The search strategy identified 155 studies. After duplication, 142 results remained, of which 65 articles were excluded following the initial screening of titles and abstracts. Three researchers further excluded 66 papers after reviewing 77 full texts in assessment for eligibility, resulting in a total of 11 papers included in the review (see Figure 1). The 11 identified studies were published between 2009 and 2019 and were conducted in 8 different

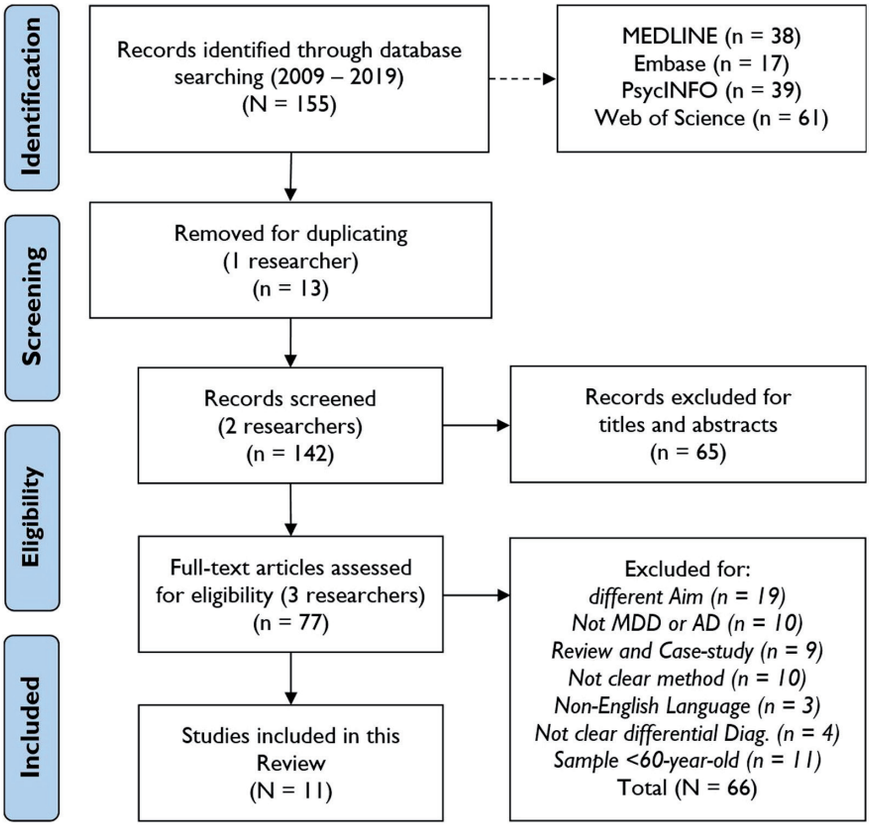

Figure 1. Selection criteria and studies screened in this review.

countries: Japan (3), Italy (2), Korea (1), Belgium (1), Brazil (1), Germany (1), Turkey (1), and UK (1). The total number of participants was 1077, and the age range was 60-92 years. Among the studies included, 25% (3) of them presented size sample between 20 and 70 (Hattori et al[15] [n=69]; Lee et al[16] [n=22]; Parra et al[17] [n=42]).

Appraisal of Included Studies

One reviewer (RD) abstracted details about the population, interventions/exposure, and outcomes. A second investigator (JY) reviewed data for accuracy. Two independent researchers applied predefined criteria to evaluate study quality as good, fair, or poor, based on ROBIS guidance. Discrepancies were resolved through consensus and a third review (FS).

Population Representativeness

Three studies[20,23,25] were assessed as having good representative sample. Four studies[18,19,21,24] had fair representative sample, whereas 4 had poor representative sample[15-17,22].

