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Article type : Original Article

Non-memory cognitive symptom development in Alzheimer's disease

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ene.14185](https://doi.org/10.1111/ene.14185)

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Key words

Alzheimer's, cognition, symptom change, age, symptom history, progression

Non-memory cognitive symptom development in Alzheimer's disease

Abstract

BACKGROUND: Memory is known to be the most common first symptom in Alzheimer's Disease.

Assessing non-memory cognitive symptom development in Alzheimer's Disease is important for understanding disease progression and the potential identification of treatment-responsive subtypes.

METHODS: Data from the National Alzheimer Co-ordinating Center were examined. Logistic regression models were fitted evaluating development of judgement, language, visuospatial and attention symptoms at first and second visits to Alzheimer's Disease Centers. Predictors were age and prior symptoms, adjusting for symptom length and sex. The models were then refitted assessing APOE- ϵ 4 effects.

RESULTS: Each decade reduction in presentation age increased the odds of language, visuospatial and attention symptom development at both visits by 8-18% ($p < 0.05$, all tests), and judgement symptoms at second visit by 13% ($p < 0.05$). Prior symptoms were not equally predictive of symptom development. For example, having first-predominant language symptoms carried the lowest risk of developing other first-visit symptoms and having memory symptoms was a stronger predictor of developing judgement than other symptoms. The APOE- ϵ 4 gene showed little impact on symptom development when included as a predictor.

CONCLUSIONS: Our findings provide support for the concept that younger-onset AD is associated with the progressive development of more non-memory symptoms beyond the first time point. Associations between symptoms were evident, which may reflect that pathology can remain isolated in a network for

some time. APOE- ϵ 4 status had little influence on cognitive symptom development which may indicate that the effect it has occurs very early in the disease course.

1. Introduction

It is increasingly recognised that memory dysfunction is not always the first or the only cognitive symptom experienced by those with Alzheimer's disease (AD) [1–7]. Many patients experience non-memory cognitive symptoms as their first symptom and those with younger onset (usually onset before 65 years) are more likely to have early non-memory symptoms than older patients [3–7]. There is increased recognition of non-amnestic subtypes of AD including language, visuospatial presentations and executive dysfunction [2]. Less understood is whether there is a pattern of non-memory cognitive symptom development and whether patient variables are important predictors. It has been suggested that the biggest genetic risk factor for sporadic AD (the APOE- ϵ 4 allele [8]) may influence the presentation [9,10]. For example, those with an ϵ 4 allele are more likely to have memory as the first predominant symptom or an isolated amnestic presentation [11].

The presence of cognitive symptoms, as opposed to neuropsychological test scores, is important to investigate as symptoms are easy to evaluate and closely relate to patients' experiences. Further, non-memory symptom data associate with activities of daily living suggesting that patients' lives are affected when symptoms are present [12,13]. However, symptom data can be difficult to analyse due to their categorical nature. A high prevalence of specific symptoms can also be problematic if comparisons are made between individuals with and without a symptom, or in analyses assessing predictors of developing a symptom, so large datasets are required.

In this study we used an AD patient dataset to examine the relationship between age and the development of new non-memory cognitive symptoms, and whether previously-recorded symptoms influenced non-memory symptom development. Finally, the influence of APOE- ϵ 4 was examined. We hypothesised that: younger AD patients would be more likely to develop non-memory cognitive symptoms; there was likely to be an influence of prior symptoms on symptom development; those without an APOE- ϵ 4 gene were more likely to develop non-memory symptoms.

2. Methods

2.1 Subjects

AD patient data collected by the National Alzheimer's Coordinating Center (NACC) were analysed. NACC maintains a database of standardized clinical research data from individuals with normal cognition, mild cognitive impairment and neurodegenerative diseases, collected from past and present NIA-funded US Alzheimer's Disease Centers (ADCs). Written informed consents were obtained from participants and the study was approved by an Institutional Review Board (IRB) at each ADC. Research using the NACC database was approved by the University of Washington IRB. NACC recruitment and data collection has been described previously [14]. Data included patients seen at 34 ADCs between study inception in 2005 and May 2016. Our study required subjects diagnosed with probable or possible AD according to standard diagnostic criteria [15] at their first NACC visit (n>9000).

