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To cite this article: Madia Lozupone, Maddalena La Montagna, Francesca D'Urso, Carla Piccininni, Rodolfo Sardone, Vittorio Dibello, Gianluigi Giannelli, Vincenzo Solfrizzi, Antonio Greco, Antonio Daniele, Nicola Quaranta, Davide Seripa, Antonello Bellomo, Giancarlo Logroscino & Francesco Panza (2018) Pharmacotherapy for the treatment of depression in patients with alzheimer's disease: a treatment-resistant depressive disorder, Expert Opinion on Pharmacotherapy, 19:8, 823-842, DOI: [10.1080/14656566.2018.1471136](https://doi.org/10.1080/14656566.2018.1471136)

To link to this article: <https://doi.org/10.1080/14656566.2018.1471136>



Published online: 04 May 2018.



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REVIEW



Pharmacotherapy for the treatment of depression in patients with alzheimer's disease: a treatment-resistant depressive disorder

Madia Lozupone^a, Maddalena La Montagna^b, Francesca D'Urso^b, Carla Piccininni^b, Rodolfo Sardone^c, Vittorio Dibello^d, Gianluigi Giannelli^e, Vincenzo Solfrizzi^e, Antonio Greco^f, Antonio Daniele^g, Nicola Quaranta^h, Davide Seripa^f, Antonello Bellomo^b, Giancarlo Logroscino ^{a,i} and Francesco Panza ^{a,f,i}

^aNeurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy; ^bPsychiatric Unit, Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy; ^cDepartment of Epidemiology and Biostatistics, National Institute of Gastroenterology "S. de Bellis" Research Hospital, Castellana Grotte, Bari, Italy; ^dInterdisciplinary Department of Medicine (DIM), Section of Dentistry, University of Bari Aldo Moro, Bari, Italy; ^eGeriatric Medicine-Memory Unit and Rare Disease Centre, University of Bari Aldo Moro, Bari, Italy; ^fGeriatric Unit & Laboratory of Gerontology and Geriatrics, Department of Medical Sciences, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Foggia, Italy; ^gInstitute of Neurology, Catholic University of Sacred Heart, Rome, Italy; ^hOtolaryngology Unit, University of Bari "Aldo Moro", Bari, Italy; ⁱDepartment of Clinical Research in Neurology, University of Bari Aldo Moro, "Pia Fondazione Cardinale G. Panico", Tricase, Lecce, Italy

ABSTRACT

Introduction: Pharmacotherapy for the treatment of depressive disorders in Alzheimer's Disease (AD) represents a clinical challenge. pharmacological options are often attempted after a period of watchful waiting (8–12 weeks). monoaminergic antidepressant drugs have shown only modest or null clinical benefits, maybe because the etiology of depressive symptoms in AD patients is fundamentally different from that of nondemented subjects.

Areas covered: The following article looks at the selective serotonin reuptake inhibitor sertraline, which is one of the most frequently studied antidepressant medications in randomized controlled trials (RCTs). It also discusses many other pharmacological approaches that have proven to be inadequate (antipsychotics, acetylcholinesterase inhibitors, anticonvulsants, hormone replacement therapy) and new drug classes (mainly affecting glutamate transmission) that are being studied for treating depression in AD. It also gives discussion to the phase II RCT on the alternative drug S47445 and the potential effect on cognition of the multimodal antidepressant vortioxetine in older depressed patients. Finally, it discusses the N-methyl-D-aspartate antagonist ketamine.

Expert opinion: The present RCT methodologies are too disparate to draw firm conclusions. Future studies are required to identify effective and multimodal pharmacological treatments that efficiently treat depression in AD. Genotyping may boost antidepressant treatment success.

ARTICLE HISTORY

Received 22 March 2018
Accepted 26 April 2018

KEYWORDS

Citalopram; sertraline; escitalopram; venlafaxine; mirtazapine; antipsychotics; anticholinergic drugs; mood stabilizers; diet; lifestyle

1. Conceptual framework for the definition of depressive symptoms in Alzheimer's disease

Alzheimer's disease (AD) is often complicated by neuropsychiatric symptoms (NPS), which occur in one-third of patients at an early stage of the disease [1]. Factor analysis of cross-sectional data from the European Alzheimer's Disease Consortium has proposed four neuropsychiatric sub-syndromes with overlapping symptoms in AD: psychosis (delusion, hallucination, and sleep disorder), affective (depression and anxiety), apathy (apathy and appetite disorder), and hyperactivity [2]. Recognition and treatment of depression is crucial in individuals with dementia, because the presence of depression has been associated with higher rates of disability, impaired quality of life, and greater mortality particularly for suicide ideation [3]. Furthermore, the treatment of depression may also improve other NPS associated with depression such as aggression, anxiety, apathy, and psychosis [4,5].

The prevalence of depression in dementia ranges from 16% to 45%, depending on diagnostic definitions used, study designs, and the sample populations [6]. The best approach to diagnosing depression in the context of dementia is not yet unambiguous. Provisional criteria for depression of AD have been proposed but not yet validated [7]. The Depression and Bipolar Support Alliance Consensus Statement Panel reported that the diagnostic criteria for depression in individuals with neurocognitive disorders must be revised [8]. The Panel recommended that the criteria take into account the instability and oscillation of symptoms over time, the reduction in positive affect or pleasure, and the inclusion of irritability, social withdrawal, and isolation as indicators of depression [8]. Until criteria for depression in dementia are established, patients should be carefully evaluated for any of the symptoms of depression outlined in Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR [9], although mood disorders in dementia could not fulfill DSM criteria.

Article Highlights

- Among neuropsychiatric symptoms, depressive disorders are often more distressing and disabling rather than cognitive symptoms in patients with Alzheimer's disease (AD).
- There is still a need for effective treatment of depression in AD and dementia, when non-pharmacological approaches fail and after a period of watchful waiting (8-12 weeks).
- Evidence coming from recent randomized controlled trials (RCTs) showed only partial or no clinical benefits in treating depression in AD.
- The classical antidepressant drugs for treating AD-related depression showed only modest efficacy or no benefits compared with placebo, and often RCTs methodologies are controversial.
- Antipsychotics, acetylcholinesterase inhibitors, anticonvulsants, hormone replacement therapy have proven to be inadequate.
- Other RCTs on novel glutamatergic drugs are ongoing, evidencing that many demented patients may benefit from agents affecting glutamate transmission.
- Further evidences may come from multimodal antidepressants as promising novel drugs for treating depression in AD patients, that could be considered a treatment-resistant depressive disorder.

This box summarizes key points contained in the article.

Depression in AD may occur on a spectrum ranging from very mild 'sub-threshold' forms to major depression differing only quantitatively regarding severity of symptoms [6].

The relationship between depressive symptoms and the clinical presentation of dementia has led to debate as to the direction of causality, i.e. if depression is a prodromal symptom preceding impending cognitive deficits or an independent risk factor for dementia. A meta-analysis published in 2006 suggested that depression is associated with a two-fold increased risk for AD [10], but studies covering the same period also evidenced that depression may be a prodromal feature of dementia [11,12], implying no causal effect of depression on dementia. Therefore, as shown recently, the association between depressive symptoms and dementia in older adults may be primarily due to common causes or depressive symptoms being a feature of the preclinical phase of dementia [13], deriving from neurobiological changes in common brain areas.

Neurotransmission may play a crucial role in the pathogenesis of NPS in AD [14]. Neuropathology features of AD are important, in fact, depression is associated with selective loss of noradrenergic cells in the locus coeruleus, and possibly the serotonergic raphe nuclei [15–17]. Furthermore, more severe presence of neuropathological markers [tau, amyloid- β (A β), and vascular disease] was observed in AD patients with depression compared to those without [18]. These patients also showed severe loss of serotonin receptors and serotonin transporter binding [19]. The apparent central role for glutamatergic-mediated transmission in late-life major depression and AD offers the possibility that significant overlap may occur in the signaling transduction mechanisms in these two disorders [20]. These findings may have implications for the treatment of depression, specifically, the manipulation of relevant neurotransmitter systems in treating AD-associated depression, particularly serotonin, noradrenalin, and also glutamate.

However, the relationship between AD and depression is incompletely understood and its nature and treatment are probably multifactorial, also for secondary mechanisms or systemic

conditions (end-stage renal disease and diabetes). Anemia could be a consequence of malnutrition linked to loss of appetite, an important depressive symptom and systemic conditions should be considered for a complete pharmacological treatment of depression in AD [21]. Effective treatments are necessary to alleviate the emotional and financial burdens created by these symptoms, but unfortunately, safe and robust treatments are lacking. Currently there are no FDA approved medications for the treatment of depressive symptoms in AD [22]. The lack of effective treatments does imply that a non-responsive depressive mood (to conventional antidepressants) in dementia could be considered a treatment-resistant form of depression. The present study sought to provide a comprehensive review of principal randomized clinical trials (RCTs) on pharmacological intervention efficacy in treating depression in AD patients. Introducing also possible underlying neurobiological mechanism explaining the different impact of antidepressant drugs in AD.