Assessment of Interventions

One study[22] was assessed as having good quality exposure measures because it used brain images, neuropsychological measures for AD and MDD, and biomarkers. Six studies[17,19,20,22,24] were assessed to have fair exposure measurement due to the use of neuropsychological battery for AD and MDD measures. Three studies (Baykan et al[18] [biomarker]; Hattori et al[15]; Joko et al[23]; Lee et al[16] [both brain imaging]) had poor quality exposure assessment measures because they used only one measure for differential diagnosis, although it was the aim of investigation.

Comparator Appraisal

Three studies had good quality[22,24,25] in comparison assessment, 5 studies were assessed to have fair quality,[17,19,20,21,23] and 3 had poor quality.[15,16,18]

Outcome Assessment

All studies had valid outcome appraisals once they used established and recognized worldwide measures for AD and MDD diagnostic criteria, such as supportive biomarker evidence (imaging, serum, and CSF), measures based on *DSM*-IV/5 and on National Institute on Aging Alzheimer's Association and National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association.

DISCUSSION

The objective of the current review was to identify the establishment of differential diagnosis protocols between AD and MDD. Results might help clinicians in patient intervention and researchers in future investigations. In a meta-analysis, based on findings, Cherbuin et al[26] pointed out that major depression is likely linked to 80-100% increased risk of AD. It may make differential diagnostic more challenging.

Neuropsychological Assessment

da Silva Novaretti et al[19] showed that AD patients may have the lowest scores in linguistic expression, linguistic comprehension, verbal episodic memory, visuospatial construction, and mental status. Besides, major depressive patients may present poorer performance, except in naming, conceptualization, executing commands, repetition, and understanding sentences when reading. Mental status, episodic memory, and visuospatial construction seemed to be the best of them for discriminating between MDD and AD.

In a study using voxel-based specific regional analysis system for AD, a technique of MRI, Tokumasu et al[27] in order to discriminate patients into 2 groups, MDD and AD, observed changes for a long-term that is for 6 months. The authors indicated higher cognitive problems in the MDD group and more impairment in psychological, social, and occupational functioning. On the other hand, in a retrospective study, Tao et al[28] point out that AD and MDD patients in the early stages present clinical symptoms, such as memory deficit, social distancing, apathy, and mild cognitive impairment. Also, Girtler et al[21] showed that AD patients were significantly impaired on temporal orientation as compared to depressive patients. On the 5-word test, the AD group score was lower than that of MDD. Regarding semantic verbal fluency, the AD score was lower than that of MDD. In global cognitive functioning, executive functions, visuospatial abilities, and semantic knowledge, AD patients were more impaired than MDD patients.

Hofrichter et al[22] indicated that MDD patients might significantly obtain higher performance in verbal knowledge as compared to AD patients with comorbid MDD. In our study, this AD patients with comorbid MDD exhibited decrement in primacy performance when compared to patients diagnosed with only AD. Depressive patients showed better performance on verbal fluency than AD patients with and without comorbid MDD. According to Parra et al.[17] visual short-term memory (STM) binding may differentiate between AD and MD diagnosis in elderly with higher sensitivity. Short-term memory binding deficits are specific to AD, compared to MD. These impairments may be further evident than other memory deficits. Brain changes occurring in the form of new compensatory connections may indicate normal performance in MD patients on relatively low-demanding tasks. However, it might be less likely in AD patients. As compared to long-term memory and attention functions, STM binding has been shown to be more effective in differentiating AD and

MD. In addition, Dierckx et al[20] indicated that AD patients had a significantly lower score on the delayed recognition task than MD elderly patients. Patients with AD presented a significantly higher risk percentage of memory deficits than MD patients.

Furthermore, AD might present more severe impairment in category fluency, on the other hand, depression might involve more severe selective impairment of letter fluency. Memory impairment in AD patients might be more severe than that in MD patients. Rotomskis et al[2] suggested the Addenbroke Cognitive Examination, a cognitive test battery, as a successful tool for dementia screening and also as a potential for differentiating AD from MD diagnosis. In addition, Hattori et al[15] suggested that AD patients may show a greater tendency toward apathy when compared to depressive patients. These findings corroborate the studies of Thorpe[29] and Tagariello et al[30] in which show that apathy and dysfunctions in basal ganglia and frontal symptoms, such as disinhibition and initiative reduced, point to dementias with a strong frontal component further than in MD patients.

