ORIGINAL RESEARCH

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Evaluation of Polypharmacy and Potentially Inappropriate Medication Use in Older Adults with Dementia Using the TIME Criteria

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Abstract

Objective: Polypharmacy and potentially inappropriate medication (PIM) are well-known risk factors for several negative health outcomes. However, polypharmacy, undertreatment, and PIMs in Turkish patients with dementia are not well-described. This study aimed to examine and compare the prevalence of polypharmacy, potential prescription omissions (PPOs), and PIMs in older adults with and without dementia in a nationwide population.

Materials and Methods: This study retrospectively evaluated the older patients (aged ≥65 years) who were admitted to the outpatient clinic of a university hospital. Patients were classified as dementia and no-dementia according to the International Classification of Diseases codes, mini-mental state examination score, clinical dementia rating scores, and clinical history. Polypharmacy, PIM, and PPO rates were compared among patients with and without dementia. The Turkish Inappropriate Medication Use in the Elderly criteria was used to define PIMs and PPOs.

Results: This study analyzed a total of 265 patients, wherein 21.5% of patients had at least one PIM and 20% had at least one PPO. Patients with dementia were more frequently exposed to polypharmacy (dementia: 51.9% vs. no-dementia: 48.1%, p<0.001) and likewise PPOs (dementia: 34.3% vs. no-dementia: 12.1%, p<0.001). Additionally, PPO prevalence increased with the severity of dementia. However, PIM prevalence was similar between patients with and without dementia (p=0.52).

Conclusion: Polypharmacy and PPOs were widespread in the older population and more in people with dementia.

Keywords: Dementia, inappropriate prescribing, older adults, polypharmacy, potentially inappropriate medication, Turkish, TIME criteria

Introduction

It is estimated that 55 million people are living with dementia, and there are nearly 10 million new cases worldwide every year (1). Dementia patients experience higher levels of comorbidities and may receive more medications than their cognitively intact counterparts (2). Prescribing for older people is a complex process where benefits of treatment must be weighed against the risks. In people with dementia, prescribing is further complicated by difficulties with communication, changing goals of care, and a high prevalence of multi-morbidity. Dementia patients may receive suboptimal care for diseases, as well as could be exposed to potentially inappropriate medications (PIMs) (3). Potentially inappropriate prescribing (PIP) has been associated with an increased risk of adverse drug events, hospitalization, mortality, and lower quality of life in older people with and without dementia (4,5).

Polypharmacy defined as the concurrent use of multiple (i.e., five or more) medications by a patient and it is common in dementia patients (6,7). Polypharmacy is not always means inappropriate but adds possible adverse side effects and lead potential drug interactions (8). Polypharmacy and PIMs could cause serious medical problems, increased hospitalizations, costs, falls and

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deaths (9-11). Herewith, several tools have been developed to identify PIMs and PPOs in older people for use in research and in clinical settings. Beers criteria and STOPP/START criteria are the most commonly used tools (12,13). Prescribing habits and locally available drugs may vary between countries. Recently, The Turkish Inappropriate Medication Use in the Elderly (TIME) criteria were created by national experts for screening PIPs in older adults (14). TIME criteria composed of 112 TIME to STOP and 41 TIME to START criteria (14). The TIME criteria have been developed primarily for use in Turkey and the Eastern European region. However, the validation study suggests that the TIME criteria set could be used in both central and Eastern European countries (15).

The higher number of co-morbidities and excess medications give tendency to PIMs use and adverse drug reactions in dementia patients. So, that could lead to increased risk of hospital admission, higher health care costs and mortality. However, few studies have focused on the appropriateness of prescribing, particularly in the presence of chronic conditions in dementia patients. The aims of the study were describing the prevalence of PIMs and PPOs, report the medications identified as inappropriate, and compared polypharmacy, PIMs, and PPOs rates between the patients with and without dementia.

