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Real-world effectiveness, its predictors and onset of action of cholinesterase inhibitors and memantine in dementia: retrospective health record study

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Background

The efficacy of acetylcholinesterase inhibitors and memantine in the symptomatic treatment of Alzheimer's disease is well-established. Randomised trials have shown them to be associated with a reduction in the rate of cognitive decline.

Aims

To investigate the real-world effectiveness of acetylcholinesterase inhibitors and memantine for dementia-causing diseases in the largest UK observational secondary care service data-set to date.

Method

We extracted mentions of relevant medications and cognitive testing (Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores) from de-identified patient records from two National Health Service (NHS) trusts. The 10-year changes in cognitive performance were modelled using a combination of generalised additive and linear mixed-effects modelling.

Results

The initial decline in MMSE and MoCA scores occurs approximately 2 years before medication is initiated. Medication prescription stabilises cognitive performance for the ensuing 2–5 months. The effect is boosted in more cognitively impaired cases at the point of medication prescription and attenuated in those taking antipsychotics. Importantly, patients who are switched between agents at least once do not experience any beneficial cognitive effect from pharmacological treatment.

Conclusions

This study presents one of the largest real-world examination of the efficacy of acetylcholinesterase inhibitors and memantine for symptomatic treatment of dementia. We found evidence that 68% of individuals respond to treatment with a period of cognitive stabilisation before continuing their decline at the pre-treatment rate.

Keywords

Pharmacological effectiveness; dementia; Alzheimer's disease; real-world data; electronic health records.

The evidence for cholinergic loss in dementia[1,2] that correlates with severity of disease informed the development of a class of drugs that inhibit the enzyme acetylcholinesterase, thus increasing the neuronal availability of acetylcholine. Three acetylcholinesterase inhibitor (AChEI) agents have been approved (donepezil, rivastigmine and galantamine) for the treatment of mild to moderate forms of Alzheimer's disease.[3–5] Memantine is the fourth available option which is thought to counteract some of the neurotoxicity in Alzheimer's disease through antagonism of the glutamate *N*-methyl-D-aspartate (NMDA) receptor.[6] In contrast to AChEIs, memantine is approved for the treatment of the more advanced forms of Alzheimer's disease.[4,7,8]

The currently approved symptomatic treatment for Alzheimer's disease rests on evidence from randomised controlled trials (RCTs) showing an effect of stabilising cognitive decline or marginally improving cognitive function for a period of 3–6 months before, typically, the patients resume their cognitive deterioration. Besides cognition, these medications are often associated with improvements in global functioning, behavioural and psychological symptoms of Alzheimer's disease and quality of daily activities in patients.[3] Efficacy over the neuropsychiatric symptoms of Alzheimer's disease may underlie the observation that withdrawal of these medications in the severe stages of the disease is associated with a higher risk of placement into institutionalised care.[5] The symptomatic benefits of these medications are associated with disease severity, as individuals with moderate to severe Alzheimer's disease tend to benefit more in comparison with those with mild disease.[9,10] Response rates reportedly vary between 20 and 60%, depending on medication dosage, sociodemographic factors (e.g. education and lifestyle) as well as presumed dementia aetiology.[4,7,8]

Although RCTs are the gold standard when investigating the effects of an intervention, they provide information only on how well the intervention performs in an ideal clinical circumstance ('efficacy'). The frequently unattainable information is how well the medication performs in real-world conditions, where a number of confounding factors are at play ('effectiveness').[11] A notable instance of an investigation into AChEI effectiveness reported it to be similar to clinical trial settings, whereby patients stabilise cognitively for a period of 6 months after the medication prescription.[12]

We sought to provide further evidence for the real-world effectiveness of AChEIs as well as memantine on cognition in people with varying severity of dementia. We used the UK-Clinical Record Interactive Search system (UK-CRIS), which transforms routinely collected clinical data into a pseudonymised resource, to study relevant medical data from two UK National Health Service (NHS) trusts. We hypothesised that we would replicate the observation that both AChEIs and memantine are associated with a temporary stabilisation in the cognitive decline of up to 6 month's duration that is predicted by severity of disease (better effectiveness in moderate-to-severe Alzheimer's disease), type of dementia (better effectiveness in

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Alzheimer's disease and mixed dementia compared with other forms), age (worse cognitive outcomes with older age), effect of other medication (worse effectiveness in patients receiving antipsychotics). We also hypothesised that a subgroup of primary non-responders would be evident and that they would be characterised by medication switches and would be associated with worse cognitive outcomes.

