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Real-World Effectiveness, Its Predictors and Onset of Action of Cholinesterase Inhibitors and Memantine in Dementia: A Retrospective Health Record Study of 7400 Individuals using the UK CRIS Platform

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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 associate with a reduction in the rate of cognitive decline. The aim of this study was to investigate the real-world effectiveness of acetylcholinesterase inhibitors and memantine for dementia causing diseases in the largest UK observational secondary care service dataset to date.

Methods

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 NHS Trusts. The 10-year changes of cognitive performance were modelled using a combination of generalized additive and linear mixed-effect modelling.

Results

We found that 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 to 5 months. The effect is boosted in more cognitively impaired cases at the point of medication prescription and attenuated in those taking antipsychotics. Importantly, we identify that patients who switch at least once between agents do not experience any beneficial cognitive effect from pharmacological treatment.

Conclusion

This study presents 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

Introduction

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 (AD)[3–5]. Memantine is the fourth available option which is thought to counteract some of the neurotoxicity in AD through antagonism of the glutamate NMDA receptor[6]. In contrast to AChEIs, memantine is approved for the treatment of the more advanced forms of AD[4,7,8].

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

While RCTs are the gold standard when investigating the effects of an intervention, they only provide information 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 patients with varying severity of dementia. We used the UK-CRIS system 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 associate with a temporary stabilisation in the cognitive decline of up to 6-month duration that is predicted by severity of disease (better effectiveness in moderate-to-severe AD), type of dementia (better effectiveness in AD and mixed dementia compared to other forms), age (worse cognitive outcomes with older age), effect of other medication (worse effectiveness on patients that receive antipsychotics). We also hypothesised that a sub-group of primary non-responders would be evident and that they would be characterised by medication switches and will 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 is 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. International Classification of Disease 10th revision, ICD-10, codes) and demographic information, as well as unstructured text information, e.g. clinical notes. The data sources contain rich free-text information on the history of the mental health 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 that 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])). For more information on the model and accuracy of extractions, please see the supplemental materials (i.e. Table S1 and S2). The final structured data used in the study consisted of 7,415 patients diagnosed with dementia with 23,794 MMSE scores and 4,187 patients with 8,873 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 download from the Open Science Framework page (see https://osf.io/4xev5/).

Data Analysis

The data was analysed using Generalized Additive Mixed-effect Modelling (GAMM)[15]. GAMM is a data-driven method designed to estimate the nonlinear relation between numeric predictors and dependent variables[16]. This method enabled study of nonlinear 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 nonlinear 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 supporting materials) and we separated the analysis based on MMSE and MOCA scores. Due to the smaller number of observations for the MOCA scores, for subgroup analyses we focused only on the MMSE scores. We tested nonlinear changes of cognitive performance dependent on the MMSE score at the moment of medication prescription, dividing patients into four groups: normative decline (30 to 25 MMSE points), mild (24 to 20 MMSE points), moderate (20 to 13 MMSE points) and severe cognitive impairment groups (12 points or less). We calculated the periods of statistically significant changes in the slope of the nonlinear 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. Firstly, we investigated the change in MMSE scores for patients that either switched between medications or received monotherapy throughout. Secondly, to calculate the percentage of responders, we looked at the patients that had at least two observation of MMSE scores taken in the period of 6 months before and after the medication was prescribed, and then calculated the raw change in MMSE between these two measurements. A summary table for all main variables is included in the supplemental materials (see Table S3).

To investigate the intermediary effects of individual predictors on the slope of the cognitive declines, we used linear mixed-effect models as implemented in the lme4 package in R[19]. Similar to the GAMMs, linear mixed-effect models allow modelling of repeated measures contributed by

numerous patients while quantifying effects of predictors on cognitive changes across the time. Even though these models are not developed to answer questions regarding nonlinearities and time changes, adding complex interactions to GAMM model can overfit the data, due 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 dataset. 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 five 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 (MMSE at prescription) severity as a predictor in the model.

The standard estimation of the parameters in the linear mixed-effect 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 referential 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 change in a non-linear fashion relative to the time point of medication prescription. In the three-year period prior to medication prescription patients scored in the region of 28 MMSE points and remained broadly cognitively stable. Approximately two 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 (see Figure 1). This period of statistically significant stability period lasted on average for 4 months, ranging from 2 to 5 months, OHFT and SHFT data respectively (see Figure S4 and S5 in supplementary materials; nonlinear effect of age and time since diagnosis is presented in Figures S2 and S3). After this period of stabilisation, the cognitive decline continued at the rate prior to symptomatic treatment initiation.

INSERT FIGURE 1

A split by cognitive impairment severity, defined by MMSE score at medication prescription time, shows that patients with severe deficits tended to benefit more from medication (see Figure 1B). Patients that scored between 25 to 30 MMSE points, started to decline almost immediately after starting the medication (Figure 1C). Patients with mild deficits (MMSE 20-24) stabilise in their cognition for a period of 4 months post-treatment initiation (Figure 1D), while the ones with a moderate degree of impairment (MMSE 13-20, Figure 1E) stabilise for a period of 10 months. Finally, patients with severe deficits (MMSE scores <12, Figure S5D) also experience 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 (see Figure S1 in supplemental materials).

