Polypharmacy is associated with functional decline in Alzheimer's disease and Lewy body dementia

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ABSTRACT

Background: In dementia, a number of factors may influence functional decline in addition to cognition. In this study, we aim to study the potential association of the number of prescribed medications with functional decline trajectories over a five-year follow-up in people diagnosed with mild Alzheimer's disease (AD) or Lewy Body dementia(LBD).

Methods: This is a longitudinal analysis of a Norwegian cohort study entitled "The Dementia Study of Western Norway". We included 196 patients newly diagnosed with AD (n = 111) and LBD (n = 85), followed annually for 5 years. We conducted linear mixed-effects models to analyze the association of the number of medications with functional decline measured by the Rapid Disability Rating Scale – 2.

Results: The mean prescribed medications at baseline was 4.18∓2.60, for AD 3.92∓2.51 and LBD 4.52∓2.70. The number of medications increased during the follow-up; at year five the mean for AD was 7.28∓4.42 and for LBD 8.11∓5.16. Using more medications was associated with faster functional decline in AD (Est 0.04,SE0.01, p-value 0.003) and LBD (Est 0.08, SE 0.03, p-value 0.008) after adjusting for age, sex, comorbidity, neuropsychiatric symptoms, and cognition. For each medication added during the follow-up, functional trajectories worsened by 1% for AD and 2% for LBD. The number of medications was not associated with cognitive decline.

Conclusion: We found that higher number of medications was related to a faster functional decline, both in AD and LBD. Prescription especially in dementia should be carefully assessed, thus prognosis in dementia might possibly be improved.

1. Introduction

Dementia is one of the greatest challenges of the 21st century. Around 50 million people were living with dementia by 2015, a number that is expected to increase to 130 million by mid-century (Livingston et al., 2017). Alzheimer's disease (AD) is the most common etiology of neurodegenerative dementia, followed by Lewy Body dementia (LBD) (Stevens et al., 2002). Functional status is an important predictor of complications, morbidity, and mortality, but it also reflects independence, wellbeing, and quality of life. (Bierman, 2001)

Functional decline is mandatory for dementia diagnosis, and it has to be severe enough to affect independence of function in daily life. Functional decline is also a marker for dementia progression (McKeith et al., 2017). To prevent and possibly reverse functional decline is therefore vital in the management of dementia.

In dementia, a number of factors may influence functional decline in addition to cognition (Borda et al., 2020a; Borda et al., 2021). It is therefore important to improve the functional prognosis of people with neurodegenerative diseases with more comprehensive interventions.(Namioka et al., 2015; Welsh, Gladman, & Gordon, 2014b) One poten-

tially relevant factor in older people with dementia is polypharmacy. In Europe 26% to 40% of older adults take five or more prescribed medications daily, while in the United States this applies to approximately 30%, increasing to more than the 50% when over-the-counter medications and herbal preparations are included.(Khezrian, McNeil, Murray, & Myint, 2020; Qato et al., 2008) Medication use increases with age, and people with dementia are more often exposed to polypharmacy than people without dementia.(Kristensen et al., 2018) Polypharmacy has been shown to have negative effects in older people and is associated with several geriatric syndromes such as cognitive impairment, urinary incontinence, falls, malnutrition, frailty, depression, and weight loss.(Gutiérrez-Valencia et al., 2018; Palmer et al., 2019; Saraf et al., 2016) Daily usage of a high number of medications is associated with a decline in nutritional status, functional ability, and cognitive capacity in older adults. (Jyrkkä, Enlund, Lavikainen, Sulkava, & Hartikainen, 2011) In addition, research suggests a cumulative dose-dependent relationship between the number of prescribed medications and these outcomes. (Rawle, Cooper, Kuh, & Richards, 2018)

More evidence is needed about the effect of polypharmacy in dementia in relation to functional loss, especially in people diagnosed with LBD. In this paper, we aimed to explore the potential association of the number of prescribed medications with the trajectories of functional decline in older adults living with AD and LBD over a 5-year follow-up.