Method

Data sources

We used the electronic patient records of two UK Mental Health NHS Trusts (Oxford Health and Southern Health NHS Foundation Trusts, OHFT and SHFT respectively). The data are accessible through the UK-Clinical Record Interactive Search system (UK-CRIS), which provides means of analysing de-identified secondary care clinical case records from 12 UK mental health NHS trusts (https://crisnetwork.co/). UK-CRIS allows access to structured information, such as diagnoses (i.e. ICD-10 codes) and demographic information, as well as unstructured text information, such as clinical notes. The data sources contain rich free-text information on the history of the mental disorders under treatment, relevant cognitive and other structured assessments, medication treatments and other clinically relevant information. We included in our analysis patient records that featured a diagnosis of dementia through either structured ICD-10 codes or mentions of dementia diagnosis in the clinical notes. The pool of records used in the study consisted of 24 108 patients, who collectively contributed more than 3 700 000 individual clinical documents. To extract the information from the free text, we developed a natural language processing (NLP) model that extracts any mentions of diagnosis, medication and cognitive health assessments (Mini-Mental State Examination (MMSE)[13] and Montreal Cognitive Assessment (MoCA)[14]). Further information on the model and accuracy of extractions is given in supplementary Tables 1 and 2, available at https://doi.org/10.1192/bjp.2020.136). The final structured data used in the study consisted of 7415 individuals diagnosed with dementia with 23 794 MMSE scores and 4187 individuals with dementia with 8873 MoCA scores (for descriptive statistics see supplementary materials).

We assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the local UK-CRIS oversight committees and is covered by approval for the UK-CRIS database granted by the Oxfordshire and Southern Health Research Ethics Committee. Individual patient consent was not required for the use of anonymised data. The data used in the study can be accessed using the UK-CRIS environment after receiving research approvals from the relevant UK-CRIS oversight bodies. The R code for the analysis and the NLP model can be downloaded from the Open Science Framework page (https://osf.io/4xev5/).

Data analysis

The data were analysed using generalised additive mixed-effects modelling (GAMM).[15] GAMM is a data-driven method designed to estimate the non-linear relation between numeric predictors and dependent variables.[16] This method enabled study of non-linear changes in cognitive performance across the time of disease, as well as periods when cognitive ability stabilises or starts to decline.

We used a GAMM model to analyse and describe the non-linear temporal changes in cognitive scale scores (MMSE and MoCA) in relation to the time point of medication prescription as well as the modulating effects of switching between drugs. The random structure was adjusted in each model, whereby we included by-patient random intercepts. In other words, the model allowed intercepts to vary for each patient, additionally specifying patient factor as a source of variation in the data.[17,18] All models reported in the study are adjusted for age at cognitive assessment, gender and duration of dementia. Ethnicity and marital status information was not accounted for as there was a large amount of missing data and not enough variation. The main model was fitted on the joint data from the two NHS trusts (for trust-specific analysis see the supplementary materials) and we separated the analysis on the basis of MMSE and MoCA scores. Owing to the smaller number of observations for the MoCA scores, for subgroup analyses we focused only on the MMSE scores. We tested non-linear changes in cognitive performance dependent on the MMSE score at the moment of medication prescription, dividing patients into four groups: normative decline (30–25 MMSE points) and mild (24–20 MMSE points), moderate (19–13 MMSE points) and severe cognitive impairment groups (≤12 points). We calculated the periods of statistically significant changes in the slope of the non-linear function, that is, significant stabilisation or improvement in cognition as measured by cognitive tests. These periods of change in trajectory can provide information on the duration of any observed medication-induced stabilisation in cognitive performance. Besides estimating the overall shape of the function, we also sought to characterise the cognitive trajectories of responders and non-responders to medication. First, we investigated the change in MMSE scores for patients who were either switched between medications or received monotherapy throughout. Second, to calculate the percentage of responders, we looked at the patients that had at least two observations of MMSE scores taken in the period 6 months before and 6 months after the medication was prescribed, and then calculated the raw change in MMSE between these two measurements. A summary of all main variables is included in supplementary Table 3.