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 patients who were prescribed only one AChEi or switched to memantine in their records. This group was sought as a type of medication pathway that resembles suggestions from the 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 that 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 (6,062 patients or 81% of the datasets, contributing 16,929 MMSE scores or 71% of the dataset) with the remainder (1,353 patients or 19% contributing 6,865 MMSE measures or 29% of the dataset) switching at least once to a different symptomatic agent. Our results indicate differences in the duration of disease between monotherapy patients (M = 350 days, SD= 480) and medication switch group (M = 657 days, SD = 527; $t(1893,8) = -19.66$, $p < .001$). However, we also observed that those receiving monotherapy experience benefits from the medication in the form of stabilisation in cognitive performance for approximately 5 months after medication prescription (Figure 2A). Those who switched at least once tended to continue to decline at their pre-medication rate thus not benefiting from such pharmacological interventions (Figure 2B). This effect persists after controlling for the duration of the disease in the model.

INSERT FIGURE 2

We went on to investigate the proportion of patients who could be defined as responders versus those that were non-responders. As described earlier, we focused on patients with at least two MMSE measurements, allowing calculation of raw the MMSE score change between the 6 months pre-prescription versus the 6-month period post-prescription. Using this method, we identified 1521

patients with 68% defined as responders (29% increased their cognitive score and 39% had stabilisation of scores). Respectively, 32% 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 ($\beta = -0.03$, SE = 0.01, t-value = -2.97, $p < .01$) and gender ($\beta_{male} = 0.50$, SE = 0.15, t-value = 3.38, $p < .001$) were associated with lower MMSE score, while over time (prior to medication) the patients declined in their cognitive performance ($\beta = -1.26$, SE = 0.06, t-value = -18.6, $p < .001$).

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. Patients that received memantine or that discontinued medication had a steeper decline in MMSE scores than patients receiving symptomatic treatment continuously. More significant cognitive impairment, indicated by lower MMSE score 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. Patients with more severe forms of the disease tended to benefit more from medication. Specifically, patients with observation 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). Patients with mild deficits (20-24 MMSE points) saw an increase in MMSE scores (Slope + Slope x $Severity_{Mild}$ = 0.7 MMSE points increase per year), while the patients 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 are observed for patients that received antipsychotic medication at any time point. Specifically, patients with concomitant antipsychotic medication do not benefit from receiving dementia-related medication, but rather they tend to decline stronger in their cognitive performance (Table 1).

INSERT TABLE 1

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

INSERT TABLE 2

Discussion and conclusion

The efficacy of AChEIs and memantine is well established, whereby previous studies have shown a short-term stabilisation of cognitive decline in AD[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 represent an ideal environment to investigate the extent to which the effectiveness of treatments coincides with efficacy derived from randomised clinical 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 the 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 gets 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, whereby SHFT patients had a longer period of cognitive stabilisation (5 months) as opposed to the OHFT cohort (2 months). A potential reason for this is the larger sample size of the SHFT relative to OHFT data. More importantly, the SHFT Trust has more patients that are followed throughout the disease course, whereby it contributes twice the number of cases with over 5 observations per patient in comparison to OHFT (see descriptive statistics in supplemental materials). Therefore, the longer duration of stabilisation observed in the SHFT is likely to be a closer estimate of the real-world effectiveness of these drugs.

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 is prescribed there is 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.

Not all patients benefit from treatment and our study estimates that approximately a 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 patients that make at least one medication switch tend to receive less or no benefits at all. In contrast, patients 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 dataset is higher than the rate identified in clinical trials and prospective cohorts (68% in our analysis vs 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 patients receive once prescribed medication or diagnosed with the disease might lead to improvements in cognitive performance.

Analysis of the impact of concomitant medications shows a significant influence of antipsychotics on cognitive trajectories, whereby patients prescribed this medication class do 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 patients that receive antipsychotics[12]. We extend previous studies by showing that this effect continues throughout the disease course as these patients both have lower cognitive scores at AChEI/memantine prescription and experience a steeper cognitive decline thereafter.

The degree of cognitive impairment at the time point of medication prescription attests as an equally important factor. We found that once the medication is prescribed, patients with lower MMSE scores respond much better. Patients with MMSE scores in the normal range continue to

decline cognitively despite being prescribed symptomatic treatment, while patients 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 dataset was significantly smaller in comparison to all other groups. We found that these patients are not re-assessed 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 AD 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, whereby most of the patients recorded in the system received donepezil (57% in SHFT and 62% in OHFT data).

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 does not allow the 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 impact cognition (e.g. anticholinergics[24]) beyond antidepressants and antipsychotics due to the pattern of an inconsistent or missing recording of GP-initiated in secondary mental health records. An additional factor that our analysis was not able to differentiate was the potential impact of the level of informal and formal (i.e. Community Mental Health Team coordination, Social Services Package of Care) support that patients may have received, which could be one of the multiple factors that drives differences between two NHS Trusts. Additionally, our automated NLP model extracted

generally well the concepts of interest, reaching around 90% of accuracy (see supplementary materials). However, this accuracy decreases with certain categories (experiencer or modality subcategories) and increases the noise in the data.

Beyond these limitations, we show that the combination of NLP and statistical models provides an unprecedented opportunity to examine large real-world datasets to estimate how well RCT reported efficacy translates into effectiveness. Finally, 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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Declaration of interest:

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

Data Availability

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