2. Some neurobiological mechanisms of antidepressants in Alzheimer's disease

The impact of antidepressants on the pathogenesis of dementia remains unclear despite depression and dementia are closely related. Most of the studies were conducted on animal models. These experiments have suggested that selective serotonin reuptake inhibitors (SSRIs) may reduce A β plaque burden and cognitive impairment, presumably by shifting the balance from pro-amyloidogenic toward non-amyloidogenic processing of the amyloid precursor protein (APP) [23–25]. Only few studies were conducted in humans and in cognitively normal individuals, long-term medication with the SSRI citalopram has been found to be associated with lower A β plaque load [23,26], and acute treatment with citalopram was found to reduce the rate of newly generated A β [26]. Furthermore, a growing body of evidence points toward the complex role of neuroinflammation in amyloidogenesis, neurodegeneration, and cognitive decline [27]. SSRIs can modulate key inflammatory factors, such as tumor necrosis factor alpha [28], interleukins-1b and -6, and reactive oxygen stress. Interestingly, in a mouse model, SSRIs were found to ameliorate experimental allergic encephalitis-induced symptoms [29]. SSRI-mediated modulation of neuroinflammation and neurodegeneration could therefore explain the favorable outcomes of patients with AD under long-term SSRI treatment.

Fluoxetine, as a representative SSRI, could reduce the level of soluble A β and protect hippocampal neurons *in vitro* model of AD, moreover, inhibit activated astrocytes and microglia, and improve behavioral performance in APP/presenilin 1 (PS1) mice [30,31]. Some evidences indicated that A β_{1-42} could concurrently mimic the depression-like behavior and working memory disorders in mice, while desipramine could effectively reverse both the deficits induced by A β_{1-42} . The neuroprotection of desipramine may be involved in the up-regulation of phosphorylated cAMP response element binding protein level in the hippocampus of mice [32]. Some studies have recently demonstrated that fluoxetine is neuroprotective against A β -induced neurodegeneration via a paracrine signaling mediated by transforming-growth-factor- β 1 (TGF- β 1), which,

interestingly, does not depend on the serotonin transporter blockade [33]. The deficit of TGF- β 1 might contribute to cognitive deficits and depressive disorder treatment resistance in AD patients, by increasing A β accumulation and promoting the so called ‘amyloid-related depression’ [34].

At the same time, an ‘astroglia-centric’ perspective of neurodegenerative diseases proposed an astrocyte dysfunction involvement in the impairment of proper central nervous system functioning. Recent evidences coming from *in vitro* studies supported the hypothesis that sertraline and paroxetine may increase calcium influx and induce mitochondrial damage-mediated apoptosis, causing astrocyte dysfunction. This impairment may be involved in the pathogenesis of neurodegenerative diseases, and neuronal injury *in vitro* could be attenuated by N-methyl-D-aspartate (NMDA) antagonists [35].

The elucidation of the molecular mechanisms underlying the rapid antidepressant effect of the potent NMDA antagonist ketamine has offered novel potential therapeutic target, whose mode of action may prove to be pertinent to AD treatment. The mammalian target for rapamycin signaling, mTOR is an atypical Ser/Thr kinase and a central controller of protein synthesis required for new synaptic connections [36]. It has recently been demonstrated that the antidepressant effect of ketamine is mediated by activation of the mTOR pathway [37]. mTOR dysregulation has also been found in AD, with several signaling proteins involved in mTOR-regulated pathways, including protein kinase B, also known as Akt, and mTOR itself, found to be altered in the postmortem brains of AD patients [38].

3. Clinical trials and meta-analysis regarding classical and alternative antidepressants drugs for the treatment of depression in Alzheimer’s disease

SSRIs are considered the first-line treatment for late-life depressive disorders without dementia [39], but the evidence in support to the use of antidepressants to treat depression in dementia is quite mixed and the data are difficult to interpret, because of small sample sizes, heterogeneity, use of multiple outcome measures, and a general paucity of good quality data. It is very likely that failures in clinical trials are associated with different factors such as heterogeneity of the sample and concomitant treatments. Most of the positive studies limited the mood diagnosis to major depression, whereas most of the negative RCTs defined depression more broadly [40] (Table 1).

Both the 2001 US Expert Consensus Guidelines [41] and the 2006 Guidelines from the Canadian Coalition for Senior’s Mental Health [42] recommend the use of SSRIs as first-line antidepressant, favoring citalopram and sertraline in older adults. Although these drugs remained the mainstay of treatment for AD patients with depression, the evidences from systematic reviews and meta-analyses did not appear to be clear enough to support this practice. For its continuous score as outcome measure, the majority of studies used the Hamilton Depression Rating Scale (HDRS) [43], which has not been validated for use in patients with AD, while the remaining studies used the Cornell Scale for Depression in Dementia (CSDD) and fewer the Montgomery Asberg Depression Rating Scale (MADRS)

[44,45]. Only one antidepressant discontinuation study was conducted, although the difference between continuation and withdrawal groups was not statistically significant [46] (Table 1).

In looking at the individual SSRI RCTs, the first trial also known as the Depression in Alzheimer Disease Study (DIADS) found sertraline to be superior in reducing depression compared with placebo at 12 weeks of treatment in a sample of 44 outpatients who have probable AD and major depressive episodes [47] (Table 1). This rigorous trial was positive for sertraline to a 150 mg maximum daily dose on primary depression outcomes because the treated group had greater improvements in the scores for the CSDD and the HDRS. Furthermore, the active treatment was favored over placebo for the secondary outcomes of behavioral disturbance, role functioning, and caregiver distress. A statistical trend toward less decline in activities of daily living was also observed on the Psychogeriatric Depression Rating Scale–activities of daily living subscale, but not on the Mini-Mental State Examination (MMSE) [48] (Table 1). Conversely, a previous fluoxetine RCT did not find any statistically significant difference in reducing depressive symptoms as rated by the HDRS between fluoxetine treatment (using doses of up to 40 mg/daily), and placebo [48] (Table 1). Overall, the methodologies of these RCTs are too disparate to draw firm conclusions.

The efficacy of citalopram was originally assessed in a 4-week RCT (doses of up to 30 mg daily) on a combined sample consisting of 98 patients with moderate AD and vascular dementia (VaD), with a DSM-III diagnosis of primary degenerative dementia and multi-infarct dementia [49] (Table 1). The MADRS score (ranging from 0 for absence to 30 for more severe symptomatology) showed a significant improvement in depressed mood, emotional bluntness, confusion, irritability, anxiety, fear/panic, and restlessness only for the AD group, compared to the placebo group and not in motor or cognitive functions [49] (Table 1). More recently, the Citalopram for Agitation in Alzheimer Disease Study (CitAD) randomized 186 participants with moderate-to-severe AD and significant agitation to 9 weeks of citalopram 30 mg/daily dose or matching placebo [50]. A positive effect for citalopram compared to placebo on agitation (primary outcome) as measured by the Neurobehavioral Rating Scale agitation subscale (NBRS-A), the modified Alzheimer Disease Cooperative Study–Clinical Global Impression of Change scale (ADCS-CGIC), and the total Neuropsychiatric Inventory (NPI) score was reported [22,50]. A subsequent planned secondary analysis examined the effect of citalopram on specific NPI domain scores and found a statistically significant effect for citalopram on delusions, anxiety and irritability, but not on depression/dysphoria [51] (Table 1). However, QTc prolongation and cognitive worsening were observed in the citalopram group representing safety concerns for clinicians [52].

The only one Cochrane review about antidepressants for treating depression in dementia was published in 2002 [3]. There were seven included RCTs with a total of 1140 subjects of which 769 met inclusion criteria. This review included only four trials in the meta-analysis for efficacy: two studies using tricyclic antidepressants (TCAs) (clomipramine [53] and imipramine [54]) (Table 1) and two studies using SSRIs (sertraline [47] and fluoxetine [48]) (Table 1). Overall, the meta-analysis was hampered by a limited number of studies of small sample size suggesting that the evidence to support the efficacy of the antidepressants on

Table 1. Principal randomized clinical trials evaluating the efficacy of antidepressant interventions in the treatment of depressive disorders in Alzheimer's disease.