To investigate the intermediary effects of individual predictors on the slope of the cognitive declines, we used linear mixed-effects models as implemented in the lme4 package in R on Windows 10 operating system.[19] Similar to the GAMMs, linear mixed-effects models allow modelling of repeated measures contributed by numerous patients while quantifying effects of predictors on cognitive changes across time. Even though these models are not developed to answer questions regarding non-linearities and time changes, adding complex nonlinear interactions to the GAMM model can overfit the data, owing to the relatively small sample sizes in subcategories of factors. For the same reason, the linear mixed-effect models were fitted only on MMSE scores using the combined OHFT and SHFT data-set. We utilised these models by fitting linear functions on subsets of the data, defined in relation to the time point of medication prescription (i.e. before medication prescription, first 5 months of medication, and effects beyond 5 months). Using this approach, we examined whether factors of interest influence stages of disease differently, especially in terms of short- and long-term effects of medication. Linear models were used to test the modifying effects of severity and presumed dementia aetiology, as well as type of medication, concomitant medications (e.g. antipsychotics, antidepressants or diabetes-related medication) and gender, on the positive effects of medication using interaction terms. We also included cognitive impairment severity (MMSE at prescription) as a predictor in the model.

The standard estimation of the parameters in the linear mixed-effects analysis is a comparison between the factor combinations used in the experiment. The analysis utilises standard dummy coding of categorical predictors to estimate the regression coefficients. Specifically, one level for each factor is chosen to serve as a

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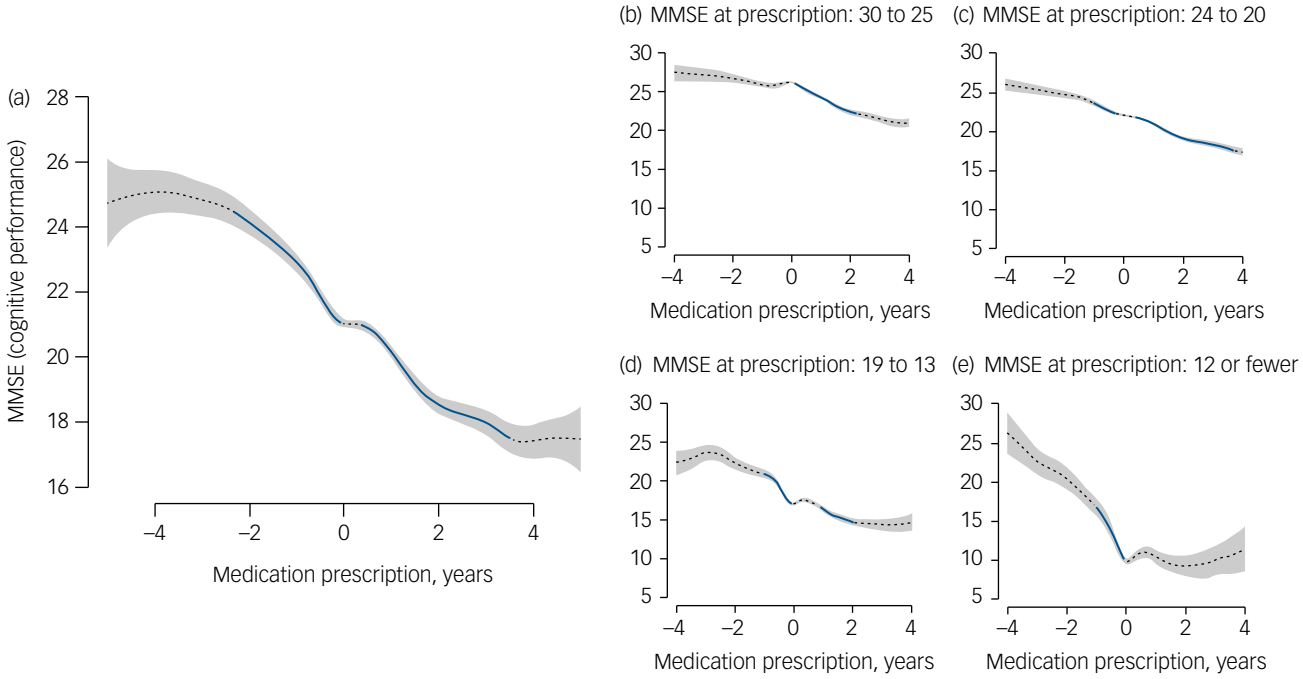

Fig. 1 Change in Mini-Mental State Examination (MMSE) scores over time in relation to the time point of medication prescription (year 0 on the *x*-axis). The solid lines indicate periods with statistically significant change in MMSE scores relative to the trajectory projected by the analysis. (b)–(e) show changes in MMSE score in patients with normal, mild, moderate and severe dementia at the time of prescription respectively.

reference level against which all other levels and their combinations are compared.

