Review Article

Anti-dementia drugs: what is the evidence in advanced stages?

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Abstract Dementia is a major public health concern due to its increasing prevalence, substantial caregiver burden, and high financial costs. Currently, the anti-dementia drugs aim only at a symptomatic effect. The subject of prescribing these drugs in advanced stages is a matter of considerable debate, with different countries making distinct recommendations. In this review article, we analyzed the evidence regarding cognitive and functional outcomes, adverse events, health-related costs, and caregiver burden in patients with advanced Alzheimer disease (AD) and mixed dementia. We included 35 studies. Most studies are heterogeneous, focus exclusively on AD, and show small benefits in terms of cognitive and functional scales. The overall evidence seems to suggest a benefit in introducing or maintaining anti-dementia drugs in patients with advanced dementia, but clinical meaningfulness is difficult to ascertain. The issue of costs and caregiver burden is significantly underexplored in this field but also seems to favor treatment continuation, despite a reduced overall effect. The decision of introducing or withdrawing anti-dementia drugs in advanced stages of dementia should be individualized. Future studies with homogeneous designs and outcomes are warranted.

Keywords: dementia, Alzheimer disease, cholinesterase inhibitors, memantine, deprescription

Introduction

Dementia is a complex syndrome leading to a progressive and persistent deterioration of higher mental functions, severe enough to interfere with independent daily living. It has multiple etiologies. Alzheimer disease (AD), vascular cognitive impairment, and mixed forms (copathology of AD and vascular lesions) are the most prevalent subtypes of dementia.[1]

Independent of its etiology, dementia is a leading cause of disability in the world. The number of people with dementia is increasing related to an aging population.[2] In 2015, it was estimated that nearly 50 million people in the world had dementia, and this number is expected to increase to 150 million by 2050.[3]

The loss of autonomy and independence affects individuals, their families, and caregivers and places a significant strain on society, health care, and the economy, with costs averaging higher than those of cancer and heart disease combined.[4]

Despite extensive investigative efforts and various pharmacological approaches to different therapeutic targets, particularly in the field of AD, the primary therapeutic options currently used have remained largely unchanged.[5] Existing treatments for AD include symptomatic strategies, such as cholinesterase inhibitors (ChEIs) (donepezil, rivastigmine, and galantamine) and memantine. They are licensed for AD dementia, meaning they are not approved for prescription in very early cognitive impairment or presymptomatic stages, where functionality and autonomy are preserved.[6] ChEIs are approved for all stages of dementia while memantine is approved for moderate-to-severe stages of dementia. Their actions on the symptoms of dementia are modest.[7] For example, donepezil 10 mg shows an improvement of 2–3 points in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog, a 70-point scale) and approximately 1 point in the Mini-Mental State Examination (MMSE, a 30-point scale) at 3, 6, and 12 months of use. Its effects in daily living and global assessment are mild compared with placebo.[8] Even though its effect has also been established in severe dementia, its magnitude is within the same range.[7] This raises the question of whether these results are clinically meaningful and whether anti-dementia drugs should be discontinued at a certain point, particularly in severe stages. This decision is usually performed on an individual basis, considering the well-being of the patient and the families or caregivers' opinions.

The evidence regarding the effect of anti-dementia drugs in advanced stages of dementia is limited for several reasons. First, there is no universal definition of "advanced dementia." This may encompass individuals with very low scores in the MMSE, who may be dependent for most activities of daily living, but who can still recognize and interact with family members. At the same time, it can include people who are bedridden and approaching end of life. Second, the parameters used to quantify effect may not be sensitive enough or clinically meaningful on an individual basis, for example, cognitive scales in people with significant

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Table 1

Main findings available in the literature regarding cognitive and functional outcomes in patients with advanced dementia.

