Potentially inappropriate medication use in older adults with mild-moderate Alzheimer's disease

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RESEARCH PAPER

Potentially inappropriate medication use in older adults with mild-moderate Alzheimer's disease: prevalence and associations with adverse events

Claire Murphy[1,2], Adam H. Dyer[1,2], Brian Lawlor[2,3], Sean P. Kennelly[1,2], for the NILVAD Study Group[†]

[1]Department of Age-Related Healthcare, Tallaght University Hospital, Dublin, Ireland
[2]Department of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland
[3] Mercer's Institute for Research on Ageing, St James's Hospital, Dublin, Ireland

Address correspondence to: Dr Claire Murphy, Department of Age-Related Healthcare, Tallaght University Hospital, Dublin, Ireland. Email: clairemurphy1104@gmail.com

[†]Full author list of NILVAD Study Group listed under 'Acknowledgements'.

Abstract

Aim: Potentially inappropriate medication (PIM) use is prevalent in older adults and is associated with adverse events, hospitalisation and mortality. We assessed the patterns and associations of PIM use in older adults with mild-to-moderate Alzheimer's Disease (AD), who may represent a particularly vulnerable group.
Design: Analysis of data from NILVad, an 18-month Randomised Control Trial of *Nilvadapine* in mild-to-moderate AD. The v2 STOPP criteria were applied in duplicate to identify PIM use. Associations between PIM use and adverse events/unscheduled healthcare visits in addition to the associations between PIM use and AD progression were evaluated.
Setting and Participants: 448 older adults with mild-to-moderate AD from 23 centres in nine European countries.
Results: Of 448 participants (mean age: 72.56 ± 8.19 years), over half (55.8%) were prescribed a PIM with 30.1% being prescribed 2+ PIMs. The most frequent PIMs were (i) long-term benzodiazepines (11.6% $N = 52/448$), (ii) selective serotonin reuptake inhibitors without appropriate indication (11.1% $N = 50/448$), and (iii) Proton-Pump Inhibitors (PPIs) without appropriate indication (10.7% $N = 48/448$). Increasing number of PIMs was associated with a greater risk of adverse events (IRR 1.17, 1.13–1.19, $P < 0.001$), serious adverse events (IRR 1.27; 1.17–1.37, $P < 0.001$), unscheduled hospitalisations (IRR 1.16, 1.03–1.30, $P = 0.016$) and GP visits (IRR 1.22, 1.15–1.28, $P < 0.001$). PIM use was not associated with dementia progression.
Conclusions and Implications: PIM use is highly prevalent in mild-to-moderate AD and is associated with adverse events and unscheduled healthcare utilisation. Further attention to de-prescribing in this vulnerable group is warranted.

Keywords: adverse events, dementia, hospitalisations, older people, potentially inappropriate prescriptions

Key points

- There is an increased rate of unscheduled hospitalisations and GP visits associated with PIMS.
- Over half of older adults with mild-to-moderate Alzheimer's dementia were on at least one potentially inappropriate medication.
- The most frequently encountered PIM was benzodiazapine use for >4 weeks and proton pump inhibitor use without indication.

Introduction

A potentially inappropriate medication (PIM) is one prescribed without indication or where the net clinical benefit does not outweigh the risk. PIM use is a common cause of adverse drug reactions in older adults [1,2]. Those with dementia have a higher incidence of polypharmacy and PIM use, with prevalence estimates of PIM use ranging from 14 to 74% in those with dementia, whom may represent a particularly vulnerable cohort [3–7].

Both polypharmacy and PIMs are associated with numerous adverse events, greater healthcare utilisation and even mortality in community-dwelling older adults [8,9]. In nursing home residents with dementia, PIMs have been associated with a reduced quality of life, malnutrition and depression [10–12]. Whilst the effects of PIM use have been well studied in older adults without dementia, the prevalence, associations and factors associated with ongoing PIMs in those with mild-to-moderate dementia are less well explored [13].