Materials and Methods

Study population and Data collection

This was a single-center, retrospective, observational study at a tertiary hospital outpatient clinic. We included ≥65 years' old patients according to their first admission records, who were admitted at 2016-2020. The study included patients with and without dementia as control cases. Dementia patients were identified as individuals registered with dementia diagnosis on ICD-9 codes. Also, these patients' diagnosis was confirmed with medical history and/or imagining results. Severity of the dementia was determined according to clinical dementia rating (CDR) scale scores (16). We excluded the patients whom dementia diagnosis was suspicious. Also, individuals were excluded if they had missing medical history, laboratory results, drug name and doses or any data. Among the 24.512 patients admitted to the outpatient clinic between 2016-2020, 265 patient files were selected for statistical analysis as described above protocol (Figure 1). Demographic variables such as age, gender, marital status, body mass index, living condition were recorded. Chronic diseases, current diagnoses, medications were noted, and Charlson comorbidity index score was calculated for each person. Also, we recorded comprehensive geriatric assessment results and geriatric syndromes. Functional capacity was assessed by Katz basic activities of daily living (Katz ADL) and Lawton-Brody instrumental activities of daily living scales (17,18). Cognitive status was assessed by the Mini-Mental State

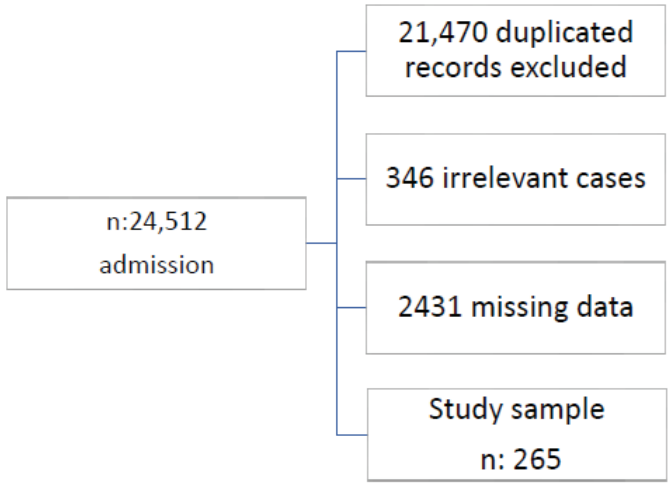

Figure 1. Study flowchart

Examination (MMSE) (19). Mood was evaluated by Yesavage Geriatric depression scale short-form (20). Nutritional status was evaluated by mini nutritional assessment short form which was validated in Turkish culture (21). The study protocol was approved by Local Ethics Committee.

Polypharmacy was defined as ≥5 drug usage (6). Total number of used drugs excluding topical agents was counted per patient. We used TIME to STOP and TIME to START criteria to define PIMs and PPOs (14). TIME criteria composed of 112 TIME to STOP and 41 TIME to START criteria. Due to the study protocol, we examined all patients' medications and doses according to TIME criteria. Person-based dichotomous variables were constructed indicating whether PIMs and PPOs, by matching the names and formulations of all medications taken by the subject with medications listed in the TIME criteria. Also, we recorded the drug formulations of PIMs and PPOs for the analysis.

Statistics

All statistical analyses were conducted using IBM SPSS 22. Descriptive statistics were shown as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for skew distributed variables, and percentages in case of categorical variables. Patients were divided and compared into two groups as dementia patients and no-dementia patients. Chi-square test was used to determine differences between categorical variables. The comparison of quantitative data was done by independent samples t-test for normal distributed variables and categorical data were compared by chi-square test. For non-normally distributed variables, Mann-Whitney U test were conducted for two groups and Kruskal-Wallis test were conducted to compare parameters for more than 2 groups. Also, Mann-Whitney U test was performed to test the significance of pair wise differences using Bonferroni correction to adjust for multiple comparisons. For the multivariate analysis, the possible factors identified with univariate analyses were further entered

into logistic regression analysis to determine independent correlates for dementia. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A 5% type-1 error level was used to infer statistical significance.