Author	Methodology and follow-up	Population	n	Anti-dementia drug evaluation	Dementia stage	Main result
Howard et al (2012)[11]	RCT; 52 weeks	Community-dwelling patients with AD	295	Donepezil or placebo ± memantine or placebo	Moderate-to-severe (MMSE score 5–13, mean = 9)	Donepezil was superior to placebo in MMSE (1.9 [1.3–2.5]) and BALDS (3.0 [1.8–4.3]). Memantine was superior to placebo in MMSE (1.2 [0.6–1.8]) and BALDS (1.5 [0.3–2.8]). No benefit in combined therapy.
Yun Jeong Hong et al (2018)[27]	RCT; 12 weeks	Community-dwelling patients AD	65	Discontinuation of donepezil or memantine	Severe (MMSE score 0–5; mean = 1)	No differences in changes from baseline on MMSE, CGIC, CDR-SB, NPI, ADCS-ADL, BI, or FAST. Patients assigned to discontinue therapy showed a better performance in BPMSE score (improvement of 0.4 pts [1.9] vs. decrease of 0.4 pts [3,0]).
Bullock et al (2005)[34]	RCT; 2 years	Community-dwelling patients with AD	994	Rivastigmine vs donepezil	Moderate-to-severe (MMSE score 10–20; mean = 15)	No difference between donepezil and rivastigmine.
Winblad et al (2006)[12]	RCT; 6 months	Nursing facility patients with AD	249	Donepezil vs placebo	Severe (MMSE score 1–10; mean = 6)	Donepezil was superior to placebo in SIB (LSMD 5.7 [1.5–9.8]), ADCS-ADL-severe (LSMD 1.7 [0.2 – 3.2]), and MMSE (LSMD 1.4 [0.4–2.4]) scores. No difference in NPI.
Black et al (2007)[13]	RCT; 24 weeks	Community-dwelling patients with AD	343	Donepezil vs placebo	Severe (MMSE score 1–12)	Donepezil was superior to placebo in MMSE (LSMCB 0.65 [0.27] vs. −0.03 [0.28]), SIB (LSMCB 0.19 [0.97] vs. −5.13[1.01]), and CIBIC-Plus (LSMCB 4.11 [0.10] vs. 4.45 [0.10]). No differences in ADL scales or NPI.
Kurz et al (2004)[35]	Pooled analysis of 3 studies[36–38]; 26 weeks	Community-dwelling patients with AD	283	Rivastigmine vs placebo	Moderate-to-severe (MMSE ≤15; mean = 13)	Rivastigmine was superior to placebo in ADAS-Cog score (MCFB −0.12 vs. 4.8) and PDS-All Item (MCFB −1.3 vs. 5.26).
Burns et al (2009)[19]	RCT; 6 months	Nursing facility patients; AD and possible AD associated with vascular dementia	407	Galantamine vs placebo	Severe (MMSE 5–12)	Galantamine was superior in SIB (1.9 [−0.1 to 3.9] vs. − 3.0 [−5.6 to 0.5]). No differences in MDS-ADL.
Karaman et al (2005)[14]	RCT; 12 months	Community-dwelling patients with AD	44	Rivastigmine vs placebo	Moderate-to-severe (MMSE < 14)	Rivastigmine was superior in MMSE (1.2 [0.1] vs. 0.20 [0.1]), PDS (−5.44 [0.3] vs. −1.14 [1.1]), GDS (−0.34 [0.1] vs −0.10 [0.2]), and ADAS-Cog (−4.45 [0.8] vs. 0.82 [0.71]).
Grossberg et al (2018)[21]	Post hoc analysis of RCT[20]; 24 weeks	Community-dwelling patients with AD	676	Memantine vs placebo	Moderate-to-severe (MMSE score 3–14)	Memantine ER was superior to placebo in SIB, CIBIC-Plus, NPI, and verbal fluency tests.
Blesa et al (2003)[15]	Post hoc analysis of RCT[39]; 12 months	Community-dwelling patients with AD	237	Galantamine vs placebo	Moderate-to-severe (MMSE ≤14)	Galantamine was superior in maintaining or improving baseline ADAS-Cog > 30 (51% vs. 13%), MMSE ≤ 14 (48% vs. 4%).
Grossberg et al (2013)[20]	RCT; 24 weeks	Community-dwelling patients with AD	677	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	Memantine was superior to placebo on the SIB (LSMD 2.6 [1.0, 4.2]), CIBIC-Plus (3.8 ± 1.2 vs. 4.1 ± 1.2), NPI (LSMD −2.7 [−4.5, −0.8]), and verbal fluency test (LSMD 0.5 [0.2, 0.9]).
Homma et al (2009)[32]	Open-label extension of RCT[40]; 52 weeks (wash-out period of 2–4 vs. 4–8 weeks)	Community-dwelling patients with AD	189	Donepezil 5 mg/ 10 mg vs placebo	Severe (MMSE 1–12)	Donepezil group retained some treatment benefits after a washout of 2–4 weeks but lost all benefits after a washout of 4–8 weeks. After washout, SIB scores began to decline, indicative of loss of function due to disease progression. No difference in ADCS-ADLsev or BEHAVE-AD scores.
Feldman et al (2001)[16]	RCT; 24 weeks	Community-dwelling patients with AD	290	Donepezil vs placebo	Moderate-to-severe (MMSE score 5–17)	Donepezil was superior in CIBIC-Plus (LSMD 0.54), sMMSE (LSMD 1.79), SIB (LSMD 5.62), DAD (LSMD 8.23), NPI (LSMD 5.64), and FRS (LSMD 1.28).
Farlow et al (2015)[25]	Open-label extension of RCT[41]; 48 weeks	Community-dwelling patients with AD	396	4.6 titrated up to 13.3 mg/day vs 13.3 mg/24 h rivastigmine	Severe (MMSE 3–12)	Continued treatment with 13.3 mg/24 h was superior in ADCS-ADL-SIV (−3.9 [8] vs. −4.6 [8,7]) and SIB (−4.7 [16,8] vs. −7 [16,6]) vs. up titration from 4.6 to 13.3 mg/ 24. No difference in ADCS-CGIC scores.
Rive et al (2004)[42]	Post hoc analysis of RCT[22]; 28 weeks	Community-dwelling patients with AD	252	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	Memantine-treated patients were three times more likely [OR 3.03 [1.38, 6.66]) to remain autonomous after 28 weeks.
Feldman et al (2003)[43]	RCT; 24 weeks	Community-dwelling or nursing home setting patients with AD	290	Donepezil vs placebo	Moderate-to-severe (MMSE score 5–17)	Donepezil was superior in IADL (LSMD 6.83) and PSMS (LSMD 1.32).