A recent study of PIM use in older adults with dementia across seven European countries found a high prevalence of PIM use [14]. Additionally, those using multiple PIMs were older (80+ years), more likely to be in residential care, with greater comorbidity and functional impairment. Whilst studies have reported a high prevalence of PIM use in severe dementia, and in those residing in nursing homes, the impact of ongoing PIM use in those with mild-to-moderate dementia was less well explored.

We analysed data from the NILVAD study to assess the prevalence of and factors associated with PIM use, in addition to the association between PIM use and adverse events in older adults with mild-to-moderate AD.

Methods

Background, setting and participants

The current study analysed data from NILVAD, a multicentre investigator-led phase-3 clinical trial of *Nilvadipine* in AD (Clinicaltrials.gov NCT02017340; EudraCT number 2012-002764-27). The protocol and main results paper have been previously published [15,16]. Briefly, participants with mild-to-moderate AD were recruited from 23 academic centres in nine European countries. Participants were community-dwelling adults, aged 50 years or older, with a diagnosis of AD as per the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease (NINCDS-ADRDA) Criteria with a standardised Mini-Mental State Examination score from 12 to 26.

Medication records

A detailed medication history was obtained from patients and caregivers at initial trial visit. As the current study investigated inappropriate prescriptions (and not omissions), the STOPP criteria v2.0 only were applied to each participant's medication list taking into account participant's medical history and laboratory parameters. The STOPP criteria have demonstrated validity and utility in predicating adverse outcomes in older adults [1,17].

We included regular medication use (medications used for at >4 weeks) and excluded medications only used occasionally or historically. Given the extensive data available all STOPP criteria except two (which required class of heart failure) were applied. This was performed in duplicate by two physicians with a background in geriatric medicine with disputes resolved by a consultant in geriatric medicine.

Adverse events, unscheduled GP visits and hospitalisations

Participants in the NILVAD trial attended follow-up at 0, 6, 13, 26, 39, 52, 65 and 78 weeks. At each visit, adverse events were reported and medication lists updated. Detailed description of adverse and serious adverse events (SAEs) can be found in the original protocol [15]; specifically adverse events included any untoward medical event that did not necessarily have a causal relationship to the treatment studied. Adverse events and SAEs were based on clinical judgement. All unscheduled hospitalisations or GP visits were recorded. For the current analysis outcomes were selected based on the data available from the initial study protocol [15,16]. For each PIM user, the adverse events logs were reviewed and cross-referenced to the prescribed PIMs in order to assess for a potential/definite link. This was performed in duplicate. Adverse event-PIM links were categorised as follows: unrelated, potentially related or definitely related. We did not assess mortality in the current analysis due to the rare occurrence of this outcome in the NILVAD study (1.37%, $N = 7$).

Cognitive and dementia severity assessment

Cognition was measured at baseline using the Alzheimer disease assessment scale-cognitive subsection (ADAS-Cog) [18]. Dementia severity was rated using the clinical dementia rating-sub of boxes (CDR-sb). We examined the link between ongoing use of PIMs and change in ADAS-Cog and CDR-sb at 18 months to examine for an effect of PIMs on AD progression.

Statistical analysis

STATA V.15 (Stata Corp, College Station, TX, USA) was used for all analysis and statistical significance considered as $P < 0.05$. Descriptive statistics were reported as means (standard deviations [SDs]) and medians (interquartile ranges [IQRs]). For each participant, the total number of PIMs was calculated in addition to a binary PIM versus no-PIM variable and an 'appropriate medication' variable (total no. of non-PIM medications). The total proportion using PIMs was expressed as a percentage of the overall study population. Between-group differences were assessed using *t*-tests, Wilcoxon rank sum tests and chi-square tests as appropriate.

Multivariate predictors of PIM use were modelled using logistic regression.

Poisson regression models were used to analyse the association between PIM use and adverse outcomes over 18 months. These models were adjusted for overall health (age, medications and comorbidities) and AD (diagnosis duration, AD severity and cognitive score, and years of education) covariates. In order to check for over-dispersion, analyses were re-run using negative binomial regression and the predictive value of models compared.