Results

Effectiveness of medication on cognitive scale scores (MMSE and MoCA scores)

We found that MMSE scores changed in a non-linear fashion relative to the time point of medication prescription. In the 3-year period prior to medication prescription, patients scored in the region of 28 MMSE points and remained broadly cognitively stable. Approximately 2 years before medication was prescribed, a statistically significant decline in cognitive performance, i.e. MMSE scores, was evident. The decline in MMSE scores lasted up to the moment when the medication was prescribed, at which point a stabilisation in cognitive change occurred (Fig. 1). This period of statistically significant stability lasted on average for 4 months, ranging from 2–5 months, OHFT and SHFT data respectively (supplementary Figs 4 and 5; the non-linear effect of age and time since diagnosis is presented in supplementary Figs 2 and 3). After this period of stabilisation, the cognitive decline continued at the rate prior to symptomatic treatment initiation.

A split by cognitive impairment severity, defined by MMSE score at medication prescription time, shows that individuals with severe deficits tended to benefit more from medication. Individuals who scored between 25 and 30 MMSE points started to decline almost immediately after starting the medication (Fig. 1(b)). Individuals with mild deficits (MMSE 20–24) stabilised in their cognition for a period of 4 months post-treatment initiation (Fig. 1(c)), whereas those with a moderate degree of impairment (MMSE 13–20, Fig. 1(d)) stabilised for a period of 10 months. Finally, individuals with severe deficits (MMSE scores <12, Fig. 1(e)) also experienced a period of stabilisation in terms of cognitive decline, but the analysis is limited by the small number of observations. An identical effect was observed when we used MoCA instead of MMSE scores as an outcome measure (supplementary Fig. 1).

Effect of medication switch

In the second step of the analysis, we examined how the observed medication effect is dependent on whether patients were switched between agents or remained on monotherapy. The monotherapy group was defined as individuals who were prescribed only one AChEI or were switched to memantine. This group was sought as a type of medication pathway that resembles suggestions from the National Institute for Health and Care Excellence (NICE) guidelines, that is, patients were prescribed one of the AChEIs and, once benefits subsided, they were switched to memantine. The switch group were all patients who were switched between symptomatic agents or took a combination of memantine and AChEIs. Contrary to the monotherapy group, these medication pathways might indicate treatments that diverge from the NICE guidelines. The majority of patients were treated with monotherapy (6062 patients or 81% of the data-sets, contributing 16 929 MMSE scores or 71% of the data-set), with the remainder (1353 patients or 19%, contributing 6865 MMSE measures or 29% of the data-set) switching at least once to a different symptomatic agent. Our results indicate differences in the duration of disease between the monotherapy group (mean 350 days, s.d. = 480) and the medication-switch group (mean 657 days, s.d. = 527; $t(1893,8) = -19.66$, $P < 0.001$). However, we also observed that those receiving monotherapy experienced benefits from the medication in the form of stabilisation in cognitive performance for approximately 5 months after medication prescription (Fig. 2(a)). Those who were switched at least once tended to continue to decline at their pre-medication rate, thus not benefiting from such pharmacological interventions (Fig. 2(b)). This effect persists after controlling for the duration of the disease in the model.

We next investigated the proportion of patients who could be defined as responders versus those who were non-responders. As