Since most patients only had early visit data, analyses were restricted to the first two NACC visits. At each visit, patients were assessed by their clinician for the presence or absence of up to seven cognitive symptoms and "other" cognitive symptoms. The clinician's judgement was used to determine symptom presence in consultation with the patient and caregivers. Missing data were typically due to information not being collected or changes in versions of datasheets. The first predominant cognitive symptom was recorded by the clinician, indicating which of the symptom categories was first recognized as a decline in the subject's cognition. The age at which the clinician estimated cognitive decline began was also recorded.

Descriptive summaries of each first predominant cognitive symptom were used to identify symptoms as outcome variables in the analysis. Memory was excluded since its high frequency meant that few patients were at risk of developing this symptom during follow-up. Cognitive symptoms reported in only small numbers of patients were excluded as outcome variables since their rarity would make the statistical power of analyses low.

2.2 Variables

We used first predominant cognitive symptoms reported at first visit, first and second visit cognitive symptoms, symptom duration (between age of decline and age of presentation), interval between the first and second visits, age of presentation, and gender. Mini-mental state examination scores at first visit were also used for group characterisation.

2.3 Statistical analysis

All analyses were conducted in Stata v15. Summary statistics were produced for the variables of interest. Missing responses for symptom presence were explored for both visits.

Logistic regression was the primary method of analysis. The outcome in each model was the development of a symptom never previously reported. Different models were used for symptom development at the first and second NACC visits since only first predominant symptom was available for predicting symptoms at first visit, whereas presence of each of the other symptoms at first visit was also available at the second visit.

Each first visit symptom outcome was modelled separately; modelling the odds of developing the cognitive symptoms of interest at the first NACC visit, conditional on this not being the first predominant cognitive symptom. Therefore, we only explore new symptoms developed between the first predominant symptom and first visit. The predictors of interest were age at first visit, and the first predominant cognitive symptom, adjusting for gender and symptom duration.

The odds of developing symptoms at the second visit were modelled, conditional on the symptom neither being the first predominant cognitive symptom nor reported at visit 1. Predictors of interest were age at first visit, first predominant cognitive symptom, first visit cognitive symptoms, with adjustment for gender, symptom duration prior to first visit and the inter-visit interval. Joint Wald tests assessed whether there was evidence that the first predominant cognitive symptom remained a predictor at visit 2, after adjusting for visit 1 symptoms. Models were fitted omitting the first predominant symptom if found not to improve model fit. Joint Wald tests assessed whether there was evidence that the odds ratios associated with each first visit cognitive symptom predictor were heterogeneous.

To explore APOE- ϵ 4 effects, each of the models described above was re-fitted, adjusting for categorical ϵ 4 allele number.

3. Results

3.1 Demographics

9484 patients attended the first NACC visit, with 87% reporting memory impairment as the first predominant cognitive symptom (see table 1 for summary statistics). Proportions of patients with each reported cognitive symptom at each visit are shown in figure 1. Four non-memory symptoms (impairments of judgement, language, visuospatial function and attention) were deemed sufficiently

prevalent to include as outcomes in the symptom development models. See supplementary table S1 for missing baseline variables and supplementary figure S1 for age of presentation distribution.

Table 1: Patient characteristics for the whole AD group

* Data missing for 2640 (27.8%) patients

†Fluctuating cognition and orientation were added as categories in revised versions of data collection sheets

Figure 1: AD patients reporting each cognitive symptom at visits 1 (n=9484) and 2 (n=5538)

58% of patients attended both visits; orientation and “other” were the most frequently missing symptoms, with patients only asked about orientation symptoms at visit 2, so this was missing at visit 1.