2. Methods

2.1. Design and sample

We performed a 5-year longitudinal analysis of a Norwegian cohort, "The Dementia Study of Western Norway" (DemVest). This study recruited patients with a first-time diagnosis of mild dementia referred to dementia clinics in Western Norway. To reduce referral bias, the general practitioners in the area were contacted by letter prior to study start and invited to refer all patients with suspected dementia. All dementia diagnostic units (geriatric, neurology, and psychiatric) in the region recruited to the study. All residents are covered by the same National Insurance Scheme with restricted copayments, allowing the representation of a general dementia population. After the main inclusion period between 2005 and 2007 ("mild dementia cohort" (MDC)), we continued throughout 2013 to selectively recruit patients with LBD, i.e., dementia with Lewy bodies and Parkinson's disease dementia to enhance the number of patients in this group.(Aarsland et al., 2008)

For this analysis, we included patients with AD and LBD with complete information about medication use, activities of daily living (ADL), and cognition, giving a total of 196 participants (AD = 111; LBD = 85) with annual follow-up. We combined subjects with Parkinson's Disease Dementia (PDD) into a single group with Dementia with Lewy bodies (DLB), given pathological and clinical similarities. (McKeith et al., 2017) flowchart of inclusion is shown in Appendix A.

2.2. Exclusion criteria

Subjects with moderate and severe forms of dementia were excluded, as well as those with delirium, previous bipolar disorder, psychotic disorders, terminal illness, or having been diagnosed with any major somatic disease that might alter cognitive function. Further information on DemVest study methods is published elsewhere. (Aarsland et al., 2008; Rongve et al., 2016; Vik-Mo, Giil, Ballard, & Aarsland, 2018)

2.3. Diagnosis

Dementia was diagnosed after a consensus meeting with three specialists including both psychiatry and geriatric medicine according to the DSM-IV criteria, and classified for specific dementia: for AD with

the National Institute of Neurological and Communicative Disorders, Stroke-Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984), for DLB (McKeith et al., 2017), and PDD(Emre et al., 2007) with the DLB 2005 consensus criteria and the Movement Disorder Task Force based on a comprehensive clinical assessment and biomarker program. The diagnoses were reviewed regularly during the study by a multidisciplinary consensus group as previously described (Skogseth et al., 2017). In addition, 56 subjects had a pathological diagnosis, with a diagnostic accuracy above 80% when clinical criteria were applied(Skogseth et al., 2017). Criteria for a diagnosis of mild dementia included a Mini-Mental Status Examination (MMSE) score ≥ of 20 and/ or a Clinical Dementia Rating (CDR) global score = 1.

2.4. Variables

2.4.1. Medication classification

Medication names and dosage were retrieved at baseline from patient or caregiver report at each assessment. Data about over-the-counter drugs were not obtained. Drugs were classified according to the Anatomical Therapeutic Chemical classification system (ATC) (WHO, 2014). Drugs were registered at baseline and yearly during the 5 years of the study follow-up.

2.4.2. Functional decline in activities of daily living

Instrumental and basic activities of daily living were evaluated with the Norwegian version of the Rapid Disability Rating Scale-2 (RDRS-2) (Linn, 1988). RDRS-2 was performed in person by the research nurses at the various outpatient clinics. Included items were: 1. Eating, 2. Making simple food (e.g. sandwiches), 3. Cooking dinner and adhering to a diet, 4. Mobilization - inside / outside (with or without aids), 5. Daily personal care (including brushing teeth, combing hair, and maintaining personal hygiene), 6. Bathing/showering, 7. Dressing (including finding clothes) 8. Toilet usage (including occasional clothing and cleaning), 9. Usage of telephone 10. Buying food and other necessary items, 11. Handling money and paying bills, 12. Having a financial overview plan ahead and writing tax returns, 13. Taking medications as prescribed.

Items were scored from 1 to 4 (Alone = 1, with some help = 2, with a lot of help, = 3 and cannot perform = 4) and then divided over the number of items (0 minimum and 4 maximum total score). Scores were categorized by follow-up year (Borda et al., 2020b; Borda et al., 2020d). The more functional decline, the higher the score.