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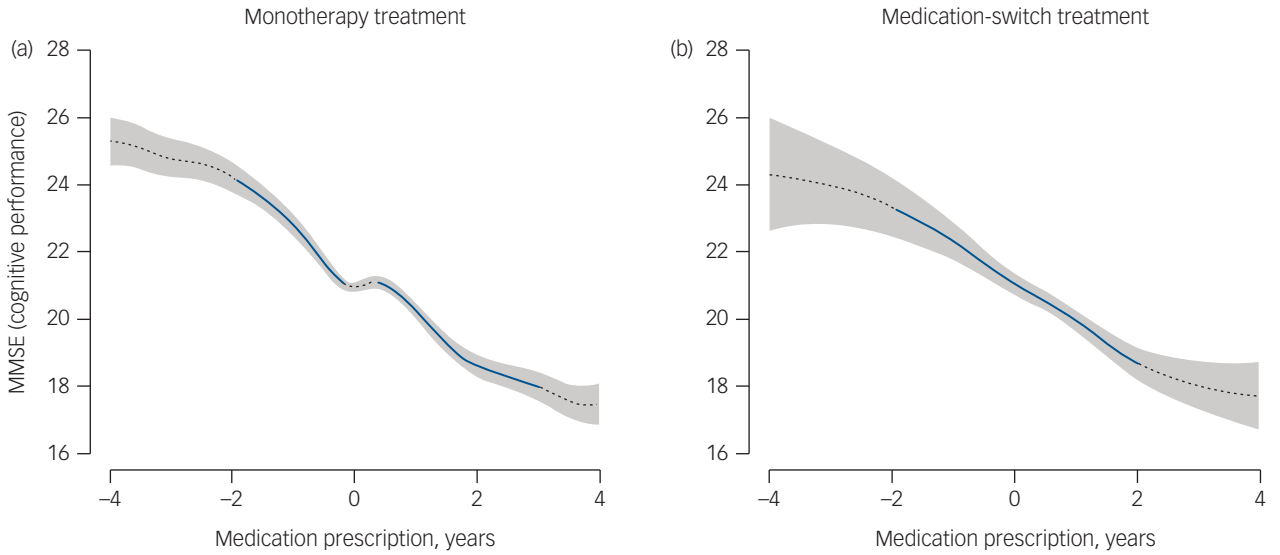

Fig. 2 Change in Mini-Mental State Examination (MMSE) scores in relation to the time point of medication prescription (represented by 0 on the *x*-axis) for individuals (a) treated with a single agent (monotherapy) and (b) who were switched agents. The solid lines indicate periods with statistically significant change in MMSE scores relative to the trajectory projected by the analysis.

described earlier, we focused on patients with at least two MMSE measurements, allowing calculation of the raw MMSE score change between the 6 months pre-prescription and the 6 months post-prescription. Using this method, we identified 1831 individuals, with 68% defined as responders (33% increased their cognitive score and 35% had stabilisation of scores) and 32% as non-responders (they continued their decline in cognitive performance from their pre-treatment score).

Predictors of response to treatment

Pre-medication period

During the pre-medication period, age and gender were significant predictors of cognitive scores. Specifically, older age ($\beta = -0.03$, s.e. = 0.01, $t = -2.97$, $P < 0.01$) and gender ($\beta_{male} = 0.50$, s.e. = 0.15, $t = 3.38$, $P < 0.001$) were associated with lower MMSE score, while over time (prior to medication) the patients declined in their cognitive performance ($\beta = -1.26$, s.e. = 0.06, $t = -18.6$, $P < 0.001$).

Immediate effectiveness (first 5 months)

During the first 5 months of medication prescription, we observed significant effects on cognitive performance from the gender factor (poorer outcome in females) but not age (Table 1). Individuals who received memantine or discontinued medication had a steeper decline in MMSE scores than those receiving symptomatic treatment continuously. More significant cognitive impairment, indicated by lower MMSE scores at the time of medication prescription, was associated with significantly lower MMSE scores at the end of the 5 months. The severity of impairment and concomitant medications affect the slope of MMSE changes and interact with the effectiveness of symptomatic dementia treatment. Individuals with more severe forms of the disease tended to benefit more from medication. Specifically, those with observations in the normal range of MMSE score at the time of medication prescription (25–30) did not seem to benefit from the medication (MMSE slope −3.21). Individuals with mild deficits (20–24 MMSE points) saw an increase in MMSE scores (Slope + Slope × $\text{Severity}_{\text{Mild}} = 0.7$ MMSE points increase per year), whereas those with a moderate and severe degree of cognitive impairment experienced an increase in their MMSE score of 3.49 and 5.77 MMSE points in a year respectively. Similar effects were observed for individuals who received antipsychotic medication at any time point. Specifically, those with concomitant antipsychotic medication did not benefit from receiving dementia-related medication, but rather they tended to decline more strongly in their cognitive performance.