3.2 First visit

Results from models relating development of first visit symptoms to age at presentation, symptom duration, gender and first predominant cognitive symptom are shown in figure 2. There was evidence that older patients were less likely to develop language, visuospatial and attention symptoms, with a decade later age of presentation associated with an estimated 8 to 18% decrease in the odds of reporting these. An increase in symptom duration prior to first visit increased the likelihood of developing all non-memory symptoms, with a one-year increase in length of symptoms associated with estimated increases in odds of reporting these symptoms of 12 to 21%. Gender effects differed according to symptom: women were more likely to develop impaired judgement (19% increase in odds) and attention (11% increase in odds) symptoms while men were more likely to develop language symptoms (11% increase in odds).

Amongst the common first predominant symptoms, memory carried the highest risk for development of impaired judgement. Language and visuospatial function carried the lowest; the odds were lower and statistically significant for both compared with memory. Having language impairment as the first predominant symptom also carried the lowest risk of developing visuospatial symptoms (statistically significantly lower than memory) and the lowest risk of developing attention symptoms, although here differences between first predominant symptoms were less marked, with only judgement carrying a higher risk than the other common first predominant symptoms. For development of language symptoms, having memory or visuospatial function as the first predominant symptom carried the lowest risks, with the risk for memory being statistically significantly lower than those for attention and judgement.

Figure 2: Comparative odds ratios (95% CI) for the development of each of four cognitive symptoms at visit 1 (n/N=number of patients who developed symptom/number at risk). Some 95% CI extend beyond the shown range.

3.3 Second visit

The estimated associations between development of second visit symptoms and age at presentation, symptom length, time between visits, gender and first visit symptoms are shown in figure 3. Wald tests indicated that after adjusting for the symptoms reported at visit 1, there was no evidence of a residual predictive effect of first predominant cognitive symptom ($p>0.1$, all tests, see supplementary table S2).

There was strong evidence that younger subjects were more likely to develop all non-memory cognitive symptoms, with increases in the odds of reporting these symptoms at visit 2 varying from 11 to 23% for a decade later presentation age. Women had 34% lower odds than men of developing judgement symptoms at visit 2. Time between visits was strongly positively predictive of the development of all non-memory cognitive symptoms.

Where there was evidence that first visit symptoms were predictive of second visit symptoms, the relationship was positive. The Wald tests suggested that visit 1 symptoms were not equally predictive of development of judgement and visuospatial function symptoms. Memory problems at visit 1 more than tripled the odds of developing judgement symptoms at visit 2. For visuospatial symptoms at visit 2, memory and judgement symptoms were the strongest predictors, each approximately doubling the odds of development. For development of visit 2 language and attention symptoms, there was no evidence that symptoms were unequally predictive.

Figure 3: Comparative odds ratios (95% CI) for the development of each of four cognitive symptoms at visit 2 (n/N=number of patients who developed symptom/number at risk). Some 95% CI extend beyond the shown range.

3.4 The effect of APOE- ϵ 4

The effect of APOE- ϵ 4 was typically small, with no consistent pattern in the direction of estimated effects (see supplementary table S3). There was one statistically significant result; notably with sixteen analyses the danger of a false-positive is high.

4. Discussion

Our study found that each decade reduction in presentation age was associated with development of non-memory cognitive symptoms over time, and first visit symptom development differed according to first predominant cognitive symptom. Memory carried the highest risk and language the lowest of

developing impaired judgement. Having language as the first predominant symptom also carried the lowest risk of developing visuospatial and attention symptoms. For development of language symptoms, memory or visuospatial functioning as first predominant cognitive symptom carried the lowest risks.

Considering non-memory cognitive symptoms at visit 2, only symptoms developed by visit 1 were predictive of symptom development. Having memory symptoms was a markedly stronger predictor than the others for developing judgement symptoms. Gender had some influence over first visit symptom development (women were more likely to develop attention and judgement symptoms, but less likely to develop language symptoms). At the second visit, men were more likely to develop judgement symptoms. There was no convincing evidence that APOE- ϵ 4 was predictive of non-memory cognitive symptoms.

Finding that younger patients were more likely to develop three of the four non-memory cognitive symptoms between the first predominant symptom occurring and first visit is consistent with the view that younger patients are more likely to have a more non-memory presentation. Further, these results show that more non-memory cognitive domains are affected faster in younger patients. The evidence for patterns of prediction of symptom development may support the theory that pathology can be isolated within specific brain networks before spreading.