2.4.3. Other variables

Cognitive function was evaluated with the MMSE, and its trajectory was examined during the follow-up as a continuous variable (Folstein, Folstein, & McHugh, 1975). For exploring comorbidities, we used the Cumulative Illness Rating Scale (CIRS) (higher value indicates more/ higher comorbidities)(Linn, Linn, & Gurel, 1968). The Norwegian version of the Neuropsychiatric Inventory (NPI) with 12 domains was used to interview family or caregivers, and the nursing home version (NPI-Nursing Home) was applied when participants were admitted to nursing homes (Cummings et al., 1994; Røen et al., 2015). Evaluations were completed by the informant who had the most day-to-day contact with the patient. The NPI domains were registered as positive or not within the last 4 weeks, and if present, rated according to their frequency 1–4 and severity 1–3. We calculated the product of the frequency and severity score for the domains.

2.5. Statistical analysis

A descriptive analysis was performed by estimating percentages for categorical variables and means and standard deviations for quantitative variables. We also evaluated the differences between groups using Pearson's chi-squared test for categorical variables and the Student's T-

test for quantitative variables. Random coefficient mixed models were used to analyze the potential longitudinal association of the consumption of medications and functional decline for a) AD patients, b) LBD patients, and c) all patients. For longitudinal trajectories of decline, time was used in its linear and quadratic forms. The random effects were an intercept and a slope for time to each subject in the study, assuming an unstructured covariance matrix. For model selection, Bayesian Information Criterion (BIC) was used, and variables' significance was carried out at 0.05. The model for ADL prediction was adjusted for confounders: age, sex, comorbidities at baseline (CIRS), NPI, and cognition.(Borda et al., 2020a) The model for MMSE prediction was adjusted for the same variables, with ADL in place of MMSE. Since medications are likely to be used to treat NPS and comorbidities, and the use itself may lead to worsening of cognition and function by them-

Fig. 1. Number of medications used per diagnosis during the follow-up.

selves, we included the interaction effect NPI-polypharmacy and CIRS-polypharmacy in the model (Scarmeas et al., 2005). We show unadjusted and adjusted model results. Statistical analyses were performed using STATA 15®.

3. Results

Descriptive analysis is shown in Table 1. The mean age was 75.30 ± 7.36 years, with no significant difference between the groups. In AD the majority of participants were women (73%), meanwhile, in the LBD group, 55.3% were men. The CIRS score was significantly higher in the LBD group 6.59 ± 2.55 compared to AD 5.33 ± 2.44, p-value 0.001. Functional activities of daily living were more compromised at baseline in the LBD group, with an RDRS-2 score of 1.96 ± 0.64 vs 1.58 ± 0.47 in AD and worsening to year 5 in both groups; AD 2.90 ∓ 0.55, LBD 3.21 ∓ 0.57. The mean number of medications was 4.52 ± 2.70 in LBD compared to 3.92 ± 2.51 in AD and it increased to 8.11 ± 5.16 in LBD and 7.28 ± 4.42 in AD after 5 years. Table 1. Fig. 1.

Table 2 presents the estimation of the coefficients for an unadjusted and adjusted model. The estimations are followed by their standard er-

Table 1
Baseline characteristics of the study sample.

Variable	AD (n = 111)	LBD (n = 85)	Total (n = 196)	P-Value
	n (%) or Mean ∓ SD			
Age	75.20 ∓ 7.73	75.42 ∓ 6.90	75.30 ∓ 7.36	0.837
Sex				<0.001
Female	81 (72.97)	38 (44.71)	77 (39.29)	
Male	30 (27.03)	47 (55.29)	119 (60.71)	
CIRS	5.33 ∓ 2.44	6.59 ∓ 2.55	5.83 ∓ 2.55	0.001
NPI total	16.04 ∓ 16.77	24.53 ∓ 18.68	19.28 ∓ 17.97	0.004
MMSE	23.61 ∓ 2.32	23.76 ∓ 3.17	23.68 ∓ 2.72	0.690
RDRS-2	1.58 ∓ 0.47	1.96 ∓ 0.64	1.75 ∓ 0.58	<0.001
Numb. of Medic.	3.92 ∓ 2.51	4.52 ∓ 2.70	4.18 ∓ 2.60	0.110

Abbreviations: AD = Alzheimer´s disease, RDRS-2 = Activities of daily living measured by the Rapid Disability Rating Scale-2, CIRS = Cumulative Illness Rating Scale, SD = standard deviation, LBD = Lewy bodies dementia, MMSE = Mini-mental state examination, NPI total = Total score of the Neuropsychiatric Inventory.
- Differences between AD and LBD were assessed by Pearson's Chi-square test for gender and by Student's T-test for all other variables
- Females given as frequencies and (percentages), otherwise mean ± standard deviations

Table 2
Association between medication use and functional decline across 5 years follow-up in AD and LBD.