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Reifler et al., 1989 [53]	61 patients with AD	Imipramine	6 weeks	HDRS, MMSE, OARS, and DRS	Those receiving imipramine showed no significant improvement in HDRS, MMSE and OARS scores compared with placebo. DRS scores declined more significantly in the placebo group compared with patients receiving placebo
Nyth and Gottfries, 1990 [48]	28 AD patients with depression: 13 randomized to imipramine and 15 to placebo 33 AD patients without depression: 14 randomized to imipramine, 19 to placebo Mean age: 72 ± 8 years 89 patients with dementia	(mean dose 83 mg/day) Placebo Citalopram	4–8 weeks	GBS and MADRS	MADRS score significantly declined between baseline and week 4, however, there was no between group differences on MADRS improvement. CGI scores worsened in the placebo group, but remained unchanged in the citalopram group. Anxiety and depressed mood items of the GBS significantly improved in the citalopram group. Only depressed mood items of the GBS were significantly more improved in the citalopram group compared with the placebo group
Teri et al., 1991 [78]	Mean age: 77.6 years 65 patients with AD, mean age: 77.2 years (31 randomized to citalopram and 34 placebo) 24 patients with vascular dementia, mean age: 78.5 years (13 randomized to citalopram and 11 placebo) 61 patients with AD	(target dose 30 mg/day) Placebo Imipramine	8 weeks	MMSE, DRS, WMS, and FOM	There was no significant time by group effects on measures of MMSE, DRS, WMS, or FOME
Fuchs et al., 1993 [79]	28 patients had coexistent depression and dementia 13 patients randomized to imipramine, mean age: 76 ± 7 years 15 patients randomized to placebo, mean age: 71 ± 9 years 33 patients had dementia only 14 patients randomized to imipramine, mean age 68 ± 7 years 19 patients randomized to placebo, mean age 71 ± 8 years 127 patients with dementia and mild depression	Placebo Placebo Maprotiline	8 weeks	Video rating of global impression, MMSE, and GDS	Video ratings of global impression, cognitive impression and depressive impression were not significantly different between the treatment or placebo group. MMSE scores were not significantly different between treatment groups. GDS score improved significantly more in the maprotiline group in comparison with the placebo group
Petracca et al., 1996 [52]	(DSM-III-R), median age: 80 years (48–96 years) 64 patients randomized to maprotiline 63 patients randomized to placebo 24 depressed patients with AD	(25–75 mg/day) Placebo Clomipramine	14 weeks	HDRS, MMSE, and FIM	There was a significant time effect on HDRS scores, but participants taking clomipramine showed greater improvement during the first 6-week treatment period. Remission (HDRS ≤ 7) numbers were greater for participants that started on clomipramine compared with those that started on placebo. Significantly lower MMSE scores in the clomipramine group compared with placebo. No significant treatment effects on FIM scores
	11 patients randomized to intervention group, mean age: 71.5 ± 7.2 years	(target dose 100 mg/day)			

(Continued)

Table 1. (Continued).

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Roth et al., 1996 [77]	10 randomized to placebo, mean age: 72.4 ± 7.3 years 694 older patients with DSM-III diagnosis of dementia and/or of major depression	Placebo Moclobemide	6 weeks	HDRS, MMSE, SCAG, and BGP	Significantly greater mean improvements were seen in the moclobemide group compared with placebo on the HDRS, the cognitive disturbance items on SCAG, and MMSE at 6 weeks. Improvement in total SCAG score and BGP in the moclobemide group did not significantly differ to placebo
Magai et al., 2000 [65]	Mean age: 73.6 ± 8.4 years 511 patients with dementia with depressive symptoms (74.4 ± 8.5 years) 183 patients with depression and cognitive decline (71.4 ± 7.6 years) 368 patients randomized to moclobemide 358 patients randomized to placebo 31 female nursing home patients with late-stage AD	(400 mg/day) Placebo Sertraline	8 weeks	CSDD, GS, CMAI, FAST, MMSE, AFBS, and Facial behaviors	For all measures, there was a tendency for both Treatment and Placebo groups to improve over time, with significant Time effects noted for the CSDD, GS, and AFBS. There were no treatment by time interactions for CSDD, GS, CMAI and Facial behaviors ($p > 0.05$). The authors noted that the treatment by time interaction approached significance on the knit-brow face measure in favor of sertraline ($p < 0.10$)
Petracca et al., 2001 [47]	Mean age: years 89.2 ± 6.3 years 17 patients randomized to sertraline (88.4 ± 6.1 years) 14 patients randomized to placebo (90.1 ± 6.5 years) 41 patients with AD meeting DSM-IV criteria for major or minor depression	(target dose 100 mg/day) Placebo Fluoxetine	6 weeks	HDRS, MMSE, HAM-A, FIM, SCID, and CGI	HDRS, HAM-A, and FIM scores improved in both groups over time, however, there was no significant group effect or group by time interaction. MMSE scores showed no significant time, group or group by time interaction
Lyketos et al., 2003 (DIADS) [46]	17 patients for the intervention group, mean age 70.0 ± 6.3 years 24 patients for the placebo group, mean age 71.3 ± 6.9 years 44 patients with probable AD and major depressive episode	(target dose 40 mg/day) Placebo Sertraline	12 weeks	CSDD, HDRS, PDRS-ADL, MMSE, NPI total, NPI caregiver distress, EOWPVT-R, HVLT-R, WISC-R, and RBMT	Depression symptoms improved in the sertraline treatment group. Both CSDD and HDRS significantly differed between treatment groups in favor of the sertraline treatment. There were no treatment effects on measures of NPI total, NPI caregiver distress, PDRS-ADL and MMSE. There was no treatment effect on the slope of decline over time on any cognitive measures (EOWPVT-R, HVLT-R, WISC-R, and RBMT)
De Vasconcelos Cunha et al., 2007 [68]	24 for the intervention group, mean age: 75.5 ± 9.5 years 20 for the placebo group, mean age: 79.9 ± 5.2 years 31 mild or moderate dementia patients according to DSM-IV and depression 14 patients on intervention group, mean age: 77.67.3 years	(mean dose 95 mg/day) Placebo Venlafaxine	6 weeks	MADRS and CGI	Significant time effect observed in MADRS score. No significant treatment effect in MADRS score or CGI scores

(Continued)

Table 1. (Continued).

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Rosenberg et al., 2010 (DIADS-II) [58]	17 patients on placebo group, mean age: 77.6 ± 5.8 years 131 patients with AD and depression according to Olin criteria	Placebo Sertraline	24 weeks	moodADCS-CGIC, CSDD, NPI, ADRQL, ADCS-ADL, and MMSE	There were no significant differences on measures of moodADCS-CGIC and CSDD at 12 weeks between sertraline and placebo groups. There was no treatment effect on moodADCS-CGIC and CSDD scores at endpoint. NPI, ADRQL, ADCS-ADL, and MMSE change scores did not significantly differ between treatment groups. Sertraline treatment was not superior to placebo at 24 weeks on moodADCS-CGIC or CSDD in participants with major depression in dementia. No differences in between treatment groups for either outcome in those with minor depression or AD-associated affective disorder
Banerjee et al., 2011 (HTA-SADD) [57]	Median age: 79 years 52 (39.7%) met criteria for major depressive episode 54 (41.2%) for minor depressive episode 90 (68.7%) for AD-associated affective disorder 67 randomized to sertraline 64 randomized to placebo 326 patients with probable or possible AD and co-existing depression according to Olin criteria	(target dose 100 mg/day) Placebo Sertraline	39 weeks	MMSE, BADL, NPI, ZCBI, GHQ-12, SF-12 PCS, SF-12 MCS, CSDD, EQ5D life quality, and DEMQOL life quality	Improvement in CSDD was found in sertraline, mirtazapine and placebo groups between baseline and endpoint (significance not reported). At endpoint, no significant difference between placebo and sertraline or mirtazapine ($p > 0.05$): MMSE, BADL, NPI, DEMQOL, DEMQOL-proxy, self-rated EQ5D, proxy-rated EQ5D, ZCBI, GHQ-12, SF-12 PCS and SF-12 MCS. Sertraline and mirtazapine were not cost-effective versus placebo in reducing depressive symptoms using the CSDD. There was evidence, however, that mirtazapine may be cost-effective if considering wider outcomes including impact on caregivers and quality of life.
Bergh et al., 2012 (DESEP study) [45]	107 patients randomly allocated to receive sertraline; mean age: 79 years 108 patients randomly allocated to receive mirtazapine; mean age: 80 years 111 patients randomly allocated to receive placebo; mean age: 79 years 128 nursing home patients with: AD, VaD or mixed dementia and neuropsychiatric symptoms	(target dose 150 mg/day) Mirtazapine (target dose 45 mg/day) Placebo Treatment discontinuation: escitalopram, citalopram, sertraline, paroxetine.	25 weeks	CSDD, PSMS, patient QoL-AD, carer QoL-AD, CDR, SIB, and NPI	Compared with those that discontinued treatment, CSDD was significantly lower at 25 weeks. No significant difference was reported at 25 weeks between groups on measures of NPI (including psychosis, agitation and apathy clusters), PSMS, patient QoL-AD, carer QoL-AD, CDR or SIB
Mokhber et al., 2014 [75]	63 patients randomized to treatment discontinuation, mean age: 85.3 ± 8.2 years 68 patients randomized to treatment continuation, mean age: 86.1 ± 6.7 years 59 moderate AD patients with major depressive disorder	Sertraline	12 weeks	HDRS, MMSE, and Barthel index	In the sertraline group, the results of HDRS, MMSE and Barthel at week 12 showed significant improvements in comparison to the baseline. In the venlafaxine group, the results of MMSE and Barthel revealed significant improvements. In the desipramine group, there was a significant improvement only in the Barthel test at week 12

(Continued)

Table 1. (Continued).