The effects of age on presentation observed are consistent with other studies indicating that younger patients have more non-memory cognitive symptoms [3–7]. One similar study assessing development of cognitive problems demonstrated that younger patients were more likely to develop language and concentration problems over time [16].

Finding that language impairment carried the lowest risk for developing other non-memory cognitive symptoms at first visit is possibly attributable to isolated and focal damage at early disease stages [17].

We found some influence of gender on symptom development, particularly at first visit. Results in the literature are mixed. Two studies have shown no significant differences in gender between typical and atypical AD groups [5,18]. Other studies have shown differences: one showed the visual variant of AD were slightly more likely to be female [11]; another that women were more likely to have first predominant memory symptoms than non-memory symptoms [3].

Our lack of significant predictive results for APOE- ϵ 4 seems at odds with the literature [3,11,19]. However, results are mixed: recent work has shown the ϵ 4 allele to be associated with increased risk of posterior cortical atrophy (PCA) [20]. Other work has shown that visuospatial, executive functioning and attention problems differ in early vs. late AD and this age effect is unchanged by adjusting for APOE- ϵ 4 [21]. Our

current work differs from previous analyses as it assesses non-memory cognitive symptom development, including those with memory as a first symptom, adjusting for whether an individual had the symptom previously. Therefore, many non-carriers will have memory as the first symptom. Our data may thus imply that the APOE- ϵ 4 effect on presentation occurs early in the disease and little effect remains once prior symptoms are accounted for.

The main strength of our study is that it is a large multi-site study with systematic data collection.

However, we did not examine autopsy-confirmed AD cases; our findings may be influenced by misdiagnoses which may be more prevalent in younger-onset cases [5]. Missing data was present in our analyses due to rolling recruitment and subject withdrawal and not all subjects had APOE testing.

Collection of first predominant symptom and age of decline carries risks of recall bias; more objective measures of cognitive function, such as neuropsychological test results, were not investigated. The NACC dataset represents a convenience dataset; the patients are not necessarily representative of the wider AD population. We cannot make conclusions regarding the weight of specific symptoms beyond the first predominant symptom. The initial symptom may still predominate patients' experiences throughout the disease [11].

Younger-onset patients develop more non-memory symptoms, allowing for already-acquired symptoms, suggesting a different course of AD in these patients. APOE- ϵ 4 genotype does not explain these findings, suggesting that other genes may have a role in non-memory symptom development. Non-memory cognitive symptoms are important to assess, especially in younger-onset cases.

Acknowledgements

The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50

AG047270 (PI Stephen Strittmatter, MD, PhD). The Dementia Research Centre is supported by Alzheimer's Research UK, Brain Research Trust, and The Wolfson Foundation. This work was supported by the NIHR Queen Square Dementia Biomedical Research Unit and the National Institute for Health Research Biomedical Research Centre (BRC). J Barnes is an Alzheimer's Research UK Senior Research Fellow.

Conflicts of interest

None

Funding sources

JB: Alzheimer's Research UK

Data Availability

The data that support the findings of this study are available from the National Alzheimer's Coordinating Center (NACC). Restrictions apply to the availability of these data, which were used under license for this study. Data are available at <https://www.alz.washington.edu/> with the permission of NACC.