	Alzheimer's disease			Dementia with Lewy Bodies			Total		
	Estimation	Standard Error	P-value	Estimation	Standard Error	P-value	Estimation	Standard Error	P-value
Unadjusted models									
Intercept	1.53	0.07	<0.001	1.76	0.09	<0.001	1.62	0.06	<0.001
Numb. of Medic.	0.02	0.01	<0.001	0.02	0.01	0.006	0.03	0.01	<0.001
Time	0.31	0.04	<0.001	0.45	0.05	<0.001	0.36	0.03	<0.001
Time2	-0.01	0.01	0.311	-0.03	0.01	0.005	-0.02	0.01	0.005
Adjusted models									
Intercept	1.51	0.36	<0.001	1.73	0.58	0.004	1.60	0.31	<0.001
Numb. of Medic.	0.04	0.01	0.003	0.08	0.03	0.008	0.05	0.01	<0.001
Interaction with CIRS	0.00	0.00	0.191	0.00	0.00	0.215	0.00	0.00	0.067
Interaction with Total NPI	0.00	0.00	0.184	0.00	0.00	0.046	0.00	0.00	0.043
Time	0.22	0.03	<0.001	0.26	0.06	<0.001	0.24	0.03	<0.001
Time2	-0.01	0.01	0.029	-0.02	0.01	0.041	-0.02	0.01	<0.001
Age	0.01	0.00	0.043	0.01	0.01	0.172	0.01	0.00	0.013
Sex vs. Female	-0.16	0.08	0.044	-0.14	0.10	0.177	-0.23	0.06	<0.001
CIRS	0.02	0.02	0.245	0.03	0.03	0.412	0.03	0.02	0.051
Total NPI	0.01	0.00	<0.001	0.01	0.00	0.002	0.01	0.00	<0.001
MMSE	-0.04	0.00	<0.001	-0.05	0.01	<0.001	-0.04	0.00	<0.001

BIC for Unadjusted models AD (620.0) LBD (548.1) Tot (1150.8) Adjusted models AD (616.5) LBD (501.3) Tot (995.0)
* Size effect for Numb. of medic. for AD (0.05) LBD (0.06) Tot (0.07) adjusted models.
Abbreviations: AD = Alzheimer´s disease, CIRS = Cumulative Illness Rating Scale, LBD = Lewy body dementia, MMSE = Mini-mental state examination, NPI total = Total score of the Neuropsychiatric Inventory.
- P values < 0.05 are printed in bold.
-Time was evaluated with its quadratic and linear terms.
- Linear mixed models, RDRS-2 measured longitudinally and its association with the functional trajectory
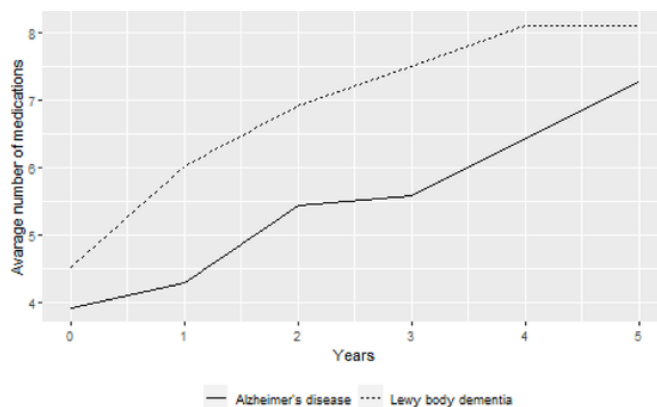
ror and statistical significance. For the adjusted model the use of more medications was associated with faster functional decline in AD (Est 0.04, SE 0.01, p-value 0.003) and LBD (Est 0.08, SE 0.03, p-value 0.008) after adjusting for age, sex, comorbidity, neuropsychiatric symptoms, and cognition. For each medication added during the follow-up, function, as measured with the RDRS-2, in total decreased by 1% for AD and 2% for LBD. Table 2. Fig. 2.