Dias et al[1] suggest that cognitive impairments seem to be mediated by apathy in the elderly with MDD and AD. In neuroimaging review studies, Burke et al[31] suggest that apathy has been linked to cortical dysfunction in the posterior cingulate or inferior temporal cortex and also may present in these regions during atrophy, hypometabolism, and hypoperfusion. Besides, high levels of tau and phospho-tau in the CSF and cholinergic, GABAergic, and dopaminergic dysfunction may act as important biomarkers.

In a cross-sectional study, Ferreira et al[32] investigated 108 healthy, major depression, and Alzheimer group individuals s with age over 60 years. The AD patients group presented a lower performance in all dual-task (used to measure individual's ability to perform 2 simultaneous tasks) variables compared to MD and suggested that it might be associated with the cognitive impairment provoked by AD. The MDD patients presented preserved physical capabilities, and it could have influenced their better performance in dual tasks. However, it is important to emphasize that all patients with MD diagnosis in the study were being treated with selective serotonin reuptake inhibitors. Good performance in dual-task activities demands a further activation of brain areas when compared to a single task, especially in the prefrontal cortex. According to Burke et al.[31] smaller hippocampal volumes may be linked to memory performance.

Brain Imaging Assessment

Although several questions remain unanswered in relationship between AD and MDD in the elderly, neuroimaging, besides helping in diagnosis and treatment based on biomarkers, has been a potential way toward understanding the complex pathophysiology.[31] In MRI, it is possible that the region of atrophy in MDD patients may differ from that of patients with AD. Although hippocampal atrophy has been identified in both AD and MDD diseases, Joko et al[23] pointed out that, in general, only AD patients presented marked atrophy of the hippocampus. Thus, findings of atrophy of the hippocampus may indicate AD. On the other hand, localized atrophy of the anterior hippocampal formation (12 mm dorsal to the amygdala) may indicate MDD.

In addition, Kito et al[24] found temporal and parietal lobe atrophy in all AD patients; however, no MD patients presented significant pathological findings. Their results also showed significantly lower cortical activation in visuospatial task in the parietal cortex in MDD patients compared to that of AD patients. In a meta-analysis study, Boccia et al[33] presented that AD is associated with considerable atrophy in the left anterior hippocampus and bilateral posterior cingulate cortex; however, MDD in the elderly is linked to notable atrophy in the precuneus, superior frontal gyrus, and ventromedial frontal cortex. Regarding verbal fluency task, there might be similar tendencies; however, further investigation is necessary. The results of imaging in this review corroborate to those of Burke et al[31] and Cherbuin et al[26] who present the hippocampal atrophy as the strongest characteristic structural imaging biomarker of AD, although these findings were not specific for AD but may be found in other neurodegenerative diseases (cf. Kempton et al[34]). In addition, Lee et al[16] in an imaging analysis study suggested the AD group had higher global power in the theta band than the MDD group. In the MDD group, the relative powers of the beta, beta1, and beta2 bands were higher in the mid-central region compared to the left-central or right-central regions and higher in the mid-frontal compared to the left-frontal region. Such regional differences were not noted in the AD group. Alzheimer's disease groups had higher theta relative power than MDD groups in both the resting state (1 minute with eyes open) and in the rapid eye movement (REM)-sleep state. As abovementioned, the most characteristic structural imaging biomarker of AD has been shown in hippocampal atrophy. Magnetic resonance imaging morphometric studies of late-life depression (LLD) have demonstrated atrophy of different brain structures, such as lower gray matter volumes in the frontal temporal lobes, hippocampus, para-hippocampal gyrus, amygdala, putamen, pallidum, and thalamus, compared to controls,[31] and increased neuroinflammation, oxidative stress, and white matter lesions.[26] Volumetric hippocampal changes in LLD might reflect one or more pathophysiological processes, for example, early neurodegenerative disease and depressive illness.[31,34] The association between hippocampal volume and AD has been discussed several times worldwide.[35]