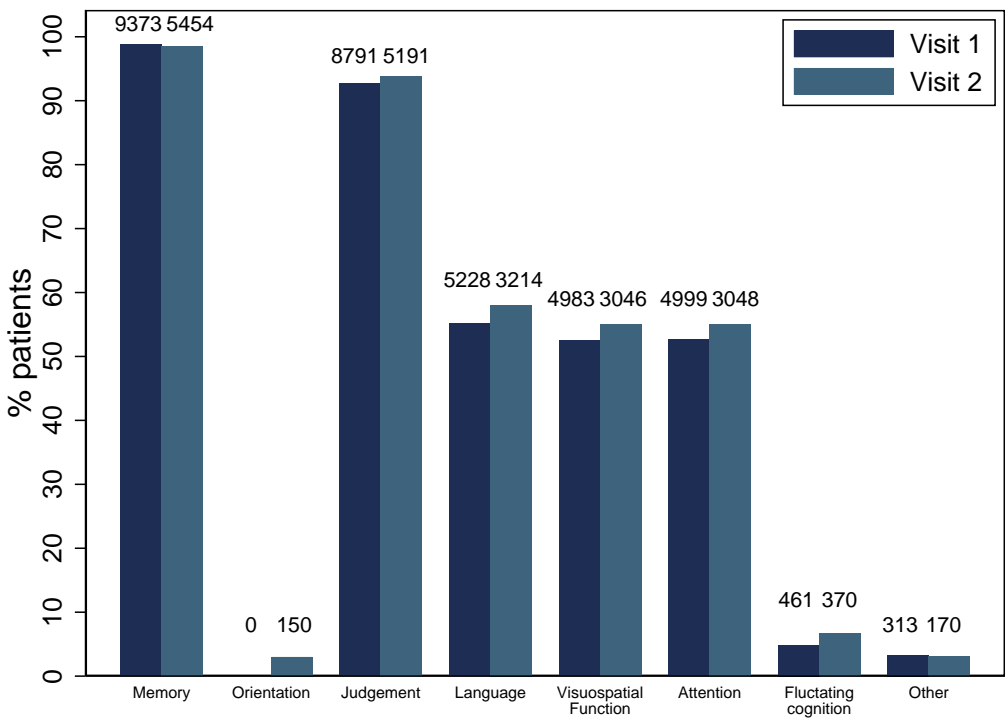
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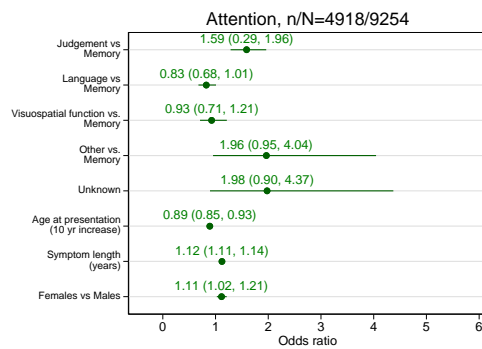
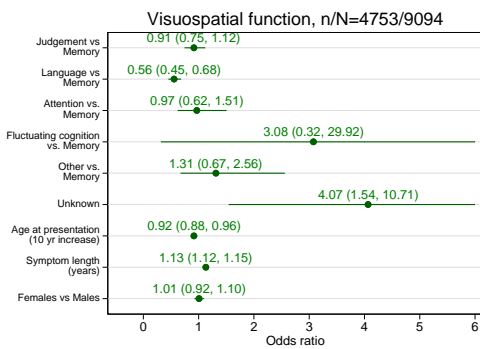
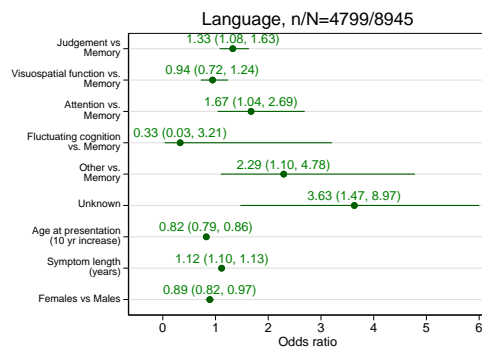
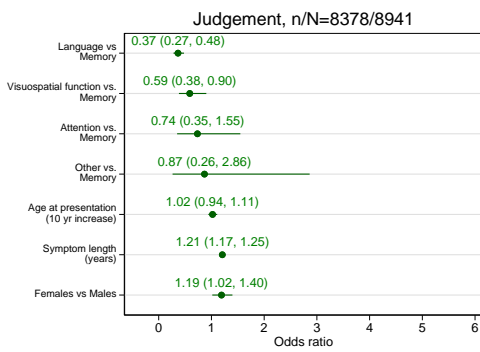
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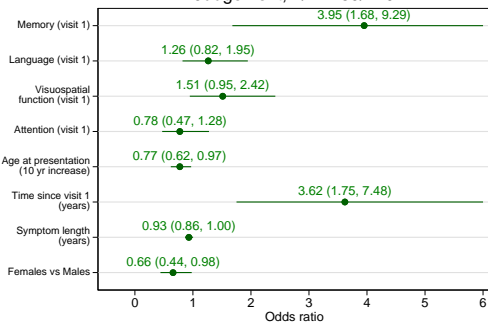
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		Summary statistics
N		9484
Mean age at first visit (SD) [Range]		74.9 (9.9) [35-110]
Mean MMSE at first visit (SD) [Range]		19.3 (6.8) [0-30]
Women (%)		5283 (56)
Symptom duration in years (SD)		4.8 (3.4)
Time between visits 1 and 2, years (SD)		1.2 (0.4)
Attended visit 1 (%)		9484 (100)
Attended visit 2 (%)		5538 (58)
APOE-ε4 alleles (%)*	0	2913 (30.7)
	1	3046 (32.1)
	2	885 (9.3)
First predominant cognitive symptom (%)†	Memory	8257 (87)
	Orientation	0 (0)
	Judgement	413 (4)
	Language	429 (5)
	Visuospatial function	230 (2)
	Attention/concentration	82 (0.8)
	Fluctuating cognition	4 (<0.1)
Other	38 (0.4)	