In order to assess for the impact of PIM use on AD progression at 18 months, mixed-effects linear regression models were used with country considered as a random effect with change in either ADAS-Cog or CDR-sb scores at 18 months as the dependent variable. Associations were tested unadjusted (model 1), followed by adjustment for age, sex baseline score (ADAS-Cog/CDR-sb) and study group (nilvadipine or placebo) (model 2) in addition to years of formal education, years since AD diagnosis, total number of appropriate medications and total number of comorbidities (model 3). Linear models were examined for multicollinearity and residual versus fit plots examined.

Results

Participant characteristics

In total, 448 patients with mild-to-moderate AD (aged 72.56 ± 8.19 years; 62.28% female) had complete follow-up data available. The median number of regular medications was 5 (3–7), and comorbidities was 4 (2–5). Median years since diagnosis was 1.09 (0.47–2.26) and for symptom onset was 3.7 (2.45–5.42). Median baseline ADAS-Cog was 32 (27–41) and median AD severity (CDR-sb) was 4 (3–6.5). Of note, the study included 15.4% ($N = 69/448$) aged 65 years of age or younger.

Prevalence of PIM use

Over half (55.8%, 250/448) were prescribed a PIM. Of these, just under half (46.0%, $N = 115/250$) were prescribed a single PIM, with over half (54%, $N = 135/250$) being prescribed 2+ PIMs. Of those prescribed a PIM, 24.8% ($N = 62/250$) were prescribed 3+ PIMs.

The most frequent PIMs used were (i) benzodiazepines >4 weeks without indication (11.6%, $N = 52/448$), (ii) selective serotonin reuptake inhibitors without appropriate indication (11.1%, $N = 50/448$), (iii) proton pump inhibitors (PPIs) without appropriate indication (10.7%, $N = 48/448$), (iv) antipsychotic medications without appropriate indication (8%, $N = 36/448$) and (v) regular non-steroidal anti-inflammatory drugs without PPI cover (4.2%, $N = 19/448$), for a full list of the PIMs used see supplementary data. The prevalence of PIM use significantly differed by country and ranged from 35% in Greece ($N = 28/80$) to 74% in France ($N = 40/54$) ($P < 0.001$, $\chi^2 = 29.3$).

Factors associated with PIM Use

Baseline characteristics, presented by PIM use, are given in Table 1. On univariate analysis, patients prescribed a PIM at baseline were older and had a higher total number of appropriate medications, longer duration since symptom onset and a longer duration since AD diagnosis ($P < 0.05$). On logistic regression, associations persisted for greater likelihood of PIM use with an increased total number of (non-PIM) medications (OR 1.52, 1.34–1.70, $P < 0.001$).

PIM use and adverse events over 18 months

The median number of adverse events per participant was 3 (IQR: 1–6), which did not differ by study group (Nilvadipine versus Placebo) ($P = 0.39$). SAEs were reported for 14.3% ($N = 64/448$). Unadjusted, PIM use was associated with both adverse events (IRR 1.14, 1.12–1.17, $P < 0.001$) and SAEs (IRR 1.24, 1.16–1.32, $P < 0.001$). Both total PIMs (IRR 1.17, 1.13–1.19, $P < 0.001$) and appropriate medications were associated with adverse events (IRR 1.08, 1.06–1.10, $P < 0.001$) under a fully adjusted model (Table 2). Similarly, for SAEs using the fully adjusted model, associations were seen for both total PIMs (IRR 1.27; 1.17–1.37, $P < 0.001$) and appropriate medications (IRR 1.23; 1.17–1.31, $P < 0.001$) (See Table 2).

Overall, 80 participants (17.9%; $N = 80/448$) had a potential/definite link between the PIM used and a subsequent adverse event. The most frequent adverse events potentially caused by a PIM were falls (4.2%, $N = 19$), increasing confusion (3.7%, $N = 17$), over-sedation (2.4%, $N = 11$) and agitation (2.4%, $N = 11$).