Ferreira et al Porto Biomed. J. (2024) 9:2

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Table 1 (*continued*)

Author	Methodology and follow-up	Population	n	Anti-dementia drug evaluation	Dementia stage	Main result
Reisberg et al (2003)[22]	RCT; 28 weeks	Community-dwelling patients with AD	252	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	Memantine was superior in CIBIC-Plus (4.4 ± 1.12 vs. 4.7 ± 1.13), the ADCS-ADLsev (2.5 ± 6.27 vs. 5.9 ± 6.78), SIB (4.5 ± 11.48 vs. 10.2 ± 12.66), and FAST (0.1 ± 1.24 vs. 0.5 ± 1.38). No differences MMSE, GDS and NPI.
Reisberg et al (2006)[23]	RCT extension[22]; 24 weeks	Community-dwelling patients with AD	175	Initiating memantine vs. continuing memantine	Moderate-to-severe (MMSE 3–14)	Patients who switched from placebo to memantine therapy experienced a benefit in the decline rate of ADCS-ADL (MCFB −2.28 ± 5.60), CIBIC-Plus (MCFB −0.25 ± 1.22), and SIB (−4.48 ± 10.82) scores. The rate of decline for the group continuing memantine was faster during the open-label period vs double-blind period.
Van Dyck et al (2007)[33]	RCT; 24 weeks	Community-dwelling patients with AD	350	Memantine vs placebo	Moderate-to-severe (MMSE score 5–14)	No difference between groups was noted in SIB, ADCS-ADL, and CIBIC-Plus at the 24-week end point.
Schulz et al (2011)[31]	Single-arm CT; 16 weeks	Outpatients with AD	97	Memantine	Moderate-to-severe (MMSE<20)	Compared with baseline, memantine treatment after 12 weeks was superior in CERAD-NP (5.9 ± 8.8) and FLCI (4.4 ± 6.8). CGI-C indicated that the majority of patients experienced an improvement or stabilization of the disease after 12 weeks. No significant difference in ADCS-ADL19.
Herrmann et al (2016)[28]	RCT; 8 weeks	Institutionalized patients with AD	40	ChEI continuation vs placebo	Moderate-to-severe (MMSE <15, mean = 8.1)	No difference in clinical worsening between groups on CGI-C (28.6% vs. 36.8%), sMMSE, SIB, NPI-NH, ADCS-ADL-sev, and QUALID.
García-García et al (2020)[29]	Prospective observational study; 3 months	Institutionalized patients with AD	44	Deprescribing vs continuation of ChEIs	Severe (MMSE <5)	No clinical deterioration in MMSE, GDS, NPI, or BI scores. No differences between the groups in behavioral and psychological symptoms of dementia.
Tariot et al (2004)[24]	RCT; 24 weeks	Community-dwelling patients with AD	404	Memantine vs placebo in patients receiving donepezil	Moderate-to-severe (MMSE score 5–14)	Memantine was superior in SIB (0.9[0.67] vs. −2.5[0.69]), ADCS-ADL19 (−2.0 [0.50] vs. −3.4 [0.51]), CIBIC-Plus (4.41 [0.07] vs. 4.66 [0.08]) NPI (−0.1 [0.98] vs. 3.7 [0.99]), and BGP Care Dependency Subscale (0.8 [0.37] vs. 2.3 [0.38]). All other secondary measures showed significant benefits of memantine treatment.
Ferris et al (2013)[26]	Post hoc analysis of RCT[44]; 24 weeks	Community-dwelling patients with AD	1467	Donepezil 23 mg vs donepezil 10 mg	Moderate-to-severe (MMSE <20)	Donepezil 23 mg/day was superior in 6/9 SIB domains. In a more advanced cohort of patients (MMSE 0–16), donepezil 23 mg/day was superior in 5/9 SIB domains.
Rainer et al (2011)[17]	Prospective observational study; 4 months	Outpatients with AD	377	Memantine	Moderate-to-severe (MMSE <20)	Memantine produced benefits from baseline in MMSE (1.63 ± 3.45-point improvement); ADL (1.08 ± 1.86-point improvement); and CGI-C (0.38 ± 0.76 point improvement). Results were similar in patients receiving memantine as the first line and patients who switched from ChEIs.
Cummings et al (2005)[30]	CT; 26 weeks	Nursing facility patients with AD	173	Rivastigmine	Moderate-to-severe (MMSE score 6–15)	Regarding patients with behavioral disturbances at baseline, rivastigmine provided a 3.2-point mean improvement from baseline NPI-NH. Rivastigmine showed no difference from baseline in NPI-NH for all treated patients.
Feldman et al (2005)[18]	Post hoc analysis of RCT[16]; 24 weeks	Patients with AD in community or assisted living facilities	290	Donepezil vs placebo	Moderate-to-severe (MMSE score 5–17)	Donepezil was superior in CIBIC-plus (LSMD 0.70), MMSE (LSMD 1.99), SIB (LSMD 7.42), DAD (LSMD 7.18), and NPI (LSMD 6.86).

95% confidence intervals, standard deviations, or standard errors are represented between [] in accordance with the original reported units.

AD, Alzheimer's disease; ADD, anti-dementia drug; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; ADCS-ADL-SIV, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale-severe impairment version; ADCS-ADL-sev, modified Alzheimer's Disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease; ADCS-CGIC, The Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale; ADL, activities of daily living; aOR, adjusted odds ratio; BALDS, Bristol Activities of Daily Living Scale; BI, Barthel index for activities of daily living; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale; BGP care dependency subscale; BPMSE, Baylor Profound Mental State Examination; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CERAD-NP, neuropsychological assessment battery; CGIC, Clinical Global Impression of Change; ChEIs, cholinesterase inhibitors; CIBIC-plus, Clinician's Interview-Based Impression of Change with caregiver input; CMAI, Cohen-Mansfield Agitation Inventory; CT, controlled trial; DAD, disability assessment for dementia; FAST, Functional Assessment Staging; FLCI, Functional Linguistic Communication Inventory; FRS, Functional Rating Scale; GDS, Global Deterioration Scale; IADL, instrumental activities of daily living scale; LSMD, least square mean difference; LSMCB, least square mean change from baseline; MCFB, mean change from baseline; MDS-ADL, Minimum Data Set Activities of Daily Living Scale; MMSE, Mini-Mental State Examination; MTD, mean treatment differences; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory Nursing Home Version; OR, Odds ratio; PDS, Progressive Deterioration Scale; PSMS, Modified Physical Self-Maintenance; QALYs, quality-adjusted life years; QUALID, quality of life in late-stage dementia scale; RCT, randomized controlled trial; SIB, severe impairment battery; sMMSE, standardized MMSE.