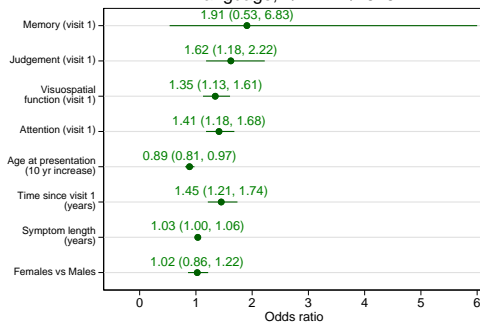




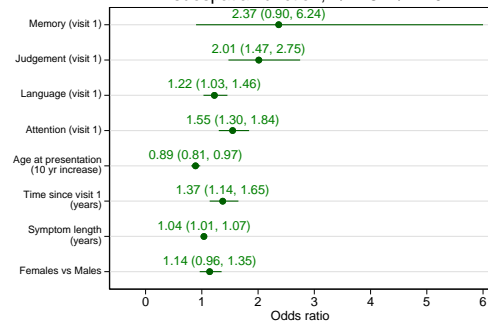
Judgement, n/N=259/449



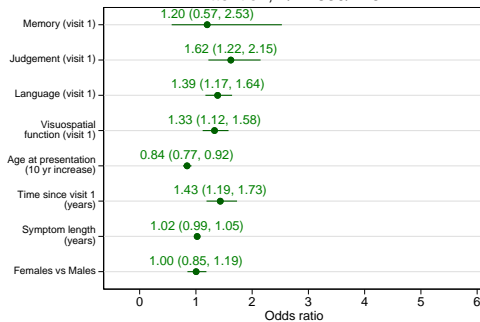
Language, n/N=771/2646



Visuospatial function, n/N=817/2720



Attention, n/N=830/2752



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1. ONgentys® Summary of Product Characteristics.
2. Rocha J et al. Eur J Clin Pharmacol 2014;70:909-17.
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5. Tasmor® Summary of Product Characteristics.

* Catechol-O-Methyltransferase

** Randomized, double-blind, gender-balanced, parallel-group study performed in 4 groups of 20 healthy subjects each. Eligible subjects were enrolled into one of the dosing groups. From the 20 healthy subjects per group, 4 received placebo (PLC) during the entire study, 16 subjects in one of the groups received PLC once daily for 11 days, and on day 12, 200 mg entacapone (ENT) concomitantly with each levodopa/carbidopa (LC) dose (3 times separated by a 6-h interval).

16 subjects in each of the remaining three groups received respectively 25, 50, and 75 mg opicapone (OPC) once daily for 11 days, and on day 12, PLC concomitantly with each LC dose.