Biomarkers Assessment

Neutrophil to lymphocyte ratio (NLR), used as a marker of subclinical inflammation, can also be used as another biomarker in the differential diagnosis between AD and

Table 1. Description of Included Studies in This Review

Author/Year/ Country	Participants (Sample/Age)	Interventions/ Measures[a]	Comparison[b] (Study Design)	Outcomes/Differential Diagnosis
Hattori et al[15] (2010), Japan	n = 69; aged 65 years or older	GDS, Apathy Scale	AD-D (n = 38); MD (n = 31); Cross-sectional study.	In AD patients, the Apathy Scale score was greater than the GDS30 score, suggesting a strong tendency toward apathy. There was a significant difference in the GDS30/Apathy Scale score ratio between the 2 groups. In AD-D group, the proportion of patients in whom the tension score was higher than the depression score was significantly larger. In the MD group, the proportion of patients in whom the depression score was higher than the tension score was significantly greater (OR: 10.3, 95% CI: $4.06 \leq OR \leq 27.52$).
Lee et al[16] (2017), Korea	n = 22; ≥60-year-old.	MRI	AD (n = 11), MDD (n = 11); Retrospective cohort study.	Repeated-measures MANOVA analysis indicated that the AD had higher global power in the theta band than the MDD group ($F = 6.302$, $P = .021$). In the MDD group, the relative powers of the beta, beta1, and beta2 bands were higher in the mid-central region compared to the left-central or right-central regions ($P < .01$), and higher in the mid-frontal region compared to the left-frontal region ($P < .05$). Such regional differences were not observed in the AD group. AD patients had higher theta relative power than MDD patients in both resting state (1 minute with eyes open) and REM-sleep state.
Parra et al[17] (2010), UK	n = 42; 65-84 years old.	Visual STM, ACE, Word Lists I and II, FAS, VF-A, TMT, CFR-O.	HC (n = 14), MD (n = 14), AD (n = 14); Cross-sectional study.	MMSE showed that patients with depression and controls had a similar cognitive level, while the cognitive level of AD patients was significantly lower than that of both depressed and control participants. Visual STM binding discriminates between AD and MD in the elderly with high sensitivity. STM binding deficits are specific to AD, compared to MD and these deficits are much greater than other memory impairments for individual items. Brain changes occurring in the form of new compensatory connections may underlie the normal performance of depressed patients on relatively low-demanding tasks. However, these types of changes are less likely to occur in AD. As compared to LTM and attention functions, STM binding proved to be more successful at differentiating between AD and MD.
Baykan et al[18] (2018), Turkey	n = 95; ≥65 years old	NLR	MDD (n = 30), AD (n = 42), PD (n = 23); MDD vs. AD, PD vs. AD; Retrospective study.	NLR is significantly lower in patients with MDD than in those with AD. Simple arithmetic calculation could help clinicians in the differential diagnosis between AD and MDD, given that a complete blood cell count is a routine blood panel already in use, requiring no further sample collection to calculate the NLR.
da Silva Novaretti et al[19] (2011), Brazil	n = 85; aged over 60 years.	MMSE, BCBE, ABCD, GDS, HAM-D, MADRS, PFAQ	LLD (n = 25), AD (n = 30) compared to a CG (n = 30); CG vs. LLD and LLD vs. AD; Cross-sectional study.	AD patients had the lowest scores in all constructs of the ABCD and had poorer performance than the depression group on most subtests except confrontation naming, conceptualization, following commands, repetition, and sentence reading comprehension. The episodic memory and linguistic expression constructs were the best measures for discriminating depression patients from controls, whereas the mental status, episodic memory, and visuospatial construction constructs were the best for discriminating between depression and AD patients. The best constructs for discriminating between depression and AD patients were episodic memory and mental status.
Dierckx et al[20] (2011), Belgium	n = 124; ≥60 years old	10-RAVLT, MMSE, GDS, RCPM	AD (n = 36), MD (n = 41), CG (n = 47); Cross-sectional pilot study.	AD patients had significantly lower sores on the delayed recognition task than depressed elderly patients. AD patients had a significantly higher percentage of forgetting than depressed patients.
Girtler et al[21] (2012), Italy	n = 83; years old range 61-92	SCEB, MMSE, CDR, MRI, ADL	AD (n = 29), MCI (n = 27), MDD (n = 27), HC (n = 48) Cross-sectional study	At MANCOVA and post hoc comparisons, the AD group was significantly ($P < .0001$) impaired on temporal orientation as compared to the other groups. On the 5-word test, the AD group scored lower than the other groups ($P < .001$), while HC scored higher ($P < .0001$) compared to MDD. On clock drawing, the AD group was significantly impaired compared to HC ($P < .0001$) and DEP ($P < .05$). As for semantic verbal fluency, AD scored lower ($P < .002$) than the MDD and HC.