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Leonpacher et al., 2016 [50]	Mean age: 67.6 ± 3.8 years Patients divided into three groups for each intervention	(maximum dose 150 mg/day) Venlafaxine (maximum dose 150 mg/day) Desipramine (maximum dose 150 mg/day) Psychosocial intervention	9 weeks	NBR5-A, ADCS-CGIC, CMAI, NPI total score, NPI caregiver distress, ADCS-ADL, and MMSE	The citalopram group showed significant improvement compared with placebo in the estimated difference scores of NBR5-A and ADCS-CGIC. Compared with placebo, citalopram was associated with improved scores on the CMAI, NPI total, NPI agitation, and NPI caregiver distress. A significant negative effect was reported in those receiving citalopram compared with placebo for MMSE scores. At week 9, participants treated with citalopram were significantly less likely to be reported as showing delusions, anxiety, and irritability/labability. At week 9, significant differences favoring citalopram for hallucinations and favoring placebo for sleep/nighttime behavior disorders were found
An et al., 2017 [74]	Mean age: 65 years and older 94 patients were randomized to receive a psychosocial intervention plus citalopram	plus citalopram (target dose 30 mg/day) Psychosocial intervention plus placebo Escitalopram	12 week	CSDD, GDS-15, ADAS-Cog, IADL, NPIQ, PSQI, MMSE, and CDRSB	At week 12, differences in measures of depression and cognition between the two groups were not statistically significant. However, exploratory analysis suggested that further research on a subset of subjects with 'definite major depression' (baseline CSDD score ≥18) is needed. The number of treatment-related adverse-events did not differ between groups and no serious treatment-related adverse-events were observed.
	Mean age intervention group 74.33 ± 7.47 years Mean age placebo group 75.85 ± 6.73 years	(maximum dosage of 15 mg/day) Placebo			

AD: Alzheimer's disease; ADAS-Cog Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS Alzheimer's Disease Cooperative Study; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living scale; ADCS-CGIC: Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; ADFACS: Alzheimer's Disease Functional Assessment and Change Scale; ADL: Alzheimer's Disease Related Quality of Life; AFBS: Aversive Feeding Behavior Scale; APA: American Psychiatric Association; BADL: Bristol Activities of Daily Living; BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale; BGP: rating scale for geriatric patients; BPRS: Brief Psychotic Rating Scale; BRSD: Behavioral Rating Scale for Dementia; CAMOG: Cambridge cognitive examination; CANTAB: Cambridge Neuropsychological Test Automated Battery; CBRSD: CERAD Behavior Rating Scale for Dementia; CDR: Clinical Dementia Rating Scale; CDRSB: Clinical Dementia Rating Scale sum of boxes; CGI: clinical global impression; CGI-GI: Clinical Global Impression—Global Impression; CGI-SI: Clinical Global Impression—Severity of Illness; CIBIC-plus: Clinician Interview-View-Based Impression of Change; CMAI: Cohen-Mansfield Agitation Inventory; CSDD: Cornell Scale for Depression in Dementia; CSI: Caregiver Stress Inventory; DIADS: Depression in Alzheimer's Disease Study; DRS: Dementia Rating Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; EOWPVT-R: Expressive One-Word Picture Vocabulary Test—Revised; FAST: Functional Assessment Staging; FBDS-WAIS: Forward and Backward Digit Span Task; FIM: Functional Independence Measure; FOME Fuld Object Memory Evaluation; GBS: Gottfrieds Brane Steen Scale; GDS: Geriatric Depression Scale; GHQ-12: General Health Questionnaire-12; GMHRS: General Medical Health Rating Scales; GS: Gestalt Scale; HAM-A: Hamilton Rating Anxiety Scale; HDRS: Hamilton Depression Rating Scale; HTA-SADD: Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia; HVL-T-R: The Hopkins Verbal Learning Test-Revised; IADL: Instrumental Activity of Daily Living; MADRS: Montgomery-Asberg Depression Rating Scale; MMSE: Mini-Mental State Examination; NIMH: National Institute of Mental Health; NINCDS/ADRDA: National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; NBR5: Neurobehavioral Rating Scale; NPI: Neuropsychiatric Inventory; OARS: Activity of daily living scale; PSM5: Lawton and Brody's Physical Self Maintenance Scale; PSQI: Pittsburgh Sleep Quality Index; QoL-AD: Quality of Life—Alzheimer's Disease Scale (patient version and carer version); RBMT: The Rivermead Behavioural Memory Test; SCAG: Sandoz Clinical Assessment—Geriatric Scale; SCID: Structured Clinical Interview for DSMIV; SF-12 PCS: Short Form-12 Physical Composite Scores; SF-12 MCS: Short Form-12 Mental Health Composite Scores; SIB: Severe Impairment Battery Scale; SSRI: Selective Serotonin Reuptake inhibitors; WISC: Wechsler Intelligence Scale for Children; WMS: Wechsler Memory Scale; ZCBI: Zarit Carer Burden Inventory.

the CSDD measure for the evaluation of depression in patients with dementia was weak [3,55]. More people in the treatment groups experienced an adverse event.

Two other systematic reviews and meta-analyses in people with depression and dementia were published in 2007 and 2011, respectively [56,57], but the number of trials included and the data provided in the RCTs limited these analyses. The first meta-analysis included 165 participants from five RCTs reporting a superior and statistically significant treatment response for antidepressants (imipramine, clomipramine, sertraline, and fluoxetine) compared with placebo [56]. People taking antidepressants were also more likely to achieve remission of their depressive episode. This review also included the number needed to treat (NNT) measure which is a clinically relevant format for presenting statistical information about an intervention to promote appropriate clinical decision making. The NNT of five for one additional AD patient to achieve remission of depressive symptoms was comparable to the NNT of between one and eight estimated for the treatment of depression in cognitively intact older individuals [56]. The other review and meta-analysis of seven RCTs with 330 subjects, all included in the previous meta-analysis [56], found that the odds ratio for six trials reporting treatment response rates with antidepressant and placebo confirmed the previous analysis [57].

Most of the current evidence on antidepressants in AD patients with depression come from two relatively large RCTs with data on long-term response [58,59], both substantially negative. (Table 1). Furthermore, in both trials, there were more adverse effects associated with active treatment than placebo [58,59] (Table 1). The first was the Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) trial conducted in 326 people with AD and depression [58], therefore the largest study of SSRI treatment for depression in dementia. This was a RCT with 13- and 39-week follow-up and participants were randomized to receive sertraline ($n = 107$, target dose 150 mg daily), mirtazapine, a noradrenergic and specific serotonergic antidepressant ($n = 108$, target dose 45 mg daily), or placebo ($n = 111$). Individuals included in this study met criteria for probable or possible AD and demonstrated co-existing depression based on a score of 8 or superior on the CSDD. The results of this RCT indicated that all three groups (sertraline, mirtazapine, and placebo) demonstrated a decreased severity of depression measured by CSDD score at 13 and 39 weeks of treatment compared with baseline. There was no difference, however, between sertraline versus placebo, mirtazapine versus placebo, or sertraline versus mirtazapine, indicating an absence of clinical efficacy of these antidepressants versus placebo [57]. In looking at secondary outcomes, including disease-specific health-related quality of life, generic quality of life, withdrawal from treatment, cognition (change in MMSE), behavior problems (NPI), and drug adherence, there were no differences between sertraline and placebo. Adverse reactions were more common in the sertraline group versus placebo with gastrointestinal reactions most common in the sertraline group. There was no difference in serious adverse events between the placebo group and the sertraline group [58].

The other RCT was a follow-up study (DIADS-2) including 135 people with AD [60] and depression and also failed to show

benefit of sertraline in comparison with placebo [59] (Table 1). The DIADS-2 was a RCT with 12 and 24-week follow-up [59–62]. Participants with mild-to-moderate AD and depression were randomized to receive sertraline ($n = 67$, target dose of 100 mg daily) or placebo ($n = 64$). There was no evidence for efficacy of sertraline versus placebo on mood outcomes (modified ADCS-CGIC and CSDD scores) or remission [59] (Table 1). In looking specifically at caregivers of participants enrolled in DIADS-2, it was found that treatment of participants with sertraline versus placebo did not significantly affect a number of outcomes for caregivers including depression (measured with the Beck Depression Inventory), distress (measured with the NPI-Distress), burden (measured with the Zarit Burden Interview), and quality of life (measured with the Medical Outcomes Study Short Form Health Survey) [63]. Using a number of cognitive measures including the MMSE, the cognitive subscale of the Alzheimer's Disease Assessment Scale, Digit Span Subtest, Letter Fluency, Symbol Digit Modalities Test, and finger-tapping test, it was found that sertraline treatment did not have any significant effect in terms of improvement or deterioration on any of the cognitive outcomes [64].

A subsequent review and meta-analysis specifically focusing on SSRI and serotonin-norepinephrine reuptake inhibitors (SRNI) treatment for depression in dementia was published in 2012 [65]. This review analyzed five different RCTs on SSRI treatment for depression in dementia: sertraline (DIADS) [46], fluoxetine [48], sertraline (HTA-SADD) [58], sertraline (DIADS-2) [59], and sertraline [66] (Table 1). Overall, the meta-analysis found non-significant effects for SSRI treatment on depression in dementia concluding that the evidence supporting use of SSRIs for depression in dementia appeared to be quite weak, with small responses in those with subsyndromal levels of depression [65]. In looking at the individual RCTs included in the meta-analysis, the small study by Magai and colleagues conducted in female nursing home patients with late-stage AD and depression, found no significant effect of sertraline versus placebo on depression in dementia as measured with the CSDD [66] (Table 1). An extension of the HTA-SADD trial above mentioned [57], looked at cost-effectiveness of using sertraline for treating depression in dementia [67]. This study found that sertraline and mirtazapine were not cost-effective versus placebo in reducing depressive symptoms using the CSDD. There was evidence, however, that mirtazapine may be cost-effective if considering wider outcomes including impact on caregivers and quality of life [67,68].