RDRS-2: Rapid Disability Rating Scale-2. A higher RDRS-2 score indicates more impaired ADL. Average covariates, female reference.

Cognitive decline was not associated with the number of medications after adjustments in AD (Est -0.07, SE0.12, p-value 0.588), LBD (Est 0.07, SE 0.25, p-value 0.767) or the total group (Est 0.01, SE 0.11, p-value 0.946). Please see Appendix 2.

4. Discussion

We found the number of medications to be associated with functional decline over the 5 year study period, i.e., the more medications, the more functional decline. Importantly, we controlled this result for frequent causes of medication prescription and functional decline such as NPS, cognition, and comorbidity. We observed that for each medication added during the follow-up, function, as measured with the RDRS-2, decreased by 1% for AD and 2% for LBD.

Polypharmacy may be related to potentially inappropriate medications (PIM), a term used to describe medications that could lead to adverse outcomes that exceed benefits (Motter, Fritzen, Hilmer, Paniz É, & Paniz, 2018), increasing the risk of adverse outcomes, overall morbidity, mortality, and costs. (Gallagher, Barry, Ryan, Hartigan, & O'Mahony, 2008) Our group has previously reported a prevalence of 14% of PIM in mild dementia, clinically relevant but not as high as what has been reported in most of the studies. This might be related to the dementia stage. (Delgado, Bowman, & Clare, 2020; Oesterhus et al., 2017) People with dementia have a higher risk of having PIM and also are more vulnerable to adverse effects arising from PIM.(Underlien Kristensen, Jensen-Dahm, Gasse, & Waldemar, 2021)

However, not only the considered PIM can be harmful, as a high number of prescribed medications in itself is associated with higher risks of adverse effects (Mueller et al., 2018). Moreover, as the dementia disease progresses, deprescribing unnecessary medications is recommended.(Tjia et al., 2014) In most cases, medications can be prescribed according to the current guidelines, but might be unnecessary if a comprehensive person-centered evaluation is performed.(Bunn et al., 2017; Welsh et al., 2014a) The management of frail older adults is based on 3 main pillars: physical activity, protein-calorie supplementation, and deprescription of unnecessary medications.(Dent et al., 2019; Lee et al., 2018) Especially in dementia, prescription of medications in chronic conditions sometimes does not contribute to improving health outcomes, quality of life or reflects the needs of people with the disease.
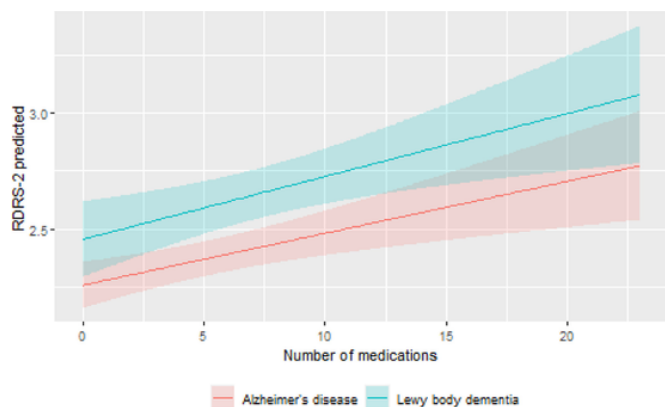

Fig. 2. The longitudinal trajectory of ADL according to the number of medications consumed.

(Motter et al., 2018; Page et al., 2018) Conversely, it may worsen prognosis and increase complications.(Borda et al., 2020c; Gnjidic, Agogo, Ramsey, Moga, & Allore, 2018; Parsons, 2017)

As seen in Fig. 1, we found an increasing prescription frequency during the 5 years of the follow-up, both in the LBD and AD groups, which on average were prescribed 8 and 7 medications, respectively. Earlier research has found similar patterns during the course of dementia. (Denholm, Morris, & Payne, 2019) With dementia progression, deprescribing is needed.(Bayliss et al., 2020) However, we found an opposite trend with disease progression. Additionally, other researchers have reported similar results when older adults with advanced dementia receive medications with questionable benefit that incur substantial associated costs.(Tjia et al., 2014)