(*Continued*)

Table 1. Description of Included Studies in This Review (*Continued*)

Author/Year/ Country	Participants (Sample/Age)	Interventions/ Measures[a]	Comparison[b] (Study Design)	Outcomes/Differential Diagnosis
Hofrichter et al[22] (2014), Germany	n = 73; years old range, 60-88	GDS, MMSE, MWTB, CERAD-NP, (CERAD [BNT, VFlu, VLea, VRec]).	AD (n = 18), MDD (n = 21), HC (n = 17); HC vs. MDD vs. AD vs. AD + MDD. Retrospective study.	Both HC and MDD patients showed significantly higher mean values in MWTB as compared to AD patients with comorbid MDD MDiffHC-(AD+MDD) = 34.19; $P < .05$; MDiffMDD-(AD+MDD) = 28.98; $p < .05$). The main finding of this study is that patients with AD and comorbid MDD exhibited decrements in primacy performance as compared to patients diagnosed with AD alone. Regarding CERAD, both HC and MDD patients showed significantly better performance on verbal fluency as compared to AD patients with and without comorbid MDD.
Joko et al[23] (2016), Japan	n = 133; ≥60 years old, range 60-88.	MRI	AD (n = 58), aMCI (n = 33), MDD (n = 20), NC (n = 22); AD + aMCI + MDD + NC. Retrospective study.	Region of brain atrophy in patients with MDD may differ from that in patients with AD. Current results showed that although hippocampal atrophy has been indicated in diseases such as AD and MDD, only AD showed marked overall atrophy of the hippocampus. Findings of prominent overall atrophy of the hippocampus may suggest AD presence, and localized atrophy of the anterior hippocampal formation (12 mm dorsal to the amygdala) may suggest MDD.
Kito et al[24] (2014), Japan	n = 91; ≥60-year-old	MRI, VFT, VFT, VST.	AD (n = 28), LLD (n = 30), CG (n = 33), Comparison: LLD vs. AD, LLD vs. HC, AD vs. HC.	MRI results showed temporal and parietal lobe atrophy in all patients with AD. No patients with depression presented notable pathological findings. The results also revealed that cortical activation in a VST was significantly lower in the parietal cortex of the LLD group than in that of the AD group. Similar but non-significant tendencies were seen in the VFT.
Liguori et al[25] (2018), Italy	n = 260; ≥65-year-old (range 60-84)	MMSE, PHQ-9, MRI, CSF biomarkers, 18F-FDG-PET.	LLD (n = 48), AD (n = 154), CG (n = 58); Observational study and longitudinal study (2-year follow-up).	LLD patients showed significant higher Aβ42 CSF levels ($P < .001$) coupled with significant lower t-tau ($P < .001$) and p-tau ($P < .001$) CSF levels compared to AD patients. All the AD patients but no LLD patients showed the t-tau/Aβ ratio (>0.52) consistent with AD pathology. A reduction of 18F-FDG-PET uptake in bilateral temporal and parietal cortices was found in AD than LLD patients. Patients showing biomarkers consistent with AD pathology and included in the AD group progressively deteriorate their cognition with nonsignificant changes of depression.