The dual antidepressant SRNI venlafaxine increases serotonin, norepinephrine, and dopamine neurotransmitters. A RCT tested the efficacy of the immediate-release venlafaxine (75 mg/day) against placebo for depression, as measured with MADRS in 31 outpatients meeting DSM-IV criteria for depression and dementia. No statistically significant differences in MADRS scores were found between drug and placebo groups [69] (Table 1). More recently, the 12-week randomized controlled trial DIADS-3 examined the safety of venlafaxine at a target dose of 225 mg daily for the treatment of depression in patients with AD, and it has ended on October 2017 (ClinicalTrials.gov Identifier: NCT01609348) [70]. Treatment would be considered efficacious if the proportion of worse categories is lower under treatment than under control on the ADCS-CGIC and improvements on the CSDD, as primary

outcomes. Furthermore, the RTC examine in a proof of concept, the safety of venlafaxine at a target dose, but no results are presently available. Moreover, a comprehensive review examined ten selected RCTs ($N = 1,646$) [71], and of these, the majority of trials that examined antidepressants in this patient group were of small sample size (six RCTs with $N < 100$), employed the HRSD to measure depression (six RCTs), included a treatment duration of six to eight weeks (seven RCTs), and four studies used sertraline as antidepressant. No difference between antidepressant and placebo was suggested in six of the ten selected RCTs [71].

Escitalopram is the active enantiomer of citalopram. Escitalopram was found to be efficacious and safe for the treatment of depressed AD at 8 weeks, in open-label study of Rao and colleagues, who used the NIMH consensus criteria for the diagnosis of depression in AD and a cut-off score in CSDD >7 [72]. Two RCTs about escitalopram in depression in AD and VaD were actually terminated [73] or completed [74] without published findings. A 12-Week RCT to evaluate the efficacy of escitalopram for the treatment of depression in AD was completed in July 2014. Change in CSDD from baseline after 12 weeks of between treatment groups was evaluated, but escitalopram was not significantly better than placebo in improving mood or cognition in dementia subjects with concurrent depressive symptoms [75] (Table 1). However, exploratory analysis suggested that further research on subjects with more severe depressive symptoms (i.e. definite major depression, baseline CSDD score ≥ 18) is needed.

More recently, Mokhber and colleagues completed a small, 12-week RCT comparing sertraline, venlafaxine, and desipramine in 59 individuals with AD [76] (Table 1). The DSM-IV criteria and a semi-structured interview by the study psychiatrist were used to diagnose major depressive disorder. Significant improvements in comparison to the baseline were found in all three outcome measures: HDRS, MMSE, and Barthel scale (a measure of function that rates variables of instrumental activities of daily living and mobility) only for sertraline compared with baseline. The small sample size, the absence of a placebo control group, and the utilization of a non-validated rating scale in this population make it difficult to draw firm conclusions from these data [76] (Table 1). Furthermore, the most recent comprehensive systematic review and meta-analysis pooled the status of recent RCTs for the pharmacological treatment of depression in AD [77]. This recent meta-analysis (6 RCTs, 297 patients treated with antidepressants and 223 with placebo) failed to show significant differences between antidepressants and placebo for response to treatment [77], although the analysis trended toward treatment response, with the smaller trials contributing a positive effect of antidepressants.

There are a number of older and generally smaller trials which have investigated TCAs and monoamine oxidase inhibitors [53,54,78,79] (Table 1). Fuchs and colleagues reported that the tetracyclic antidepressant maprotiline was significantly better at improving depression scores compared with placebo on the Geriatric Depression Scale (GDS), but with some methodological challenges [79] (Table 1). The quality of these studies reflects their age, in fact, the outcome measures used were not developed or validated for use in dementia. These RCTs often

did not meet the quality thresholds needed for inclusion in modern systematic reviews/meta-analyses. In particular, two RCTs explored the effects of imipramine on depression in dementia and found no benefit over placebo [54,80] (Table 1).

Therefore, at present, no clear pharmacological treatment algorithms for depression in AD and dementia exist. Emerging evidence on the neurobiological substrates of depression in AD has led to investigation of repositioned and novel antidepressant drugs in dementia as an alternative to classical antidepressant [81]. Idalopirdine, a serotonin 5-hydroxytryptamine-6 (5-HT₆) receptor antagonist, has cholinergic, glutamatergic, dopaminergic and noradrenergic properties and the potential to augment multiple neurotransmitter systems to improve cognition. Although two dosages of idalopirdine failed in a Phase III RCT on cognition of AD patients [82], a growing number of preclinical/clinical studies supported the use of 5-HT₆ receptor antagonism to treat not only cognitive dysfunction but also behavioral alterations in AD [19]. 5-HT₆ receptor antagonists have shown to induce antidepressant-like activity in rodents [83,84]. Systemic administration of the 5-HT₆ receptor antagonist produced a significant reduction in immobility time in the rat forced swimming test, with a similar profile in terms of 5-HT₆ receptor occupancy, measured by binding assay. These data suggest that 5-HT₆ antagonists, at doses corresponding to those that occupy central 5-HT₆ receptors, could have an antidepressant effect in humans. This may differentiate 5-HT₆ antagonists from acetylcholinesterase inhibitors (AChEIs) with respect to mood control in the symptomatic treatment of AD [85].

S47445 is a novel positive allosteric modulator of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. S47445 enhanced glutamate action at AMPA receptors on human and rat receptors and was inactive at NMDA and kainite receptors [86]. S47445 is being developed for the treatment of AD and depression. Efficacy and safety of three doses of S47445 versus placebo in 520 patients with AD at mild-to-moderate stages with depressive symptoms was ended in December 2017. A 24-week Phase II RCT in monotherapy was followed by an optional 28-week extension period in co-administration with donepezil. Biomarker ascertainment of the diagnosis was not required. The trial compared a six-month course of either 5, 15, or 50 mg of S47445 or placebo, taken once daily, against change on the Alzheimer's Disease Assessment Scale – cognitive subscale as a primary outcome. Secondary outcomes included a range of clinical measures of cognition, global function, vital signs, and depression. The trial found no significant differences between drug and placebo groups on the primary outcome or on secondary measures of daily function or depression for either of the three doses used. The drug did get into the cerebral spinal fluid (CSF), increased glutamate in the brain, and was safe, yet failed to show the desired benefit (ClinicalTrials.gov Identifier: NCT02626572) [87].

One RCT supported the potential usefulness of vortioxetine in the treatment of older depressed patients. Interestingly, the participants randomized to vortioxetine demonstrated a significant improvement in cognitive function (verbal memory and executive functioning) compared to those randomized

to placebo [88]. This finding extends to older patients similar findings reported in younger patients with major depressive disorder. However, despite a favorable recommendation of its Psychopharmacologic Drug Advisory Committee, the FDA has rejected a label expansion for vortioxetine with the claim of its specific effectiveness in the treatment of cognitive dysfunction in patients with major depressive disorder. Thus, it remains unclear to what extent vortioxetine may have an advantage over other antidepressants in this regard. The effect of vortioxetine on cognitive functions in older patients with mild cognitive impairment (MCI) or early dementia needs to be assessed with a broader neuropsychological test battery [89].

3. Clinical trials on other compounds for the treatment of depression in Alzheimer's disease

A series of open-label studies [90,91] and RCTs [92–95] (Table 2) with AChEIs have assessed depression response in AD patients. It has been well reported that SSRIs plus AChEIs treatment displayed protective effects on cognition of AD patients [91–94] (Table 2). Requena and colleagues examined the response to either donepezil alone/or in combination with a cognitive stimulation treatment in a group program in 86 individuals fulfilling criteria for AD. The combined treatment group achieved an overall better response than the only-drug group [90]. In the 28-week RCT of Gauthier and colleagues, significant differences for depression/dysphoria, anxiety, and apathy/indifference in the NPI were observed for the group treated with the AChEI donepezil [94] (Table 2). Other open-label studies [96,97] and one RCT [98] (Table 2) found only a transient improvement of depressive symptoms. Finally, some open-label studies with the AChEI rivastigmine reported stabilization on behavior parameters, whereas depressive symptoms worsened slightly after initial treatment or did not improve [99,100].