Ferreira et al Porto Biomed. J. (2024) 9:2

Porto Biomedical Journal

Table 2

Main findings available in the literature regarding cost-effectiveness outcomes in patients with advanced dementia.

Author	Methodology and follow-up	Population	n	Anti-dementia drug evaluation	Dementia stage	Main results
Knapp et al (2016)[49]	Post hoc analysis of RCT[11]; 52 weeks	Community-dwelling patients with AD	295	Donepezil or placebo ± memantine or placebo	Moderate-to-severe (MMSE score 5–13, mean = 9)	Donepezil continuation or memantine initiation was more cost-effective than donepezil discontinuation regarding health and social care perspectives. Combination of donepezil andmemantine was not more cost-effective than donepezil alone.
Weycker et al (2007)[48]	Microsimulation model	Community-dwelling patients with AD	404	Donepezil vs donepezil and memantine	Moderate-to-severe (MMSE score 5–14)	Addition of memantine reduced total costs of care. Cost-effectiveness was better for patients with less severe dementia.
Feldman et al (2004)[45]	Cost-consequence analysis of RCT[16]	Community-dwelling patients with AD	290	Donepezil vs placebo	Moderate-to-severe (MMSE score 5–17)	Economic benefits of treatment with donepezil showed a net cost saving of US $224. The mean total societal cost per patient for the 24-week period was US$ 6,686 in the donepezil group and US$6,910 for the placebo group.
Thibault et al (2015)[46]	Cost-utility analysis based on previous RCT[20]	Individual patient simulation model	677 (from RCT)	Memantine with ChEI vs ChEI monotherapy	Moderate-to-severe (MMSE mean = 10.79)	Over 3 years, combined memantine and ChEI provided lower costs than ChEI monotherapy. Discounted average savings were estimated at US$18,355 per patient, with an average increase of 0.12 in QALYs, from a societal perspective, and US$20,947 per patient, with an average increase of 0.13 in QALYs, from a healthcare payer perspective. Due to patients' increased time spent living in the community, caregiver time and its associated costs are slightly higher and caregiver QALYs are slightly lower with combined therapy.
Rive et al (2004)[42]	Post hoc analysis of RCT[22]; 28 weeks	Community-dwelling patients with AD	252	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	Dependent patients incurred in higher costs than autonomous patients (9733 [4538] vs 6937 [4769]; monthly cost in $US), for 28 weeks.
Wimo et al (2003)[47]	RCT; 28 weeks	Community-dwelling patients with AD	166	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	Memantine was superior with fewer total costs from a societal perspective (difference of $US 1089.74/month), total caregiver costs ($US −823.77/month) and direct nonmedical costs ($US −430.84/month). Patient direct medical costs were higher in the memantine group, due to the cost of memantine ($US 159.68/month).

95% confidence intervals, standard deviations or standard errors are represented between [] in accordance to the original reported units.
AD, Alzheimer's disease; ADD, anti-dementia drug; ADL, Activities of daily living; ChEIs, cholinesterase inhibitors; CT, controlled trial; LSMD, least square mean difference; LSMCB, least square mean change from baseline; MCFB, mean change from baseline; MMSE, mini-mental state examination; MTD, mean treatment differences; QALYs, quality-adjusted life years; RCT, randomized controlled trial; $US, United States Dollar.

Table 3

Main findings available in the literature regarding adverse event outcomes in patients with advanced dementia.