[a]Intervention/Measure. NLR, neutrophil to lymphocyte ratio; MMSE, mini-mental state examination; BCBE, Brief Cognitive Battery Edu; ABCD, Arizona Battery for Communication Disorders of Dementia; GDS, Geriatric Depression Scale; HAM-D, Hamilton Depression Scale; MADRS, Montgomery and Asberg Depression Rating Scale; PFAQ, Pfeffer Functional Activities Questionnaire; 10-RAVLT, The Rey Auditory-Verbal Learning Test; RCPM, Raven Colored Progressive Matrices; SCEB, Short Cognitive Evaluation Battery; CDR, Clinical Dementia Rating Scale; ADL, activities of daily living; MWTB, German version of a verbal knowledge test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (BNT, Boston Naming Test; VFlu, Verbal fluency; VLea, Verbal Learning; VRec, Verbal Recall); MRI: magnetic resonance imaging; VFT, verbal fluency task; VST, visuospatial task; PHQ-9, Patient Health Questionnaire 9; 18F-FDG-PET, 2-[18F]fluoro-2-deoxy-d-glucose positron emission tomography; CSF biomarkers, cerebrospinal fluid; STM, short-term memory visual task; LTM, Long-term memory; ACE, Addenbrookes Cognitive Examination; Word Lists I and II, (I-Recall and II-Recognition); FAS, letter fluency; VF-A, verbal fluency animals; TMT, trail making test A-B; CFR-O: Complex Figure of Rey-Osterrieth

[b]Comparison: HC, healthy control; CG, control group; MD, major depression; MDD, major depression disorder; AD, Alzheimer's disease; LLD, late-life depression; AD-D, Alzheimer's disease with depression; aMCI, amnestic mild cognitive impairment; MCI, mild cognitive impairment; HC, healthy control; NC, normal controls; PD, Parkinson's disease.

MANCOVA, multivariate analysis of covariance; MANOVA, multivariate analysis of variance; OR, odds ratio.

MDD.[36] For example, Baykan et al[31] showed that NLR might be significantly lower in MDD patients when compared with that of AD patients. The authors suggest that NLR has been already a routine blood panel in use in a complete blood cell count and thus requires no further sample collection. Biomarkers based on CSF are functional for detecting preclinical and symptomatic stages of AD and MDD.[37,38]

Liguori et al[25] showed that depressive patients presented significantly higher Aβ42 CSF levels coupled with significantly lower t-tau and p-tau CSF levels compared to AD patients. All AD patients showed the t-tau/Aβ ratio consistent with AD pathology. On the other hand, no depressive patients presented these results. Moreover, higher decrease of 18F-FDG-PET capture in bilateral temporal and parietal cortices was found in AD compared to depressive patients. Similarly, Reis et al[39] showed that CSF Aβ 42 levels were significantly higher in depressive patients compared to AD patients.

There was no significant difference in p-tau levels between AD and MDD patients. However, t-tau presented a significant difference between both conditions, although higher levels in AD. According to Schipke et al[38] and corroborating the study mentioned above, synaptic proteins in CSF biomarkers showed considerable differences between MDD and AD in terms of neurogranin levels. The t-tau levels were significantly higher in patients with moderate AD than

in the MDD patients. In addition, increased cortisol serum levels are linked to AD biomarkers in CSF. Furthermore, serum cortisol and CSF tau levels have been negatively correlated. Likewise, it is important to highlight that hyperactivation of the hypothalamic-pituitary-adrenal axis and increased cortisol levels have been noted in up to 70% of depressed patients.[32]