Longer-term effectiveness (5 months to 4 years)

During the longer-term period post-prescription, patients continued declining in their cognitive performance at a rate consistent

Table 1 Parameters estimated using linear mixed-effects models with slopes of time adjusted for the immediate post-treatment period[a]

	Estimate	s.e.	*t*	*P*
Intercept	26.4	0.44	58.8	<0.001
Slope (MMSE points per year)	−2.55	0.42	−5.95	<0.001
Time since diagnosis	−0.16	0.03	−4.42	<0.001
Age	−0.004	0.005	−0.86	0.38
$\text{Gender}_{\text{Male}}$	0.20	0.07	2.60	<0.05
$\text{Severity}_{\text{Mild}}$	−4.01	0.10	−37.7	<0.001
$\text{Severity}_{\text{Moderate}}$	−8.50	0.16	−74.5	<0.001
$\text{Severity}_{\text{Severe}}$	−15.5	0.16	−95.7	<0.001
$\text{Medication}_{\text{Memantine}}$	−0.56	0.14	−4.93	<0.001
$\text{Medication}_{\text{Discontinued}}$	−1.00	0.25	−4.46	<0.001
$\text{Diagnosis}_{\text{MixedADVaD}}$	0.15	0.23	0.67	0.50
$\text{Diagnosis}_{\text{VaD}}$	0.39	0.19	2.02	<0.05
$\text{Diagnosis}_{\text{Unspecified}}$	0.24	0.08	3.10	<0.05
$\text{Diagnosis}_{\text{Other}}$	−0.01	0.27	−0.04	0.96
$\text{Antipsychotics}_{\text{Yes}}$	0.19	0.13	−1.49	0.13
$\text{Antidepressants}_{\text{Yes}}$	0.07	0.09	0.74	0.45
$\text{Diabetes}_{\text{Yes}}$	0.10	0.19	0.55	0.58
Slope × $\text{Severity}_{\text{Mild}}$	3.25	0.51	6.38	<0.001
Slope × $\text{Severity}_{\text{Moderate}}$	6.04	0.56	10.67	<0.001
Slope × $\text{Severity}_{\text{Severe}}$	8.32	0.90	9.27	<0.001
Slope × $\text{Antipsychotics}_{\text{Yes}}$	−3.72	0.64	−5.73	<0.001
Slope × $\text{Antidepressants}_{\text{Yes}}$	0.03	0.46	0.08	0.93
Slope × $\text{Diabetes}_{\text{Yes}}$	−0.55	0.91	−0.60	0.54

MMSE, Mini-Mental State Examination; AD, Alzheimer's disease; VaD, vascular dementia.
a. Reference levels (intercepts) are female gender (gender), normal cognitive function (severity), acetylcholinesterase inhibitors (medication), Alzheimer's disease (diagnosis) and no additional medication. The estimates of effects, indicated by subscripts, are relative to the reference level.

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Table 2 Parameters estimated using linear mixed-effect models with slopes of time adjusted for the longer-term post-treatment period[a]

	Estimate	s.e.	*t*	*P*
Intercept	22.7	1.00	22.6	<0.001
Slope (MMSE changes per year)	−1.15	0.10	−11.3	<0.001
Time since diagnosis	−0.35	0.08	−4.08	<0.001
Age	0.03	0.01	2.98	<0.05
$Gender_{Male}$	0.25	0.17	1.50	0.13
$Severity_{Mild}$	−2.86	0.20	−14.2	<0.001
$Severity_{Moderate}$	−6.50	0.22	−28.7	<0.001
$Severity_{Severe}$	−11.39	0.41	−27.6	<0.001
$Medication_{Memantine}$	−0.97	0.15	−6.30	<0.001
$Medication_{Discontinued}$	−0.91	0.15	−4.54	<0.001
$Diagnosis_{MixedADVaD}$	−0.64	0.50	−1.28	0.19
$Diagnosis_{VaD}$	0.87	0.46	1.906	0.056
$Diagnosis_{Unspecified}$	0.22	0.17	1.27	0.20
$Diagnosis_{Other}$	0.52	0.62	0.84	0.40
$Antipsychotics_{Yes}$	−1.00	0.34	−2.86	<0.05
$Antidepressants_{Yes}$	0.42	0.24	1.71	0.08
$Diabetes_{Yes}$	0.44	0.50	0.89	0.37
Slope × $Antipsychotics_{Yes}$	−0.30	0.14	−2.15	<0.05
Slope × $Antidepressants_{Yes}$	−0.17	0.09	−1.76	0.07
Slope × $Diabetes_{Yes}$	−0.15	0.19	−0.78	0.43