Author	Methodology and follow-up	Population	n	Anti-dementia drug evaluation	Dementia stage	Main results
Yun Jeong Hong et al (2018)[27]	RCT; 12 weeks	Community-dwelling patients with	65	Discontinuation of donepezil or memantine	Severe (MMSE score 0–5; mean = 1)	More frequent AEs in the discontinuation group.
Winblad et al (2006)[12]	RCT; 6 months	Nursing facility patients with AD	249	Donepezil vs placebo	Severe (MMSE score 1–10; mean = 6)	No difference in AEs between groups.
Farlow et al (2011)[51]	RCT; 6 months	Community-dwelling patients with AD	1434	Donepezil 23 mg vs donepezil 10 mg	Moderate-to-severe (MMSE < 20; mean 13)	AEs of donepezil 23 mg/day similar to those of 5–10 mg/d.
Burns et al (2009)[19]	RCT; 6 months	Nursing facility patients; AD and possible AD associated with vascular dementia	407	Galantamine vs placebo	Severe (MMSE 5–12)	No difference between the treatment groups.
Karaman et al (2005)[14]	RCT; 12 months	Community-dwelling patients with AD	44	Rivastigmine vs placebo	Moderate-to-severe (MMSE <14)	Rivastigmine was not associated with any increase in risk for mortality, significant AEs, or abnormal ECG.
Blesa et al (2003)[15]	Post hoc analysis of RCT[39]; 12 months	Community-dwelling patients with AD	237	Galantamine vs placebo	Moderate-to-severe (MMSE ≤14)	Galantamine treatment appeared to be well-tolerated in patients with "advanced moderate" vs milder stages of AD.
Grossberg et al (2013)[20]	RCT; 24 weeks	Community-dwelling patients with AD	677	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	AEs experienced at twice or more the rate in the memantine group: dizziness, depression, weight increase, constipation, somnolence, back pain, and abdominal pain.
Homma et al (2009)[32]	Open-label extension of RCT[40]; 52 weeks (wash-out period of 2–4 vs. 4–8 weeks)	Community-dwelling patients with AD	189	Donepezil 5 mg/10 mg vs placebo	Severe (MMSE 1–12)	Donepezil was well-tolerated in this study, with AEs being mainly mild and transient. Nevertheless, discontinuation of treatment was noted in 19.6% of patients.
Feldman et al (2001)[16]	RCT; 24 weeks	Community-dwelling patients with AD	290	Donepezil vs placebo	Moderate-to-severe (MMSE score 5–17)	AEs in 83% of donepezil and 80% of placebo patients, the majority of which were mild. 8% of donepezil and 6% of placebo-treated patients discontinued because of AEs. Bradycardia was reported in 1.4% of patients receiving donepezil and in no patients receiving placebo.
Farlow et al (2015)[25]	Open-label extension of RCT[41]; 48 weeks	Community-dwelling patients with AD	396	4.6 titrated up to 13.3 mg/day vs 13.3 mg/24 h Rivastigmine	Severe (MMSE 3–12)	The incidence of AEs, serious AEs, and discontinuations due to AEs was similar in both groups.
Reisberg et al (2003)[22]	RCT; 28 weeks	Community-dwelling patients with AD	252	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	Memantine was not associated with a significant frequency of AEs.
Reisberg et al (2006)[23]	RCT extension[22]; 24 weeks	Community-dwelling patients with AD	175	Initiating memantine vs. continuing Memantine	Moderate-to-severe (MMSE 3–14)	Memantine treatment was globally safe and well-tolerated.
Van Dyck et al (2007)[33]	RCT; 24 weeks	Community-dwelling patients with AD	350	Memantine vs placebo	Moderate-to-severe (MMSE score 5–14)	Memantine use was well-tolerated. Only AE occurring >5% and with incidence >2x when compared with the placebo group was hypertension (7.9% vs. 2.3%).
Schulz et al (2011)[31]	Single-arm CT; 16 weeks	Outpatients with AD	97	Memantine	Moderate-to-severe (MMSE<20)	

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Ferreira et al Porto Biomed. J. (2024) 9:2

Porto Biomedical Journal

Table 3 (*continued*)

Author	Methodology and follow-up	Population	n	Anti-dementia drug evaluation	Dementia stage	Main results
						Memantine was found to have a favorable safety and tolerability profile.
Herrmann et al (2016)[28]	RCT; 8 weeks	Institutionalized patients with AD	40	ChEI continuation vs placebo	Moderate-to-severe (MMSE <15, mean = 8.1)	Similar AEs between groups.
Niznik et al (2020)[52]	Retrospective study; 1 year	Nursing facility patients with AD	37106 episodes	Deprescribing vs. continuation of ChEI	Severe (MMSE 1–12)	Deprescribing ChEI was not associated with an increase in negative events (aOR = 1.00; [0.94–1.06]) and was associated with a reduced likelihood of serious falls or fractures (aOR = 0.64 [0.56–0.73]).
Tariot et al (2004)[24]	RCT; 24 weeks	Community-dwelling patients with AD	404	Memantine vs placebo in patients receiving donepezil	Moderate-to-severe (MMSE score 5–14)	Memantine was safe and well-tolerated. The incidence of individual adverse events was similar between groups.
Tariot et al (2012)[50]	RCT extension[44]; 12 months	Community-dwelling patients with AD	915	Increasing dose of donepezil to 23 mg/day vs maintaining dose 10 mg/day (2:1)	Moderate-to-severe (MMSE<20)	The majority of patients reporting AEs (81.9%) had AEs of mild or moderate severity. The incidence of AEs in patients increasing the dose of donepezil to 23 mg/day was limited to the initial weeks.
Rainer et al (2011)[17]	Prospective observational study; 4 months	Outpatients with AD	377	Memantine	Moderate-to-severe (MMSE<20)	Memantine was well-tolerated, and no severe AEs were reported in connection with the treatment.
Feldman et al (2005)[18]	Post hoc analysis of RCT[16]; 24 weeks	Patients with AD in community or assisted living facilities	290	Donepezil vs placebo	Moderate-to-severe (MMSE score 5–17)	The majority of AEs (95%) were rated as mild or moderate. AE reported with >2-fold incidence of placebo: hostility (17% vs. 7%); headache (14% vs. 4%); diarrhea (11% vs. 3%); confusion (11% vs. 5%); fecal incontinence (8% vs. 3%); somnolence (7% vs 0%); vomiting (7% vs. 1%); back pain (7% vs. 3%); flatulence (6% vs. 0%); rash (6 % vs. 3%); and urinary tract infection (6% vs. 3%).

95% confidence intervals, standard deviations, or standard errors are represented between [] in accordance with the original reported units.
AD, Alzheimer's disease; ADD, anti-dementia drug; ADL, activities of daily living; AE, adverse effect; aOR, adjusted odds ratio; ChEIs, cholinesterase inhibitors; CT, controlled trial; ECG, electrocardiography; LSMD, least square mean difference; LSMCB, least square mean change from baseline; MCFB, mean change from baseline; MMSE, Mini-Mental State Examination; MTD, mean treatment differences; OR, odds ratio; RCT, randomized controlled trial.

behavioral impairment. Third, most trials are usually short-term, which limits the generalization of results to this specific population.[9]

Taking this into account, there is considerable uncertainty among clinicians if the issue of withdrawing anti-dementia drugs should be considered and when.[7] The subject of discontinuation usually takes into account the patient's expected overall survival, comorbidities, adverse events related to the anti-dementia drugs, and also the family and caregivers' subjective opinion. In addition, the issue of polypharmacy and the cost of care should not be neglected. Recently, the cost of treating AD over the course of one year in the elderly in Portugal has been estimated at 24 M euros for pharmacological treatment alone.[10]

In this article, we aimed at providing a critical review of the literature assessing the effects of anti-dementia drugs in advanced stages of dementia. We looked specifically at the effects in cognitive and behavioral functions, subjective caregiver opinion, adverse events, and direct and indirect costs of treatment.