PIM use and unscheduled hospitalisations/GP visits

In total, 16.3% ($N = 73$) patients had one or more unscheduled hospitalisations, while 46% ($N = 206$) had an unscheduled GP visit. The total number of PIMs was associated with a greater risk of both unscheduled hospitalisations (IRR: 1.18, 1.06–1.31, $P = 0.003$) and unscheduled GP visits (IRR: 1.18, 1.12–1.24, $P < 0.001$). Under the adjusted model, the total number of PIMs was the only factor independently associated with both the total number of unscheduled hospitalisations (IRR 1.16, 1.03–1.30, $P = 0.016$) and unscheduled GP visits (IRR 1.14 95% CI 1.05–1.31, $P < 0.001$) (Table 2). Notably, appropriate medications were not associated with unscheduled GP visits or hospitalisations.

PIM use and cognitive decline/dementia severity at 18 months

In the cohort overall, the mean ADAS-Cog score increased indicating a greater cognitive decline (mean difference: +8.98 ± 9.18) as did the mean CDR-sb (mean difference: +3.48 ± 3.15), also indicating increased dementia severity. Under all three models, there was no effect of total number of

Table 1. Characteristics of included participants by PIM use

Univariate analysis Baseline characteristic	No PIM ($N = 198$)	1+ PIM ($N = 250$) PIM	*P*-Value
Age, mean years (SD)	71.67 (8.17)	73.09 (8.18)	**0.035**
Gender, % female (*N*)	61.62% (122)	62.80% (157)	0.797
On Nilvadipine, % (*N*)	50.51% (100)	50.00% (125)	0.915
Years of education, median (IQR)	16 (13–20)	16 (14–18)	0.850
No. medications, median (IQR)	4 (2–5)	6 (4–8)	**<0.001**
No. comorbidities, median (IQR)	4 (2–4)	4 (2–5)	0.054
Yreas since symptom onset, median (IQR)	3.33 (2.05–4.73)	3.95 (2.61–5.81)	**0.004**
Years since diagnosis, med. (IQR)	0.82 (0.40–2.08)	1.32 (0.50–2.59)	**0.004**
Baseline CDR-sb score, median (IQR)	4.4 (3–6)	4.5 (3.5–7)	0.096
Baseline ADAS-Cog score, median (IQR)	32 (27–41)	32 (26–41)	0.758
Multivariate analysis **Baseline characteristic**	**OR (95% CI)**		***P*-value**
Age	1.01 (0.98–1.03)		0.744
Gender	1.07 (0.69–1.68)		0.765
Study group (*Nilvadapine* versus Placebo)	1.00 (0.65–1.52)		0.982
Years of education	1.02 (0.96–1.08)		0.563
No. medications	1.52 (1.36–1.71)		**<0.001**
No. comorbidities	0.87 (0.77–0.97)		**0.010**
Years since symptom onset	1.04 (0.95–1.15)		0.399
Years since diagnosis	1.03 (0.88–1.20)		0.723
Baseline CDR-sb score	1.12 (1.00–1.24)		0.061
Baseline ADAS-Cog score	0.98 (0.96–1.02)		0.339

Abbreviations: *N*, total number; CDR-sb score, clinical dementia rating sum of boxes score; ADAS-Cog score, Alzheimer's disease assessment scare-cognitive subscale; OR, odds ratio; CI, confidence interval.

PIMs on cognitive decline or dementia severity at 18 months (Table 3).

Discussion

The current study reports the prevalent use of PIMs in community-dwelling older adults living with mild-to-moderate AD. Particularly, concerning is the number of participants prescribed multiple PIMs. The likelihood of being prescribed a PIM increased with total medication burden and was associated with both adverse events and SAEs over 18 months, although not with AD progression. Strikingly, the total number of PIMs prescribed was associated with both unscheduled hospitalisations and GP visits over 18 months. While unscheduled hospitalisations often have multiple precipitants, our findings were independent of age, medical co-morbidity and other important co-variates. These findings have numerous important implications for de-prescribing and optimal prescribing interventions, even in those with mild-to-moderate AD.