Few studies have tested the use of mood stabilizers as a treatment for depressive symptoms in dementia. Lithium has been shown to inhibit the activity of glycogen synthase kinase-3 (GSK-3), which is considered as a mediator of AD-related hyperphosphorylation of tau, forming paired helical filaments and neurofibrillary tangles [101]. Therefore, lithium has been suggested to have potential therapeutic effects in AD. A 10-week RCT on lithium was conducted in a sample of 71 AD patients, but depression/dysphoria NPI subscores did not show a significant change, neither on CSF-based biomarker concentrations [102] (Table 2). In a RCT of tideglusib, another GSK-3 inhibitor, del Ser and colleagues evaluated its safety and tolerability as the primary outcomes and its effects on cognition and depressive state (15-item GDS) as secondary outcomes in 30 mild-to-moderate AD patients, who were already on a AChEI treatment. Although treatment was well tolerated, tideglusib did not produce statistical significant improvement in GDS scores after 20 weeks [103] (Table 2). There are also limited data available for the role of carbamazepine in treating NPS in AD also because of its side effects. Tariot and colleagues reported some benefit for carbamazepine compared with placebo in a small 6-week RCT ($n = 51$) on the scores of the Brief Psychiatric Rating Scale (which includes

items measuring emotional withdrawal and depressive mood) and clinical global impression [104] (Table 2).

Aripiprazole is the first developed antipsychotic agent that is a partial dopamine D2 receptor agonist, as well as a serotonin 5HT2A receptor antagonist and a 5HT1A receptor partial agonist. In a RCT conducted in 131 institutionalized individuals with AD and psychotic symptoms, aripiprazole demonstrated improvement in CSDD scale among other secondary measures [105] (Table 2). The primary outcome measures were the NPI-Nursing Home Version and the Clinical Global Impression-Severity of illness (CGI-SI). However, aripiprazole is not approved to treat dementia-related NPS and has received a FDA “black box” warning.

Methylphenidate is a dopamine and norepinephrine uptake inhibitor and dopamine releaser. Padala and colleagues conducted a 12-week RCT with methylphenidate, which was titrated to 10 mg twice daily within 2 weeks, in a sample of 60 veterans with AD that met the DSM-IV-TR criteria for AD [106] (Table 2). In this study, the Apathy Evaluation Scale was the primary outcome measure. However, significant improvement in depression was reported at 12-week assessments over baseline, which was measured with CSDD [106] (Table 2).

Sparks and colleagues conducted a pilot RCT with a 1-year exposure to once-daily atorvastatin calcium (80 mg; two 40-mg tablets) or placebo [107] (Table 2). An analysis design conducted in 63 subjects, pre-post treatment difference in GDS scores was found to be significant. In addition to the primary mechanism of action, the antidepressant effect may have been related to secondary mechanisms of action including anti-inflammatory or vascular effects.

The role of estrogens in improving depressive symptoms of AD patients seems to be controversial. It has been found that the apolipoprotein E (APOE) $\epsilon 4$ -negative genotype may mediate positive mood effects, resulted by the AChEI tacrine [108]. This is not true for hormone replacement therapy (HRT) administration. However, different patterns of depression response to HRT, measured with different scales, are more likely to occur when the APOE genotypes are taken into account [109,110] (Table 2), probably for the reported gender differences existing in explaining the effect of this genotype in older age [111].

Nimodipine is a calcium channel blocker, clinically used mainly as an antihypertensive. In a multicenter RCT, 90 mg of nimodipine were administered orally for 12 weeks (after a 2 weeks initiate placebo washout treatment period) in 178 patients who suffered from primary degenerative or multi-infarct dementia (DSM-III criteria). Nimodipine was found to be significantly superior to placebo in the total HDRS score [112] (Table 2). Moreover, Loeb and colleagues examined whether the antibiotics doxycycline and rifampin had a therapeutic effect in 101 AD patients, since chronic chlamydia pneumoniae infection has been suggested to play a role in AD pathology, but there were no significant differences in GDS scores between groups at 3, 6, and 12-month assessments [113] (Table 2). Similarly, Molloy and colleagues reported no statistically significant changes in depression scores as measured with CSDD and GDS in a 12 month follow-up [114] (Table 2).

Deficiencies of folate and vitamin B12, necessary co-factors in the synthesis of S-adenosyl methionine (S-AdoMet), may account

Table 2. Principal randomized clinical trials evaluating the efficacy of pharmacological intervention of compounds different from antidepressants in the treatment of depressive disorders in Alzheimer’s disease.

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Ban et al., 1990 [111]	178 patients with AD or multi-infarct dementia and mild to moderately severe cognitive decline according to DSM-III	Nimodipine Placebo	12 weeks	WMS, MMSE, Global Deterioration Scale, SCAG,	The superiority of nimodipine over placebo was consistently seen in all dimensional measures, based on rating scale scores, and categorical proportions, based on the number of patients showing improvement. It was also consistently reflected in favorable changes in psychopathology (HDRS), performance (WMS), social behavior (PLUTCHI) and overall impression (CGI-SI). Diagnosis, severity of cognitive decline, age and sex had no effect on treatment response
Tariot et al., 1998 [103]	Median age: 75.4 (9.6) years 89 patients were assigned to the nimodipine group 89 patients were assigned to placebo 51 nursing home patients with agitation and dementia	(90 mg/daily) Placebo Carbamazepine	6 weeks	PLUTCHI, CGI-GI, CGI-SI, and HDRS BPRS, CGI-GI, and MMSE	Over 6 weeks the mean total BPRS score decreased for the carbamazepine group rather than placebo group, and the weekly scores showed a gradual divergence between the two groups. CGI-GI ratings showed global improvement in 77% of the patients taking carbamazepine and 21% of those taking placebo. Secondary analyses confirmed that the positive changes were due to decreased agitation and aggression. The drug was generally well tolerated, and no change in cognition or functional status occurred. The perception of staff time needed to manage agitation showed a decrease for carbamazepine but not placebo
Gauthier et al., 2002 [94]	Mean age: 86.0 ± 6.4 years 27 patients randomized to the intervention group 24 patients randomized to the placebo group 290 patients with moderate to severe AD	(mean dosage 300 mg; serum level of 5–8 µg/ml was maintained) Placebo Donepezil	24 weeks	NPI	NPI individual item change from baseline scores at week 24 using a last observation carried forward analysis showed benefits with donepezil treatment compared with placebo for all items, with significant treatment differences for depression/dysphoria, anxiety, and apathy/indifference
Moretti et al., 2002 [91]	144 patients randomized in intervention group, mean age: 73.3 years 146 patients in the placebo group, mean age: 74.0 years 50 patients with a diagnosis of probable AD	(5 mg for 28 days and 10 mg thereafter) Placebo AChEIs plus citalopram	48 weeks	MMSE, RSS, NPI, HDRS, TPC, WF, and IADL	MMSE significantly declined from baseline in both treatment groups, however, TPC, WFs, Wfp and IADL scores remained unchanged. RSS, NPI and HDRS scores significantly improved between baseline and endpoint. Only RSS, NPI and HDRS scores were significantly lower in citalopram plus AChEI group compared with AChEI only group at endpoint
	Age range: 68 to 76 years 25 patients randomized to citalopram 25 patients randomized to AchEIs alone	(target dose 20 mg/day) AChEIs			

(Continued)

Table 2. (Continued).

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Finkel et al., 2004 [92]	Outpatients with diagnostic evidence of probable or possible AD, according to NINCDS/ADRDA criteria.	Donepezil plus sertraline	12 weeks	NPI, ADAS-cog, BEHAVE-AD, CGI-GI, CGI-SI, CDR, HDRS, ADFACS, CMAI, CBQ, and MMSE	Change scores between baseline and endpoint were not significantly different between treatment groups on NPI, ADAS-COG, BEHAVE-AD, CGI-GI, CGI-SI, CDR, HDRS, ADFACS, CMAI, CBQ or MMSE. For the CGI-GI, a significant treatment by time interaction was reported on the linear mixed model
Loeb et al., 2004 [112]	124 patients randomized to donepezil + sertraline, mean age: 75.7 ± 7.7 years 120 patients randomized to donepezil + placebo, mean age: 76.9 ± 7.4 years 101 patients with probable AD and mild to moderate dementia according to NINCDS-ADRDA criteria 51 patients randomized to doxycycline, mean age: 75 ± 9.2 years 50 patients randomized to placebo, mean age: 76 ± 6.6 years 50 female patients with mild-to-moderate AD	(50–200 mg/day) Donepezil plus placebo Daily doses of doxycycline 200 mg and rifampin 300 mg	12 months	ADAS-cog, DBRI, ADL, GDS-30, MMSE IgG and IgA chlamydia pneumoniae	There was significantly less decline in the ADAS-cog score at 6 months in the antibiotic group than in the placebo group. At 12 months, the difference between groups in the ADAS-cog was –4.31 points. The antibiotic group showed significantly less dysfunctional behavior at 3 months. There were no significant differences between groups at 3, 6, or 12 months in MMSE, DBRI ADL, or GDS Scores. There was no significant difference in adverse events between groups. There were no differences in chlamydia pneumoniae detection using polymerase chain reaction or antibodies (immunoglobulin (IgG or IgA) between groups
Wang et al., 2005	25 patients randomized in the intervention group, mean age: 72.6 ± 9.1 years 25 patients randomized in the placebo group, mean age 71.0 ± 9.1 years	Estrogen treated group (Premarin, 1.25 mg/day) Placebo group	12 weeks	CASI, CDR, CIBIC-plus, BEHAVE-AD, HAM-A, and HDRS ^{99mTc} hexamethylpropylene amine oxime SPECT of the brain	No meaningful differences were found between the outcome measures (CASI, CDR, CIBIC-plus, BEHAVE-AD, HARS, HDRS, and cerebral blood flow) taken from the estrogen-treated group and those from the control group. The estrogen group had greater but nonsignificant improvements in the HDRS and HAM-A scores at the end of the study. No intergroup difference was noted in the BEHAVE-AD score
Sparks et al., 2005 [106]	98 mild-to-moderate AD patients	Atorvastatin calcium (80 mg; two 40-mg tablets)	12 months	ADAS-cog, CGI-SI, NPI GDS, and ADL	Atorvastatin reduced circulating cholesterol levels and produced a positive signal on each of the clinical outcome measures compared with placebo. This beneficial effect reached significance for the GDS and the ADAS-cog at 6 months and was significant at the level of a trend for the ADAS-cog, CGI-SI, and NPI at 12 months assessed by analysis of covariance with last observation carried forward

(Continued)

Table 2. (Continued).