Patients with polypharmacy are at high risk of having drug interactions. (O'Mahony & Parbhoo, 2020) In an earlier publication from our group(Borda et al., 2020c) we reported how benzodiazepines have negative effects on functional prognosis and how these effects get more pronounced when a second medication such as an antidepressant is added. Drug side effects, drug-drug interactions, drug-disease interactions, or inadequate dosage may drive negative consequences that affect physical function. The risk of presenting any of these increases when more medications are added. (Katsimpris, Linseisen, Meisinger, & Volaklis, 2019)

A standardized definition of polypharmacy is still lacking, as a recent review found numerical definitions to range between 2 and 11 medications, with the most used being 5 or more medications daily. This variation in definitions makes it even more difficult to assess the appropriateness and safety of the therapy.(Masnoon, Shakib, Kalisch-Ellett, & Caughey, 2017) It is still unclear which interventions can significantly reduce polypharmacy.(Rankin et al., 2018) Useful and validated scales such as STOPP/START have been developed(O'Mahony, 2020), however, they are not fully integrated into clinical practice. These should be used together with a person-based comprehensive geriatric assessment (CGA), in which other individual conditions like nutrition, functional status, presence of geriatric syndromes, and particular individual benefit are considered before and after prescription. (Ramjaun, Nassif, Krotneva, Huang, & Meguerditchian, 2013)

Our work has some limitations. It may have potential recruitment bias because of referrals of patients from primary care, which may have led to a greater number of patients with complicated dementia, with higher comorbidity and consequently higher polypharmacy. However, GPs were encouraged to refer any patient with suspected dementia, and patients from psychiatric, neurological, and geriatric clinics were included. Since higher medication rates are associated with mortality, there may be a confounding bias, as death was a major reason for dropping out of the study. A high dropout rate and high expected mortality, particularly in LBD, may have confounded the observed course of functional decline.

Factors such as comorbidity, disease progression, and presence of NPS impact on the number of used medications and ADL, therefore we adjusted our model for MMSE, NPI, and CIRS trying to control for these interactions. The decline in cognitive function has also been related to polypharmacy after adjustments, however, we did not find an independent association. See Appendix 1. This result strengthens the reported relationship between the number of medications and functional decline, weakening the biases that exist when considering disease progression as a cause of higher prescription and thus faster functional loss. (Delgado et al., 2020; Maresova et al., 2019)

Our study has several strengths. It has a long follow-up period, with annual assessments using structured instruments and with high data integrity. Due to the long follow-up changes in the studied variables could be determined from mild to severe dementia. There is scarce evidence exploring medication and daily functioning, particularly in people with LBD. We established the diagnoses using well-validated clinical rigorous criteria, and diagnoses have shown good accuracy when compared

to neuropathological diagnoses.(McKhann et al., 1984; Skogseth et al., 2017)

In summary, we found that using a higher number of medications was related to a faster functional decline, both in AD and LBD. Additionally, we found an increasing polypharmacy prevalence with disease progression. There is a need for longitudinal studies focusing on interventions for addressing polypharmacy and PIM in dementia, with the encouragement of better and person-centered prescribing and deprescribing practices.

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Statement of ethics

This study was approved by the regional ethics committee (approval code: 2010/633) and the Norwegian authorities for the collection of medical data. All data was handled and kept following national health and data privacy protocols. All participants signed an informed consent form before inclusion in the study.

Availability of data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author´s contribution

Miguel Germán Borda: Conception of work, Formal analysis, Methodology, Visualization, Writing- Reviewing and Editing.

Nicolás Castelanos-Perilla: Preparation of the initial draft, manuscript writing, review and approval

Diego Alejandro Tovar-Rios: Formal analysis, Writing- Reviewing and Editing

Ragnhild Oesterhus: Conception of work, Methodology, Visualization, Writing- Reviewing and Editing.

Hogne Soennesyn: Methodology, Visualization, Writing- Reviewing and Editing, supervision.

Dag Aarsland: Methodology, Visualization, Writing- Reviewing and Editing, supervision.

Uncited References:

Borda et al., 2020; Welsh, Gordon, & Gladman, 2014

Declaration of Competing Interest

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2021.104459.

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