The high percentage of PIM use in this study population, with over 50% of patients prescribed at least one PIM, is largely consistent with previous literature [12,13]. The number of patients prescribed three or more PIMS (>20%) is particularly concerning given known associations between PIMs and adverse events [20]. The most frequently encountered PIM was prolonged use of benzodiazepines. Extensive literature exists highlighting the adverse effects associated with prolonged benzodiazepine use including delirium, falls, fractures and cognitive decline, dependency and mortality [19–22]. On foot of this, international guidelines advocate against the use of Benzodiazepines in older adults, particularly in those with dementia [23, 24].

PPIs were also frequently inappropriately prescribed, consistent with previous studies. Inappropriate PPI use can incur unnecessary healthcare costs but also side effects such as achlorhydria and hypergastrinemia. The large number of participants prescribed anti-muscarinic medication is also concerning, given the evidence for anticholinergic burden and cognitive decline. The inappropriate use of antipsychotic medication is also noteworthy, which have well-known adverse effects in those with dementia [25]. These medications may represent particular targets for medication reviews and optimal prescribing interventions in those with mild-to-moderate AD. With increasing availability of healthcare information and communications technology applications, the role for electronic prescribing and computerised decision support systems in reducing inappropriate prescriptions in this cohort is emerging [26].

The current study found that both PIMs and appropriate medications were independently associated with adverse events in mild-to-moderate AD. Although with increasing frailty and co-morbidity GP visits have a clear role in management of older adults and chronic disease, hospital admission and unscheduled care have been shown to be associated with poor outcomes in patients with dementia [27]. Previous literature has demonstrated an increased frequency of hospitalisation with PIM use in older adults

Table 2. PIM Use Is associated with adverse events, SAEs, unscheduled GP visits and unscheduled hospitalisations in mild-to-moderate Alzheimer's disease. Poisson regression analysis was used to assess the relationship between PIM use and adverse outcomes (total number). Results are reported as incident rate ratios and approximate 95% confidence intervals

Predictor	IRR (95% CI)	*P*-value
Adverse events		
Total PIM	1.17 (1.13–1.19)	<**0.001**
Appropriate medications	1.08 (1.06–1.10)	<**0.001**
Age	1.00 (0.99–1.01)	0.761
Gender (female)	1.08 (0.99–1.19)	0.077
Study group (*Nilvadapine* versus placebo)	0.95 (0.87–1.03)	0.201
Total no. of comorbidities	1.01 (0.87–1.03)	0.345
Years since diagnosis	0.98 (0.95–1.01)	0.081
Baseline CDR-sb score	0.99 (0.96–1.01)	0.209
Baseline ADAS-Cog score	1.00 (0.99–1.01)	0.576
SAEs		
Total PIM	1.27 (1.17–1.37)	<**0.001**
Appropriate medications	1.23 (1.17–1.31)	<**0.001**
Age	1.02 (1.01–1.05)	**0.044**
Gender (Female)	0.71 (0.51–0.98)	**0.039**
Study group (*Nilvadapine* versus placebo)	0.97 (0.63–1.48)	0.870
Total no. of comorbidities	1.02 (0.93–1.12)	0.646
Years since diagnosis	0.97 (0.79–1.04)	0.161
Baseline CDR-sb score	1.03 (0.94–1.13)	0.456
Baseline ADAS-Cog score	1.03 (1.01–1.06)	**0.026**
Unscheduled hospitalisations		
Total PIM	1.16 (1.03–1.30)	**0.016**
Appropriate medications	1.00 (0.91–1.11)	0.942
Age	1.03 (0.99–1.05)	0.149
Gender (female)	0.82 (0.68–1.62)	0.840
Study group (*Nilvadapine* versus placebo)	0.79 (0.54–1.24)	0.339
Total no. of comorbidities	1.06 (0.96–1.16)	0.255
Years since diagnosis	0.98 (0.87–1.11)	0.751
Baseline CDR-sb score	1.05 (0.97–1.03)	0.386
Baseline ADAS-Cog score	1.00 (0.98–1.06)	0.967
Unscheduled GP visits		
Total PIM	1.22 (1.15–1.28)	<**0.001**
Appropriate medications	1.05 (0.99–1.11)	0.086
Age	1.00 (0.98–1.02)	0.819
Gender (female)	1.06 (0.82–1.39)	0.707
Study group (*Nilvadapine* versus placebo)	1.06 (0.97–1.38)	0.671
Total no. of comorbidities	1.04 (0.90–1.10)	0.270
Years since diagnosis	0.98 (0.94–1.01)	0.582
Baseline CDR-sb score	1.00 (0.98–1.06)	0.891
Baseline ADAS-Cog score	1.01 (0.98–1.02)	0.666