Methods

A search was conducted on the PubMed database, on December 16, 2021, with the following MESH terms: ("Alzheimer disease" OR "dementia") AND ("anticholinesterase" OR "Cholinesterase inhibitors" OR "memantine" OR "galantamine" OR "rivastigmine" OR "donepezil") AND ("advanced" OR "late" OR

Table 4

Main findings available in the literature regarding caregiver burden outcomes in patients with advanced dementia.

Author	Methodology and follow-up	Population	n	Anti-dementia drug evaluation	Dementia stage	Main results
Howard et al (2012)[11]	RCT; 52 weeks	Community-dwelling patients with AD	295 patients	Donepezil or placebo ± memantine or placebo	Moderate-to-severe (MMSE score 5–13, mean = 9)	No differences between groups of continuation vs discontinuation in GHQ-12 score.
Rive et al (2004)[42]	Post hoc analysis of RCT[22]; 28 weeks	Community-dwelling autonomous vs dependent patients with AD	252 patients	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	Memantine-treated patients were three times more likely (OR ¼ 3.03 [¼ (1.38, 6.66)]) to remain autonomous after 28 weeks. Caregiver time (hours/month) was significantly greater for dependent patients (533 [228]) than that for autonomous patients (377 [264]).
Feldman et al (2003)[43]	RCT; 24 weeks	Community-dwelling or nursing home setting patients with AD	290 patients and 287 caregivers	Donepezil vs placebo	Moderate-to-severe (MMSE score 5–17)	Donepezil was associated with favorable CSS (LSMD 1.82) and caregivers reported spending less time assisting with ADLs in treated patients (LSMD 52.4 min/d).
Reisberg et al (2003)[22]	RCT; 28 weeks	Community-dwelling patients with AD	252 patients	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	The required caregiver time, as assessed by the Resource Utilization in Dementia score, was statistically significant, indicating that caregivers spent less time with patients receiving memantine (difference between groups: 45.8 hours/month [10.37–81.27]).
Wimo et al (2003)[47]	RCT; 28 weeks	Community-dwelling patients with AD	166 patients and 166 caregivers	Memantine vs placebo	Moderate-to-severe (MMSE 3–14)	Less caregiver time was needed for patients receiving memantine (less 51.5 hrs/month [−95.27, −7.17]).

95% confidence intervals, standard deviations, or standard errors are represented between [] in accordance with the original reported units.
AD, Alzheimer's disease; ADD, anti-dementia drug; ADL, activities of daily living; CSS, caregiver stress scale; ChEls, cholinesterase inhibitors; CT, controlled trial; GHQ-12 score, The 12-Item General Health Questionnaire; LSMD, least square mean difference; LSMCB, least square mean change from baseline; MCFB, mean change from baseline; MMSE, Mini-Mental State Examination; MTD, mean treatment differences; RCT, randomized controlled trial.

"severe" OR "end-stage"). Only articles after January 2000 were selected. We included mostly clinical trials and prospective studies. Guidelines, expert consensus, case reports, and editorials were not included. Systematic reviews and meta-analysis were not primarily addressed in this review. This generated 1,216 articles. Two authors (D.F. and R.A.) reviewed the abstracts and selected the most pertinent articles to include, based on the outcomes of anti-dementia treatment in advanced stages, especially cognitive and behavioral aspects, caregiver opinion, adverse events, and costs. This yielded 35 articles that we included for the purpose of this review. Owing to the time lapse between this search and the article's publication, an updated search was executed in January 2024, revealing no additional relevant articles addressing the impact of anti-dementia drugs in moderate-severe stages.

Results

The cognitive and functional outcomes of people with severe dementia medicated with anti-dementia drugs are presented in Table 1. Most studies include community-dwelling patients with AD. There are several randomized controlled studies with a high number of patients included (11/78.6% above n = 200).

"Advanced dementia" was generally established by the MMSE score, usually below 12–14. Most studies showed a positive outcome with anti-dementia treatment (ChEI and/or memantine) in a number of cognitive and functional scales, such as MMSE,[11-18] SIB[12,13,16,18-24], and CIBIC-plus.[13,16,18,20-24] Higher doses of the same treatment also showed a tendency to be more effective in some cognitive outcomes.[25,26] The impact of these changes was relatively small: For instance, MMSE scores differed 1–3 points in patients medicated compared with people without anti-dementia treatment. Nevertheless, in some studies, there were no significant differences in cognitive and functional scales: MMSE,[22,27-29] CGIC,[27,28] NPI,[12,13,22,27-30] ADCS-ADL.[13,27,28,31-33] Barthel Index,[27,29] and GDS.[22,29] Considering different drugs, a head-to-head comparison was only available in one study,[34] with no significant differences between donepezil and rivastigmine. Only four studies addressed the issue of drug discontinuation.[11,27-29] These were heterogeneous in design and outcomes measured, and they generally showed an absent or minimal difference between groups who continued or discontinued treatment. Of note, one study[27] even reported improvements in the cognitive scale in patients assigned to discontinue donepezil or memantine.