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Cummings et al., 2006 [97]	31 patients randomized to the placebo group, mean age: 78.9 ± 1.2 years 120 outpatients, who met diagnostic criteria for probable or possible AD using the criteria of the NINCDS/ADRDA	placebo Donepezil 10 mg plus sertraline	8–12 weeks	NPI-12 total score, BEHAVE-AD total score, HDRS, MMSE, CMAI-C, and CGI-SI	The total score of the NPI was significantly reduced over the 20 weeks of therapy with donepezil. Sixty-two percent of patients had at least a 30% reduction in the total NPI score. More patients had total or partial resolution of depression and delusions than those who had no meaningful change. Factor analysis of baseline NPI data revealed five factors, including a psychosis factor, an agitation factor, mood factor, frontal lobe function factor, and appetite and eating disorders factor. Clinically meaningful treatment effect sizes were notable for the delusion factor and the mood factor. There were significant correlations between the CGI improvement and reductions in mood and agitation scores
Mowla et al., 2007 [93]	Mean age: 76.3 years 122 patients with mild-to-moderate AD	Donepezil 10 mg plus placebo After the 8-week open-label treatment of donepezil, all patients who continued were randomly assigned to 12 weeks of double-blind treatment with either sertraline or placebo Rivastigmine plus fluoxetine	12 weeks	MMSE, WMS, ADL, HDRS, and CGI	Those receiving fluoxetine reported a significant improvement in MMSE, WMS, ADL, and HDRS from baseline to endpoint. The MMSE, WMS, and ADL change scores were all significantly improved in the fluoxetine group compared with the placebo group. CGI scores were significantly better in the fluoxetine group compared with the placebo group
Streim et al., 2008 [104]	Mean age: 69.2 years 41 patients randomized in the rivastigmine group, 41 patients randomized in fluoxetine plus rivastigmine group 40 patients randomized in placebo group 256 institutionalized patients with AD and psychotic symptoms (DSM-IV criteria)	(20 mg/day) Rivastigmine Placebo Aripiprazole	10 weeks	NPI-Nursing Home-Psychosis subscale, CGI-SI BPRS, CMAI, ADL, and CDSS	No significant differences in mean change from baseline between aripiprazole (mean dose 9 mg/day at endpoint) and placebo were detected in the efficacy endpoints of NPI Nursing Home-Psychosis subscale and CGI-SI at endpoint. However, improvements in several secondary efficacy measures (NPI- Nursing Home Total, BPRS, CGI, CMAI and CDSS) indicated that aripiprazole may confer clinical benefits beyond the primary outcome measures. Treatment-emergent adverse events were similar in both groups, except for mild-to-moderate somnolence with aripiprazole was of mild or moderate intensity, and not associated with accidental injury. Incidence of adverse events related to extrapyramidal symptoms was low with aripiprazole (5%) and placebo (4%)
	131 patients were randomized to aripiprazole, mean age: 83.0 years 125 patients were randomized to placebo, mean age: 83.0 years	(5, 10, and 15 mg/day) Placebo			

(Continued)

Table 2. (Continued).

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Hampel et al., 2009 [101]	71 patients with mild AD according to NINCDS-ADRDA criteria	Lithium	10 weeks	CSF levels of phosphorylated tau and GSK-3 activity in lymphocytes ADAS-Cog, MMSE, and NPI	No treatment effect on GSK-3 activity or CSF-based biomarker concentrations was observed. Lithium treatment did not lead to change in global cognitive performance as measured by the ADAS-Cog subscale or in depressive symptoms. Presence of depressive symptoms as measured by the depression/dysphoria subscore of the NPI changed neither in the lithium group nor in the placebo group
Valen-	33 patients randomized to intervention group, mean age: 68.2 (7.2) years 38 to placebo group, mean age: 68.9 (8.3) years	(serum level 0.5–0.8 mmol/L) Placebo	12 months		CDR, CERAD, Global Deterioration Scale, Barthel Index, and ADL Stratification by APOE genotype
Valen-	Sengstad et al., 2010	65 female patients with probable AD according to DSM-III	17β-estradiol and norethisterone HT		
Molloy et al., 2012 [113]	Nonsignificant differences between treatment groups for all efficacy variables were found. A linear model analysis, including stratifying factors in addition to treatment in the model, revealed a significant main effect on mood. The depressive symptoms were lower in the HT group than in the placebo group. Those in the HT group with a higher level of education obtained a better Global Deterioration Scale score. Those treated with HT without the APOE 4 allele had better mood				
Molloy et al., 2012 [113]	29 patients randomized to HT, mean age: 81.0 ± 5.7 years 26 patients randomized to placebo, mean age: 81.0 ± 4.5 years	(1 mg of estradiol and 0.5 mg of norethisterone/daily) Placebo	12 months	ADAS-cog, CDR-SB, MMSE, GDS, CSDD, and ADL	There was a significant deterioration in ADAS-cog over time with both rifampin and doxycycline in comparison with placebo. When the two drugs were used together, there was no statistically significant decline/deterioration in comparison with placebo. For the CDR-SB, there were no significant effects of either rifampin or doxycycline. Secondary outcome results followed similar patterns
Molloy et al., 2012 [113]	410 AD patients according to NINCDS-ADRDA criteria	Doxycycline 100 mg	12 months		
Molloy et al., 2012 [113]	101 patients randomized to rifampin, mean age: 78.6 (73.5–82.3) years	twice daily plus rifampin 300 mg daily			
Molloy et al., 2012 [113]	102 patients randomized to doxycycline, mean age: 78.7 (74.1–83.6) years	Doxycycline 100 mg twice daily plus placebo-rifampin daily			
Molloy et al., 2012 [113]	101 patients randomized to Rifampin and Doxycycline, mean age: 79.2 (74.4–83.5) years	Rifampin 300 mg daily plus placebo-doxycycline twice daily			

(Continued)

Table 2. (Continued).

Reference	Study sample	Treatment condition	Duration	Depression-related outcomes and assessment	Principal results
Del Ser et al., 2013 [102]	102 patients randomized to placebo, mean age: 78.6 (72.4–83.0) years Thirty mild to moderate AD patients, complying with NINCDS-ADRDA criteria of probable AD, 60 to 85 years old 20 subjects randomized to tideglusib; mean age: 73.1 (7.4) 10 randomized to placebo; mean age 72.6 (5.4)	Placebo-doxycline twice daily plus placebo-rifampin daily Tideglusib (400, 600, 800, and 1,000 mg) Placebo	20 weeks	MMSE, GDS, ADAS-cog, and CGA	Tideglusib produced positive trends in MMSE, ADAS-cog, GDS, and GCA without statistical significance in this small sample. Responders in MMSE were significantly higher in the active group. Patients escalated up to 1000 mg/day had a benefit of 1.68 points in the MMSE and 4.72 points in the ADAS-cog when compared to placebo
Padala et al., 2018 [105]	60 community-dwelling men veterans with mild AD according to DSM-IV criteria Mean age: 77 years 30 randomized participants to intervention group 30 randomized participants to placebo	Methylphenidate (10 mg twice daily) Placebo	12 weeks	MMSE, ADL, IADL, NPI, CGI-SI, AES, CSDD, and ZBS	After adjusting for baseline, the methylphenidate group had significantly greater improvement in apathy than the placebo group at 4 weeks, 8 weeks, and 12 weeks. At 12 weeks, there was also greater improvement in cognition, functional status, caregiver burden, CGI scores, and depression in the methylphenidate group compared with the placebo group.