when applying STOPP criteria, [28] but this is less well studied in older adults with AD. In this study, we have also demonstrated an increased incidence of SAEs associated with appropriate medications in this cohort; the role of appropriate polypharmacy in older people and those with chronic conditions is increasingly acknowledged [29] and requires physician care, frequent review and healthcare professional education.

This study included patients across nine European countries and under the care of a variety of specialists including geriatricians, neurologists and geriatric psychiatrists. The international and cross-specialty nature of this analysis is the strength of this study. Our study included detailed medication records in addition to close follow-up of participants in terms of adverse events and unscheduled healthcare visits. While clinical judgement is a key determinant for PIM identification (inevitably a limitation in all studies investigating PIM use given variability in clinician practice), by using the validated STOPP tool [30] and performing assessment in duplicate, we have minimised the bias arising from individual clinician assessment.

Conclusion and implications

The current study demonstrates that over half of older adults with mild-to-moderate AD were prescribed at least one PIM, with many prescribed multiple PIMs. Of note, there was an increased rate of unscheduled hospitalisations and GP visits associated with greater PIM use. Further efforts at designing optimal prescription interventions in this vulnerable cohort are warranted based on these results and may produce benefit

Table 3. PIM use does not predict dementia progression at 18 months. Mixed-effects linear regression analysis was used to assess the relationship between PIM use and cognitive severity (ADAS-Cog)/dementia severity (CDR-sb) at 18 months. Results are reported as coefficients and approximate 95% confidence intervals

Change in ADAS-Cog	Model 1		Model 2		Model 3	
	β-coef (95% CI)	*P*	*β*-coef (95% CI)	*P*	*B*-coef (95% CI)	*P*
Total PIMs	−0.16 (−0.78, 0.47)	0.612	0.08 (−0.524, 4.71)	0.749	0.07 (−0.65, 0.79)	0.850
Age			−0.26 (−0.3, −0.16)	<**0.001**	−0.25 (−0.35, −0.13)	<**0.001**
Gender (female)			−1.0 (−0.29, 0.68)	0.230	−0.79 (−2.58, 1.00)	0.387
Baseline ADAS-Cog			0.18 (0.09, 0.27)	<**0.001**	0.21 (0.12, 0.31)	<**0.001**
Study group (*Nilvadapine* versus placebo)			−0.61 (−2.30, 1.09)	0.484	−0.51 (−2.20, 1.18)	0.557
Education (years)					0.18 (−0.06, 0.43)	0.159
Diagnosis (years)					−0.57 (−1.08, −0.05)	0.033
Total comorbidities					0.08 (−0.34, 0.50)	0.706
Appropriate medications					0.08 (−0.33, 0.48)	0.716
Change in CDR-Sb	Model 1		Model 2		Model 3	
	β-coef (95% CI)	*P*	*β*-coef (95% CI)	*P*	*B*-coef (95% CI)	*P*
Total PIMs	0.08 (−0.12, 0.27)	0.427	0.05 (−0.14, 0.23)	0.641	0.05 (−0.14, 0.23)	0.969
Age			−0.07 (−0.10, −0.03)	<0.001	−0.07 (0.10, 0.03)	0.001
Gender (female)			−0.11 (−0.70, 0.48)	0.712	−0.11 (−0.70, 0.48)	0.849
Baseline CDR-sb			0.22 (0.12, 0.33)	<0.001	0.22 (−0.12, 0.33)	<0.001
Study group (*Nilvadapine* versus placebo)			−0.19 (−0.78, 0.32)	0.514	−0.19 (−0.76, 0.38)	0.568
Education (years)					−0.01 (−0.09, 0.03)	0.769
Diagnosis (years)					−0.21 (−0.40, −0.03)	0.024
Total comorbidities					−0.05 (−0.20, 0.09)	0.473
Appropriate medications					0.07 (−0.07, 0.21)	0.308