Results

Totally 265 patients were recruited for statistical analysis in this study. Mean age was 75.7±6.7 years and 64.5% were female. In the whole group 105 patients (39.3%) had dementia diagnosis; 18.5% had mild dementia, 14% had moderate dementia, and 6.8% had severe dementia according to CDR scores. Dementia patients were more likely to be older and to have lower ADL and IADL scores. Comorbidity rates were similar except depression and urinary incontinence between dementia patients and no-dementia patients. Polypharmacy was seen in 50.2%. According to TIME criteria, there were 57 (21.5%) patients had at least one PIM and 53 (20%) patients had at least one PPO in whole group. Demographic variables, comprehensive geriatric assessment results in the study population are summarized in Table 1.

Table 1. Characteristics of the study population

Properties		Total (n=265)	Normal cognitive functions (n=160)	Dementia (n=105)	p
Age, mean ± SD		75.7±6.7	73.8±6.2	78.7±6.3	<0.001
Gender, female n (%)		14 (53.8%)	109 (68.1%)	62 (59%)	0.13
Education, n (%)	Illiterate	75 (28.3%)	32 (30.8%)	43 (43.5%)	0.46
	<8 years	91 (34.4%)	51 (49%)	40 (40.8%)	
	8-11 years	14 (5.3%)	8 (7.7%)	6 (6.1%)	
	>11 years	22 (8.3%)	13 (12.5%)	9 (9.2%)	
Living status, n (%)	Alone	24 (9%)	18 (11.6%)	6 (5.8%)	0.13
	Non-alone	233 (87.9%)	136 (87.7%)	97 (93.3%)	
	Nursing home	8 (3.1%)	1 (0.6%)	1 (1%)	
Polypharmacy, n (%)		133 (50.2%)	64 (48.1%)	69 (51.9%)	<0.001
N of drug, median (IQR)		5 (4)	4 (4)	6 (3)	<0.001
Charlson comorbidity index score, median (IQR)		4 (2)	4(2)	5 (2)	<0.001
Co-morbidities, n (%)					
- Diabetes mellitus		96 (36.2%)	63 (39.4%)	33 (31.4%)	0.18
- Hypertension		196 (74%)	120 (75%)	76 (72.4%)	0.63
- Coronary artery disease		64 (24.1%)	39 (24.4%)	25 (23.8%)	0.91
- Congestive heart failure		18 (6.8%)	9 (5.6%)	9 (8.7%)	0.34
- Atrial fibrillation		28 (10.6%)	14 (8.8%)	14 (13.3%)	0.23
- COPD/Asthma		30 (11.3%)	20 (7.5%)	10 (3.8%)	0.55
- Chronic renal failure		11 (4.2%)	4 (2.5%)	7 (6.8%)	0.9
- Parkinsonism		9 (3.4%)	5 (3.1%)	4 (3.8%)	0.76
- Cerebrovascular accident		15 (5.8%)	7 (4.4%)	8 (7.6%)	0.26
- Depression		66 (25%)	25 (15.6%)	41 (39%)	<0.001
- Osteoporosis		76 (28.6%)	44 (28.2%)	32 (32.3%)	0.48
- Urinary incontinence		76 (28.6%)	25 (15.6%)	51 (48.6%)	<0.001
- Benign prostate hyperplasia		11 (4.2%)	4 (2.5%)	7 (15.8%)	0.22
Comprehensive geriatric assessment, median (IQR)					
- Katz ADL		6 (1)	6 (0)	5 (4)	<0.001
- Lawton-Brody IADL		7 (4)	8 (1)	3 (6)	<0.001
- MMSE		26 (10)	29 (3)	18 (10)	<0.001
- MNA-SF		13 (3)	14 (2)	12 (3)	<0.001
- Yesavage GDS-SF		2 (4)	1 (3)	2 (5)	0.11

Continuous variables with normal distribution were presented as mean (SD), and non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were given as numbers and percentages. ADL: Activities of daily living, COPD: Chronic obstructive pulmonary disease, GDS-SF: Geriatric depression scale-short form, IADL: Instrumental activities of daily living, MMSE: Mini mental state examination, MNA-SF: Mini nutritional assessment-short form