ABID: Agitated Behavior in Dementia Scale; AChEIs: acetylcholinesterase inhibitors; AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale—cognitive subscale; ADCS: Alzheimer's Disease Cooperative Study; ADFACS: Alzheimer's Disease Functional Assessment and Change Scale; ADRQL: Alzheimer's Disease Related Quality of Life; AES: Apathy Evaluation Scale—Clinician; APOE: apolipoprotein E; BADL: Bristol Activities of Daily Living; BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale; BPRS: Brief Psychotic Rating Scale; BRSD: Behavioral Rating Scale for Dementia; CASI: Cognitive Ability Screening Instrument; CBI: Caregiver Burden Inventory; CBQ: Caregiver Burden Questionnaire; CBRSD: CERAD Behavior Rating Scale for Dementia; CDR: Clinical Dementia Rating Scale; CDRSB: Clinical Dementia Rating Scale sum of boxes; CGI: clinical global impression; CGI-GI: Clinical Global Impression—Global Improvement; CGI-SI: Clinical Global Impression—Severity of Illness; CIBIC-plus: Clinician Interview-Based Impression of Change; CMAI: Cohen–Mansfield Agitation Inventory; CSDD: Cornell Scale for Depression in Dementia; CSI: Caregiver Stress Inventory; CSF: cerebrospinal fluid; DBRI: Dysfunctional Behavior Rating Instrument; DRS: The Dementia Rating Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; FAST: Clinical Developmental Stage of Dementia; FBDS-WAIS: Forward and Backward Digit Span task; FIM: Functional Independence Measure; GBS: Gottfrids Brane Steen Scale; GDS: Geriatric Depression Scale; GHQ-12: General Health Questionnaire-12; GMHBS: General Medical Health Rating Scales; GSK-3: glycogen synthase kinase-3; HAM-A: Hamilton Rating Anxiety Scale; HDRS: Hamilton Depression Rating Scale; HT: hormone therapy; IADL: Instrumental Activity of Daily Living; IDDD: interview for deterioration in daily living activities in dementia; MADRS: Montgomery–Asberg Depression Rating Scale; MMSE: Mini-Mental State Examination; NINCDS/ADRDA: National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; NBRs: Neurobehavioral Rating Scale; NPI: Neuropsychiatric Inventory; PSMs: Lawton and Brody's Physical Self Maintenance Scale; PSQI: Pittsburgh Sleep Quality Index; PLUTCHI: Plutchik Geriatric Rating Scale; QoL-AD: Quality of Life—Alzheimer's Disease Scale; RBMT: The Rivermead Behavioural Memory Test; RMBPC: Revised Memory and Behavior Problems Checklist; RSS: Relative Stress Scale; SCAG: Sandoz Clinical Assessment—Geriatric Scale; SSRI: Selective Serotonin Reuptake Inhibitors; TPC: Ten Point Clock; WF: Word fluency; WISC: Wechsler Intelligence Scale for Children; WMS: Wechsler Memory Scale; ZBS: Zarit Carer Burden Scale.

for decreased SAME levels, especially in patients with depression and dementia. Some studies have shown that with either oral or parenteral treatment, SAME crosses the blood-brain barrier and increases CSF levels, including in patients with neuropsychiatric conditions. SAME deficiency in CSF has been reported in patients with rare inherited defects in folate and methionine metabolism [115,116] as well as in more common diseases such as depressive disorders, AD, and Parkinson's disease, suggesting a possible disturbance of methylation in such patients and the need for trials of SAM treatment [117].

4. Pharmacogenetic factors

The management of depressive symptoms and/or the response to psychotropic drugs should be driven by pharmacogenetic factors, including pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes, but few studies have been conducted on the pharmacogenetic factors influencing depression in AD [118,119]. Pharmacogenetic data fingerprint the pharmacological treatment of neuropsychiatric late-life conditions throughout the analysis of metabolizing enzymes and transporters of psychotropic drugs, mainly those of the cytochrome P450 (CYP) family. Pharmacodynamic response measures as treatment effects mediated through targets (i.e. 5HT receptors) may also contribute to this image [120]. The tendency of older people to develop therapeutic failure to psychoactive medications is often due to physiological pharmacokinetics and pharmacodynamics changes associated with aging and comorbidity. Multiple allele variants of the CYP2D6, CYP2C19, CYP2C9 and CYP3A4/5 genes have been identified and were associated with a range of enzymatic activities influencing the metabolizer phenotype observed in clinical practice, making it the first candidate for a genetic analysis, in particular in patients with neuropsychiatric illnesses such as depressive disorders [120].

5. Conclusions

The findings of the present reviewed RCTs raised the possibility that the etiology of symptoms of depression in individuals with dementia may be fundamentally different than the etiology of symptoms of depression in individuals without dementia, maybe as a consequence damage and neuronal loss of the dementia process [121]. On the other hand, there is a need for further well designed multicenter RCTs which adhere to high standards of methodology and reporting and include diagnostically homogenous populations and large samples. The lack of a clear body of evidence makes it difficult to use the available findings to inform evidence-based policy about whether antidepressants are effective in treating depression in people with AD. Regarding classical antidepressant medications, sertraline was the one most frequently studied in RCTs. An alternative hypothesis to underlined deficits in monoamine and cholinergic neurotransmitters, includes dysfunction in glutamatergic transmission. Furthermore, a substantial body of evidence suggested the involvement in shared NMDA-regulated signaling pathways in depression and AD and a possible overlap of disease neurobiology. Although the RTC with the new

glutamatergic agent S47445 had a failure, the add-on with donepezil is ongoing. Coherently with this line of thought, newer data suggest that the antidepressant effect of ketamine may be due to the effect of one of its metabolites, i.e. hydroxynorketamine (HNK), that does not bind to NMDA receptors, but increases the level of the AMPAR protein receptor [122]. However, in the absence of relevant data to late-life depression, it is not clear whether older patients would benefit similarly to younger ones. Instead, the new multimodal antidepressant vortioxetine appeared to be promising, particularly in depression with MCI. Future longitudinal studies should be conducted in late-life depression and MCI patients with a 'defective' genotype of TGF- β 1 gene to assess whether antidepressant drugs, such as fluoxetine, can exert a disease-modifying activity and delay cognitive decline in preclinical AD by rescuing of TGF- β 1 signaling [35]. In conclusion, further well-powered RCTs are needed before significant changes in current clinical practice may be introduced.

6. Expert opinion

Personalized medicine, that is, diagnosis and therapy based on an individual's unique genetic, phenotypic and environmental exposure [123] could be the future of psychiatric medical practice. Therefore, there is a call for further research in identifying biomarkers [124] and treatments for depression in AD extent beyond the monoaminergic hypothesis [20].

Theoretical constructs of depression and other NPS in neurodegenerative disorders, along with instruments for their measurement, continue to evolve with methodological implications [81]. Very recently, the NPS Professional Interest Area of the International Society to Advance Alzheimer Research and Treatment (ISTAART) proposed research diagnostic criteria for mild behavioral impairment (MBI), as an extension of the preexisting MBI construct to include, but not mandate cognitive impairment, including MCI in the MBI framework [125] and depressive symptoms could be considered a MBI [126]. Practice guideline update summary for MCI recommend that clinicians should evaluate patients with MCI for modifiable risk factors, assess for functional impairment, and assess for and treat behavioral/neuropsychiatric symptoms such as depression (Level B) [127]. At present, consensus guidelines from medical organizations and working group statements recommended non-pharmacological approaches and watchful waiting be attempted for the first 8 to 12 weeks in a patient who presents with both mild-to-moderate depression and dementia as first-line treatment, except in emergency situations where these symptoms may lead to imminent danger to patients and/or requiring hospitalization [128–131].

In the next future, considering genetic background may be also important and recent studies showed that genotyping may boost antidepressant treatment success in AD [132]. Receptor and transporter-encoding gene variations can act, alone or in combination, with other genetic or molecular factors in altering depression response in general and particularly in the presence of AD pathology. Gene polymorphisms may modulate mood [133] and antidepressant action [134] as

well as interfere with pathogenic proteins and molecular processes (genes, receptors, transmitters, enzymes, neural processing cascades) [120] implicated in AD. A significant association was found between the APOE $\epsilon 4$ allele and an increase in agitation/aggression, hallucinations, delusions, and late-life depression in AD [135], suggesting a possible role of genetic factors also in RCTs designed for the treatment of depression in dementia and AD [109–111]. Therefore, of particular interest in dementia is APOE polymorphism in terms of behavior, mood and therapeutic response to conventional treatments, either anti-dementia drugs or psychotropic drugs [135]. Pioneering pharmacogenomic studies also demonstrated that the therapeutic response in AD is genotype-specific, with APOE $\epsilon 4$ carriers as the worst responders to conventional treatments [118].

In the past frame of DIADS, gene variations on 5HT2A and 2C receptors, 5HTT-LPR serotonin transporter and brain-derived neurotrophic factor revealed no influence on sertraline response [136], regardless depression severity [62]. Although the controversial cost-effectiveness of genotyping, tests for structural variants in the genes for CYP isoenzymes and for polymorphisms of neurotransmitter transporters and receptors may identify individuals with a greater or lesser likelihood of responding to psychotropic medications [120]. It seems that knowledge of certain genetic variants associated with drug metabolism aids in the prediction of the response to antidepressant treatment and the remission of symptoms, thus contributing to an improvement in the management of the disease.

Funding

This manuscript has not been funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Giancarlo Logrosino  <http://orcid.org/0000-0003-0423-3242>

Francesco Panza  <http://orcid.org/0000-0002-7220-0656>

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