in those with mild-to-moderate AD, who may represent a particularly vulnerable group.

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Multimedica, Castellanza, Italy; Giovanni Frisoni, Centro San Giovanni di Dio—IRCCS Fatebenefratelli, Brescia, Italy; Orazio Zanetti, Centro San Giovanni di Dio—IRCCS Fatebenefratelli, Brescia, Italy; Anastasia Konsta, Aristotle University of Thessaloniki (AUTH), First Psychiatric Department, Papageorgiou General Hospital, Greece; Orologas Anastasios, Ahepa University General Hospital of Thessaloniki, Greece; Styliani Nenopoulou, Papanikolaou General Hospital of Thessaloniki, Greece; Fani Tsolaki-Tagaraki, Papanikolaou General Hospital of Thessaloniki, Greece; Magdolna Pakaski, Department of Psychiatry, University of Szeged, Hungary; Olivier Dereeper, Centre Hospitalier de Calais, France; Vincent de la Sayette, Centre Hospitalier Universitaire de Caen, France; Olivier Sénéchal, Centre Hospitalier de Lens, France; Isabelle Lavenu, Centre Hospitalier de Béthune, France; Agnès Devendeville, Centre Hospitalier Universitaire d'Amiens, France; Gauthier Calais, Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL), France; Fiona Crawford, Archer Pharmaceuticals, Sarasota, Florida, and Roskamp Institute, Sarasota, Florida; Michael Mullan, Archer Pharmaceuticals, Sarasota, Florida, and Roskamp Institute, Sarasota, Florida, Pauline Aalten, PhD, Department of Psychiatry and Neuropsychology, School of Mental Health and Neurosciences, Alzheimer Center Limburg, Maastricht University, Maastricht, the Netherlands; Maria A. Berglund, RN, Sahlgrenska University Hospital, Gothenburg, Sweden; Jurgen A. Claassen, MD, PhD, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Rianne A. De Heus, MSc, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Daan L. K. De Jong, MSc, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Olivier Godefroy, MD, PhD, Centre Hospitalier Universitaire d'Amiens, France; Siobhan Hutchinson, MD, St. James's Hospital, Dublin, Ireland; Aikaterini Ioannou, MD, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Michael Jonsson, MD, PhD, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden; Annette Kent, PhD, Trinity College Dublin (TCD), Dublin, Ireland; Jürgen Kern, MD, PhD, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden; Petros Nemtsas MD, PhD, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Minoa-Kalliopi Panidou, BSc, MA, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Laila Abdullah, PhD, Roskamp Institute, Sarasota, Florida; Daniel Paris, PhD, Roskamp Institute, Sarasota, Florida; Angelina M. Santoso, MD, MSc, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Gerrita J. van Spijker, MSc, Department of Geriatric Medicine, Radboudumc Alzheimer Center, Donders Institute of Medical Neurosciences, Radboudumc, Nijmegen, the Netherlands; Martha Spiliotou, MD, PhD, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; Georgia Thomoglou, BSc, 1st Department of Neurology, Ahepa University General Hospital, Aristotle University of Thessaloniki, Greece; and Anders Wallin, MD, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden dication optimisation in this cohort.

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