Ferreira et al Porto Biomed. J. (2024) 9:2

Porto Biomedical Journal

The cost-effectiveness outcomes of anti-dementia treatment are shown in Table 2. Only six studies addressed this issue. In general, these studies show that adding or maintaining anti-dementia drugs in advanced stages of AD is cost-effective. The magnitude of savings differs between studies (average savings from a societal perspective of US$ 224 per patient for 24 weeks in one study,[45] US$18,355 per patient over 3 years in other study,[46] and US$ 1089.74 per month in other[47]). Even though direct cost medication is higher in patients with anti-dementia drugs, the overall cost of care is reduced because of lower institutionalization rates and increased autonomy.[42,45,47] Combined therapy was evaluated in three studies. Two of them showed a favorable cost-effectiveness outcome for memantine in association with ChEIs[46,48]; nonetheless, in one study, donepezil and memantine combination therapy was found not to be more cost-effective than donepezil alone.[49]

Notably, only patients with AD were included; there were no studies evaluating cost-effectiveness in mixed dementia.

The tolerability and safety profile of anti-dementia treatment are presented in Table 3. Most of the studies found no differences between treatment with donepezil,[12,28] rivastigmine,[14,28] or galantamine,[15,19,28] in comparison with placebo, and memantine was found to be safe and well tolerated in multiple studies.[17,22,23,31,50] However, two studies reported a higher rate of discontinuation in the treatment groups.[16,32] In addition, one study[18] reported that patients on donepezil had a more than two-fold increased risk of some side effects such as diarrhea, confusion, somnolence, and urinary tract infection. Nonetheless, these side effects were considered mostly mild. When comparing different doses of the same ChEIs, the adverse events were similar between groups,[25,51] with one study reporting a higher incidence of adverse effects with increasing doses of donepezil limited to the initial weeks of dose up-titration.[50]. In community-dwelling patients with AD with MMSE score <5, one study showed more frequent side effects in patients who discontinued therapy with donepezil or memantine,[27] but another study[52] showed that deprescribing ChEIs in nursing facility patients with AD with an MMSE score<12 was not associated with an increase in negative events and was actually associated with a reduced likelihood of serious falls or fractures.[43]

The caregiver burden is analyzed in Table 4. Studies in this subject are particularly scarce, and we included only five studies. Globally speaking, caregivers of patients on anti-dementia drugs experienced less burden, either in stress scales or in time associated with direct care. In some studies,[22,42,43,47] anti-dementia drugs seem to reduce the time caregivers need to allocate to strict nursing activities, such as hygiene, eating, dressing, transportation, taking medication, providing supervision, and aiding in other activities of daily life. Correspondingly, with the diminished time allocated to help the patient with their daily activities, in one study,[43] caregivers of patients treated with donepezil reported lower levels of relational deprivation and loss of self. However, in one study,[11] there were no differences in the GHQ-12 score, between caregivers of patients who continued or discontinued the medication.

Discussion

Anti-dementia drugs' efficacy is especially difficult to ascertain in people with advanced dementia. Even though the definition of advanced dementia is not consensual, most studies rely on cognitive scales. Most studies use an MMSE score of ≤14 to define this condition. This, however, may encompass people with very different health status, ranging from ambulatory but dependent for most activities of daily living, to people bedridden without any social interaction. This may curtail the generalization of results and provide a very difficult framework to interpret data in bulk.

In terms of cognitive and functional outcomes, even though the evidence usually favors the prescription of anti-dementia drugs, the magnitude of this effect is usually small. Some studies have shown small cognitive and functional benefits with either ChEIs[11–16,18,19,30,35,43] or memantine.[11,17,20–24,31,42] This evidence is supported by two recent Cochrane Library systematic reviews, which showed a mild benefit on cognitive scores in favor of donepezil[8] (4 studies including 1,102 patients) and a small benefit of memantine[53] in cognition, activities of daily living, behavior, and mood scores (14 studies including 3,700 patients). Nevertheless, whether these improvements result in clinically relevant effects is still unclear, and the short follow-up time and heterogeneous baseline characteristics of the patients do not allow for substantial conclusions to be drawn. In this regard, we noted that most studies evaluating "moderate-to-severe" stage dementia presented a wide range of cognitive and functional baseline scores, including values as high as 20 on the MMSE.[34] In fact, studies evaluating patients in a more advanced stage of dementia, with a baseline MMSE < 12,[12,13,19,25,27,29,32] failed to show clinical benefit in multiple primary and secondary outcomes. In addition, we found only two studies that evaluated therapy discontinuation in patients with an MMSE <5,[27,29] which showed no major differences in multiple cognitive, behavioral, and psychological scores. This fact underlines the necessity for a more structured and restricted selection of patients in future trials, as well as the need for additional trials evaluating discontinuation strategies of anti-dementia drugs, as these studies seem to tendentially show different results than those evaluating the initiation of a specific therapy versus placebo. In this regard, a survey of hospice medical directors[54] concluded that most directors did not consider these therapies effective in people with end-stage dementia, with 80% recommending discontinuation of donepezil and memantine at the time of hospice enrollment.