MMSE, Mini-Mental State Examination; AD, Alzheimer's disease; VaD, vascular dementia.
a. Reference levels (intercepts) are female gender (gender), normal cognitive function (severity), acetylcholinesterase inhibitors (medication), Alzheimer's disease (diagnosis) and no additional medication. The estimates of effects, indicated by subscripts, are relative to the reference level.

with their pre-medication cognitive trajectory (the slope of the MMSE changes was −1.15 per year) (Table 2). Age and time since diagnosis were significant factors: older age was associated with slightly higher MMSE scores, whereas a longer period since being diagnosed with dementia was associated with lower MMSE scores. The same held true for individuals treated with memantine or discontinuing treatment compared with those who were prescribed AChEIs throughout. Presumed aetiology of dementia and gender did not reach statistical significance, whereas the severity of cognitive impairment, defined as the MMSE score at medication prescription, was significant. In other words, individuals with lower initial MMSE scores had, on average, lower scores, and the change in MMSE scores across time did not differ between the groups. Finally, individuals who received antipsychotic medication during their treatment tended to have lower average MMSE scores and declined more steeply over time in comparison with those who did not receive this class of medication. Antidepressants and diabetes medication were not significant factors in the models.

Discussion

The efficacy of AChEIs and memantine is well-established, whereby previous studies have shown a short-term stabilisation of cognitive decline in Alzheimer's disease.[3,5] However, the performance of such medications is rarely assessed in real-world settings, where several confounders can modify the expected effects.[11] In this study, we utilised the UK-CRIS system to investigate the effectiveness of symptomatic pharmacological treatment of cognitive deficits in dementia-causing diseases. Electronic health records are an ideal environment to investigate the extent to which the effectiveness of treatments coincides with efficacy derived from randomised controlled trials. Using secondary care data from two UK mental health NHS trusts, we were able to demonstrate that the beneficial effects of cholinesterase inhibitors and memantine are also observed in real-world conditions.

Our analysis illustrates 10-year changes in cognitive performance as measured by the MMSE and MoCA scales. The results show that the first significant evidence for cognitive decline becomes observable approximately 2 years before medication prescription. Once the medication is prescribed, the patients tend to stabilise cognitively for the ensuing 4 months. Our study also shows that the beneficial effect of medications differs between the two NHS trusts, as the SHFT cohort had a longer period of cognitive stabilisation (5 months) than the OHFT cohort (2 months). A potential reason for this is the larger sample size of the SHFT data relative to the OHFT data. More importantly, SHFT has more patients who are followed throughout the disease course, and it therefore contributed twice the number of cases with over five observations per patient in comparison with OHFT (see descriptive statistics in the supplementary materials). Therefore, the longer duration of stabilisation observed in the SHFT cohort is likely to be a closer estimate of the real-world effectiveness of these drugs.

MMSE compared with MoCA

The MMSE results are also replicated when the MoCA scale is used. We observed that the patients were starting to decline 1 year and 8 months before initial medication prescription. Similar to the MMSE analysis, once the medication was prescribed there was an observable period of stabilisation of cognitive performance lasting approximately 7 months. MoCA is known to be more sensitive to subtler cognitive deficits than MMSE and is often used to detect a transition from normal cognition to mild cognitive impairment.[20] The MMSE test, on the other hand, better captures changes from moderate to severe degrees of cognitive impairment.[20] Given that the main difference between the two tests is the larger emphasis on executive function in MoCA, it may therefore be that the longer period of stabilisation with treatment observable with MoCA relative to MMSE indicates that these medications benefit preferentially neural networks underpinning this cognitive domain.

Responders versus non-responders

Not all patients benefit from treatment and our study estimates that approximately one-third (32%) can be classed as primary non-responders. We show that medication switches are a sensitive approach to distinguishing responders from non-responders, whereby individuals who have at least one medication switch tend to receive less or no benefit at all. In contrast, those who remain on monotherapy tend to respond better and stabilise in their cognitive changes for a period once the medication is prescribed. Importantly, the proportion of responders identified in this real-world data-set is higher than the rate identified in clinical trials and prospective cohorts (68% in our analysis, compared with 40% in other analyses), which increases the confidence in the rationale for prescribing such medications.[9,21] One potential reason for this discrepancy is the unmeasured placebo effect of medication. Increase in support of dementia treatment that people receive once they are prescribed medication or diagnosed with the disease might lead to improvements in cognitive performance.