Limitations and Strengths

The current review has some limitations. There may be a loss of relevant studies while filtering for the English language in criteria inclusion. In addition, we did not search for unpublished studies and informally published data, such as technical reports or studies from research groups. On the other hand, identified two strengths in this review: a) we observed methods of critical appraised, underlying data verified, validated checklists use, besides systematic assessment. Therefore, it may reduce the potential for subjectivity or bias in the subsequent findings; b) The risk of bias has been diminished by using 2 reviewers in a double-blinded method. To sum up, in the appraisal of the qualitative reviews and interpretation of findings of this review, we searched many databases to avoid bias as a consequence of streamlining process.

CONCLUSIONS

This systematic review found interesting qualitative findings for differentiating diagnosis between MDD and AD. These findings suggest that cognitive variables (such as mental status, episodic memory, visuospatial construction, delayed recognition, semantic verbal fluency, visual short-term memory) and brain structural or functional changes (atrophy of the hippocampus, cortical activation in a visuospatial task, relative powers of the beta and theta bands in the mid-central region and left-central or right-central regions, and CSF biomarkers) are good pathways for discriminating AD from MDD in elderly.

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Supplementary Table S1. Search Strategy in the databases

Database: Ovid MEDLINE(R) without Revisions <2009 to 2019> Search Strategy:		Results
#1	Alzheimer Disease/	57.581
#2	Dementia/	28.595
#3	Depressi*/	73.369
#4	Depressive Disorder, Major/	23.108
#5	1 or 2	82.37
#6	3 or 4	94.741
#7	5 and 6	2.48
#8	Diagnos*/ or diagnosis, differential/	216.329
#9	7 and 8 "humans"[MeSH Terms]	162
#10	1 and 4 and 9	38
Database: Web of Science<2009 to 2019> Search Strategy:		**Results**
#1	(TS=("alzheimer disease" OR "alzheimer's disease")) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article). Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2009-2019	61.11
#2	(TS=("major depressive disorder" OR depressi*)) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article). Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2009-2019	237.263
#3	#2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2009-2019	3.643
#4	(TS=("differential diagnosis" OR diagnos*)) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article). Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2009-2019	1.013,073
#5	#4 AND #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2009-2019	1.091
#6	#4 AND #3 Refined by: [excluding] DOCUMENT TYPES: (BOOK CHAPTER) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2009-2019	1.088
#7	((TS=("differential diagnos*"))) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article). Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2009-2019	34.793
#8	#7 AND #6 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2009-2019	61
Database: Embase<2009 to 2019> Search Strategy:		**Results**
#1	('alzheimer disease'/exp OR 'alzheimer disease') AND ('major depressive disorder'/exp OR 'major depressive disorder')	1.594
#2	('alzheimer disease'/exp OR 'alzheimer disease') AND ('major depressive disorder'/exp OR 'major depressive disorder') AND ('differential diagnosis'/exp OR 'differential diagnosis')	75
#3	#1 AND #2	75
#4	differential diagnosis'/exp OR 'differential diagnosis' OR diagnos*	6.634,809
#5	#1 AND #4	551
#6	#5 AND ('clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'diagnostic test accuracy study'/de OR 'human'/de OR 'longitudinal study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND 'article'/it	157
#7	#5 AND ('clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'diagnostic test accuracy study'/de OR 'human'/de OR 'longitudinal study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND 'article'/it AND [english]/lim	148
#8	#2 AND #7	17
Database: PsycINFO<2009 to 2019> Search Strategy:		**Results**
#1	Search For: Any Field: “alzheimer disease” AND Any Field: “major depressive disorder” OR Any Field: Depression AND Any Field: “differential diagnosis” AND Document Type: Journal Article AND Population Group: Human AND Year: 2009 To 2019 PsycINFO, PsycARTICLES, PsycBOOKS, PsycEXTRA	39