*** Pharmacokinetic studies carried out in healthy patients.

AUC Opicapone 50 mg vs levodopa/carbidopa 100/25 mg + entacapone 200 mg: 148 (CI 106; 208)

AUC Opicapone 50 mg vs levodopa/carbidopa 100/25 mg: 166 (CI 139; 196)

AUC Opicapone 50 mg vs levodopa/benserazide 100/25 mg: 195 (CI 139; 281)

Prescribing Information

ONgentys® (opicapone)

Read the SPC before prescribing. Presentation: Capsules containing 50 mg of opicapone. Indication: Adjunctive therapy to preparations of levodopa/DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations. Dose and administration: The recommended dose of opicapone is 50 mg. It should be taken once-daily at bedtime at least one hour before or after levodopa combinations. Opicapone enhances the effects of levodopa. Hence, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating the treatment with opicapone. Elderly patients: No dose adjustment is needed for elderly patients. Caution must be exercised in patients > 85 years of age as there is limited experience in this age group. Patients with renal impairment: No dose adjustment is necessary in patients with renal impairment, as opicapone is not excreted by the kidney. Patients with hepatic impairment: No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh Class B). Caution must be exercised in these patients and dose adjustment may be necessary. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh Class C); therefore, ONgentys is not recommended in these patients. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms. History of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis. Concomitant use with monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of Parkinson's disease.

Pregnancy: ONgentys is not recommended during pregnancy and in women of childbearing potential not using contraception. Lactation: Breast-feeding should be discontinued during treatment with ONgentys. Warnings and precautions: Opicapone enhances the effects of levodopa. To reduce levodopa-related dopaminergic adverse reactions (e.g. dyskinesia, hallucinations, nausea, vomiting and orthostatic hypotension), it is often necessary to adjust the daily dose of levodopa by extending the dosing intervals and/or reducing the amount of levodopa per dose within the first days to first weeks after initiating treatment with ONgentys, according to the clinical condition of the patient. ONgentys contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take ONgentys. Patients and care-givers should be made aware that impulse control disorders including pathological gambling, increased libido, hypersensitivity, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. Patients should be monitored regularly for the development of impulse control disorders and review of treatment is recommended if such symptoms develop. Increases in liver enzymes were reported in studies with the metabolite of medicinal products containing a catechol group that are metabolised by COMT, e.g. imitrex, isoprenaline, adrenaline, noradrenaline, dopamine, desopamine or dobutamine, leading to potentiated effects of these medicinal products. Careful monitoring of patients being treated with these medicinal products is advised when opicapone is used. Concomitant use with tricyclic antidepressants and noradrenaline re-uptake inhibitors (e.g. venlafaxine, maprotiline and desipramine) should be considered with appropriate caution. Particular consideration should be given to medicinal products metabolised by CYP2C19 and their co-administration must be avoided. Particular consideration should be given to medicinal products transported by OATP1B1 and their concomitant use should be considered with appropriate caution. Adverse events: Refer to the SPC for all side effects. Very common side effects (>10%): Dyskinesia. Common side effects (>10% to <10%): Abnormal dreams, hallucination, hallucination visual, insomnia, dizziness, headache, somnolence, orthostatic hypotension, constipation, dry mouth, vomiting, muscle spasms, blood creatine phosphokinase increased. Uncommon side effects (>1/1000 to <1/100): Decreased appetite, hyperglycaemia, anxiety, depression, hallucination auditory, nightmares, sleep disorder, dysgeusia, hyperkinesia, syncope, dry eye, ear congestion, palpitations, hypertension, hypotension, dyspnoea, abdominal distention, abdominal pain upper, dyspepsia, muscle twitching, musculoskeletal stiffness, myalgia, pain in extremity, chromaturia, nocturia, weight decreased. Legal Category: POM. Basic UK NHS cost: ONgentys pack of 30 (50 mg). Marketing authorisation numbers: EU/16/006/003. Marketing authorisation holder: Bial-Portela & Co., S.A. A Avenida da Siderurgia nacional 4745-487 Corcoado (S. Romão e S. Mamede) - Portugal.