Evidence of long-term treatment efficacy is also lacking in the literature, with most randomized trials lasting only 3–6 months. Only five trials[11,14,25,32,34] were found to have a follow-up period of ≥1 year, and no data are available for a treatment period beyond 2 years. This matter is of particular importance when bringing clinical trials data into the real-world practice, as patients with advanced dementia are older, have been under anti-dementia treatments for a longer period, and evidence suggests that ChEI's beneficial effects might wane over the course of 1 year.[55]

The absence of studies directed specifically at the effect of anti-dementia drugs in advanced stages of vascular dementia is also of relevance, as this group of patients represents a large percentage of all the dementia cases. Even though some studies have incorporated both patients with AD and mixed dementia, in comparison with AD, trials evaluating all stages of only vascular dementia have shown marginal cognitive effects of ChEIs, with some studies showing no improvements at all.[56] This lack of evidence limits the widespread use of anti-dementia treatment in vascular dementia, particularly in the more advanced stage. Interestingly, an ongoing RCT[57] will compare continuation versus discontinuation of ChEIs, with or without memantine, in 302 patients living in the community with severe dementia (MMSE < 10 for at least 3 months), including AD with or without vascular dementia, for 1 year, primarily assessing the

time to institutionalization and/or progression of disability. Hopefully, this will contribute to providing more evidence on whether to deprescribe anti-dementia drugs in patients with advanced dementia.

Regarding the economic impact of anti-dementia treatment, we found that most studies showed a favorable cost-effectiveness outcome from both a health and societal perspective. Direct medical costs are typically higher in the patients undergoing anti-dementia treatment, mostly due to the direct drug costs. However, this economic burden can be theoretically compensated by savings associated with institutionalization delay, less caregiver time required, and a longer period in more autonomous stages of the disease, as suggested by the evidence in the literature. Nevertheless, for this assumption to be proven, one should have had clinical trials with a duration long enough to evaluate all of these outcomes. Estimates of costs rely on statistical models based of the prediction of disease progression extrapolated from short-term trials and are also limited to the use of epidemiological and resource data from a specific health care system. These limitations contribute to the lack of precision in current cost-effectiveness analyses and, consequently, make them inadequate for an evidence-based decision point of view. Future cost-effectiveness analysis should also rely on deprescribing trials in which there would be an initial effort to sort out patients that would more greatly benefit from the treatment versus those that would not.

The tolerability and safety profile are important features to consider when deciding whether to initiate, continue, or withdraw any kind of treatment. The potential side effects of anti-dementia drugs must be weighed carefully as polypharmacy and multimorbidity are common obstacles in initiating another drug for people with severe dementia. The current literature reviewed here seems to present conflicting results regarding the presence and incidence of adverse events during the initiation or discontinuation phase of anti-dementia drugs. These findings are supported by data from a systematic review from 10,000 participants in 44 trials, indicating that there was no difference between memantine and placebo in the proportion experiencing at least one adverse event with no change between severity grades of dementia, but suggesting that patients undergoing memantine could experience more frequent events of dizziness and headache.[53] Another large systematic review, which evaluated ChEIs in mild and severe stages of dementia, showed that the discontinuation rate was higher in the treatment group (29% vs. 18%) and that, in a pooled analysis of six trials, adverse events of abdominal pain, anorexia, dizziness, nausea, vomiting, diarrhea, headache, and insomnia were significantly more frequent in the ChEI groups.[58] Based on the results of clinical trials, we believe that a risk-benefit planning is fundamental in the management of these patients and, as dementia severity evolves, deprescribing might be an effective strategy to reduce the occurrence of medication-related adverse events. Patients should be regularly monitored by a health care professional, and regular evaluation of therapeutical benefits and harm should be conducted to maximize benefit and quality of life.

The role of the caregiver is a fundamental part of the complex process of optimizing the treatment and care of patients with dementia. This feature can be easily unacknowledged by the health care professionals as the routine evaluation in the outpatient clinic setting might not be as all-embracing as it should. The burden of physical and emotional stress in caregivers is, at least in part, conditioned by the time exclusively allocated to nursing activities. This includes activities of daily living, such as hygiene, meals, transportation, taking medication, and providing supervision.[43,47]

This may potentially allow for more quality time between patients and caregivers, as well as additional free personal time for caregivers, possibly leading to a higher quality of life and less burden. In this regard, anti-dementia drugs seem to provide a satisfactory result as most of the available studies revealed a decreased caregiver overload.

Previous qualitative interview-based studies have also described the subjective views of caregivers about anti-dementia drugs in advanced stages of dementia. Opinions were diverse and ranged from a belief of improvement or slowing of decline to no impact whatsoever in the progression of the disease. In addition, the management of caregivers' expectations and preconceived ideas on the evolution of dementia and the effects of treatment should be a matter of particular focus when considering deprescription. The fear of a potential clinical decline of the patient's condition was reported as the main cause of reluctance in this matter,[59,60] and thus, a comprehensive, informed, and collaborative relationship between the patient, the physician, and the caregiver is needed to achieve an individualized approach that is best appropriated for the patients and caregivers.

Conclusion

Although there are multiple studies in anti-dementia treatment, relatively few address the severe and end-of-life stages. Minimal benefit in cognition and a relatively beneficial safety and cost-effectiveness profile were found, but whether this translates into clinically relevant effects and affects physician's options remains to be elucidated.

Medication withdrawal trials are lacking, but the available studies suggest a high potential of reducing patients' and caregivers' burden and improvement in their quality of life. Investigation in this field is also limited by the fact that most trials have a short duration, small sample size, and heterogeneous baseline severity scores as well as mainly focus on AD, excluding patients with mixed and vascular dementia.

Future studies with homogeneous designs and outcomes are warranted and should be tailored by a patient and caregiver-centered approach.

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Ferreira et al Porto Biomed. J. (2024) 9:2

Porto Biomedical Journal

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