Effects of concomitant medications and timing

Analysis of the impact of concomitant medications shows a significant influence of antipsychotics on cognitive trajectories, whereby individuals prescribed this medication class did not stabilise or improve in their cognitive performance. This effect is in line with previous studies indicating worse effectiveness of symptomatic treatment of cognitive deficits in dementia in people receiving antipsychotics.[12] We extend previous studies by showing that this effect

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continues throughout the disease course, as these individuals both have lower cognitive scores at AChEI or memantine prescription and experience a steeper cognitive decline thereafter.

The degree of cognitive impairment at the time point of ACHeI or memantine prescription attests as an equally important factor. We found that once the medication was prescribed, individuals with lower MMSE scores responded much better. Individuals with MMSE scores in the normal range continued to decline cognitively despite being prescribed symptomatic treatment, whereas those with a mild degree of impairment stabilise in their cognitive performance.[4,10] The effect is even stronger with lower MMSE scores at baseline, as patients with a moderate and severe degree of impairment experience an improvement in their cognitive performance.[12] However, the group of patients with severe impairment in our data-set was significantly smaller in comparison to all other groups. We found that these individuals were not reassessed cognitively as frequently after medication prescription relative to the milder-impairment groups and therefore these results require cautious interpretation.

Our study also showed that individuals on memantine have worse cognitive outcomes. This is unsurprising, as the UK NICE guidelines recommend memantine for moderate-to-severe Alzheimer's disease and AChEIs for the mild-to-moderate forms.[22] The guidance also states that treatment should start with the drug that has the lowest acquisition costs, resulting in donepezil being often the first choice of medication prescription. This is also illustrated in the case of our extracted NHS trust data, as most of the patients recorded in the system received donepezil (57% in SHFT and 62% in OHFT data).

Limitations

Our study illustrates the feasibility of using electronic health records to investigate the effectiveness of cognitive enhancers in dementia. There are, however, several limitations. The extracted observational data do not allow direct comparison between medications, as we cannot randomly assign patients to treatments. This is exacerbated when we take into account the heterogeneity of factors that influence patient outcomes. In particular, this study is not able to provide sufficient depth of information on the impact of concomitant medication that may affect cognition (e.g. anticholinergics[24]) beyond antidepressants and antipsychotics, owing to the pattern of inconsistent or missing recording of general practitioner-initiated prescriptions in secondary mental health records. An additional factor that our analysis is not able to differentiate is the potential impact of the level of informal and formal (i.e. community mental health team coordination, Social Services packages of care) support that patients may have received, which could be one of the multiple factors that drive differences between the two NHS trusts. Additionally, our automated NLP model extracted generally well the concepts of interest, reaching around 90% accuracy (see supplementary material). However, this accuracy decreases with certain categories (experiencer or modality subcategories) and increases the noise in the data.

Clinical implications

Beyond these limitations, we show that the combination of NLP and statistical models provides an unprecedented opportunity to examine large real-world data-sets to estimate how well RCT-reported efficacy translates into effectiveness. We believe that our paper has direct relevance to clinical practice, providing clinicians with a likelihood for the expected response and its expected duration in real-world settings (cognitive stabilisation for up to 4 months in about two-thirds of patients) to guide discussions with patients and family. It may also serve to steer debate concerning the value of switching to alternative cognitive enhancers on the basis of lack of efficacy of the initial therapy, as well as the value of antipsychotic prescription in dementia, given evidence for deleterious cognitive effects.

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Supplementary material

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Data availability

The data that support the findings of this study (textual documents and structured information) are available by application through the UK-CRIS network. Owing to the sensitivity of secondary care clinical information, access is dependent on receiving research approvals from NHS trust oversight bodies at Oxford and Southern Health NHS Foundation Trusts.

Author contributions

N.V. and I.K. wrote the manuscript; N.V., C.-H.K., A.D., G.N. and A.N.-H. designed the study; C.-H.K., A.K., C.L., A.D. and G.N. developed the natural language processing model; N.V. and Q.L. analysed the extracted data; I.K., C.-H.K. and A.H.-N. advised on the data analysis procedure; all authors revised and reviewed the manuscript.

Declaration of interest

I.K. reports membership of the Mantrah Ltd Advisory Board. A.D. reports to be a majority shareholder of Deep Cognito Ltd. A.N.-H. reports funding support from Johnson & Johnson, as well as salary support from Akrivia Health.

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EXTRA CONTENT ONLINE

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