According to TIME to STOP criteria, there were 57 (21.5%) patients with at least one PIM. Moreover, according to TIME to START criteria, there were 53 (20%) patients with at least one PPO in whole group. The more common PIMs were proton pump inhibitors (PPI) in non-ulcer patients, non-steroidal anti-inflammatory drugs (NSAIDs) in hypertension or long-term osteoarthritis management, acetylsalicylic acid with no history of vascular disease or primary protection and prolonged usage of atypical antipsychotics. The more common affected systems from PIMs were gastrointestinal system (36%), central nervous systems (21%) and cardiovascular system (19%). The more common PPOs were oral nutritional supports (ONS) for malnutrition risked patients, vitamin D and calcium supplement in osteoporosis or osteomalacia, fiber and vitamin supplementation in necessary situations. Prevalence of frequently used PIMs and PPOs summarized in Table 2.

Comparing people with and with-out dementia, polypharmacy was more frequent in people with dementia (mild: 67.3%, moderate: 62.2%, severe: 72.2%) versus no-dementia (39.8%) (p<0.001). Moreover, number of used drugs was higher in dementia patients. Post-hoc analysis showed that the difference in number of used drugs was between CDR 0 vs 1-2-3 group (CDR 0 vs 1group, p=0.004; CDR 0 vs 2 group, p=0.006; CDR 0 vs 3 group, p=0.001). Figure 1 shows the number of drug usage stratified by dementia status according to CDR score. When we compare people with and without dementia, PIMs rates were similar in people with dementia and no-dementia (p=0.52). However, PPOs was more frequent in people with dementia versus no-dementia (p<0.001). Figure 2 shows number of used drugs stratified for dementia status. Figure 3 and Table 3 shows polypharmacy, PIMs and PPOs stratified by dementia status according to CDR score.

Moreover, a binary logistic regression analysis was performed to detect the possible parameters that affect dementia. Polypharmacy, TIME to STOP and TIME to START rates were put into the equation for logistic regression analysis. Logistic regression analysis demonstrated that polypharmacy was associated with greater odds of dementia status [relative ratio (RR): 3.32 95% confidence interval (CI): 1.88-5.87, p<0.001]. Also, logistic regression analysis demonstrated that TIME to STOP and TIME to START rates were associated with dementia status (TIME to stop RR: 0.48, 95% CI: 0.24-0.97, p=0.04, TIME to START RR: 3.79, 95% CI: 1.95-7.32, p<0.001).

Discussion

To our knowledge, this is the first study to examine polypharmacy, PIMs, and PPOs among dementia and no- dementia patients with TIME criteria. Both were widespread in the older population, but significantly more in people with dementia where almost half of them were exposed to polypharmacy and quarter to

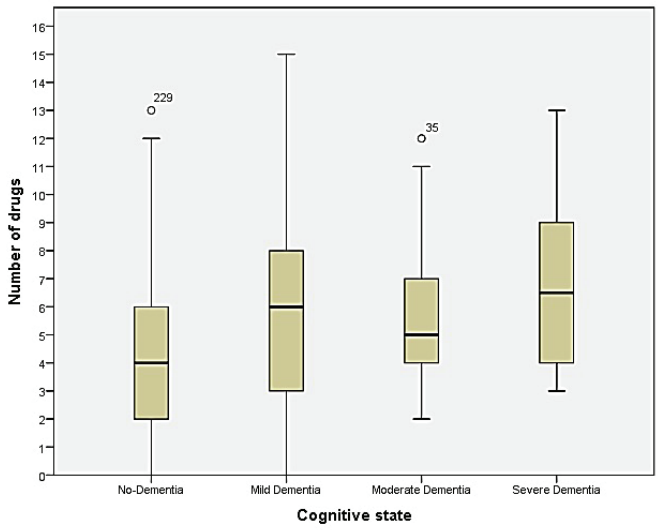

Figure 2. Number of used drugs stratified for dementia status

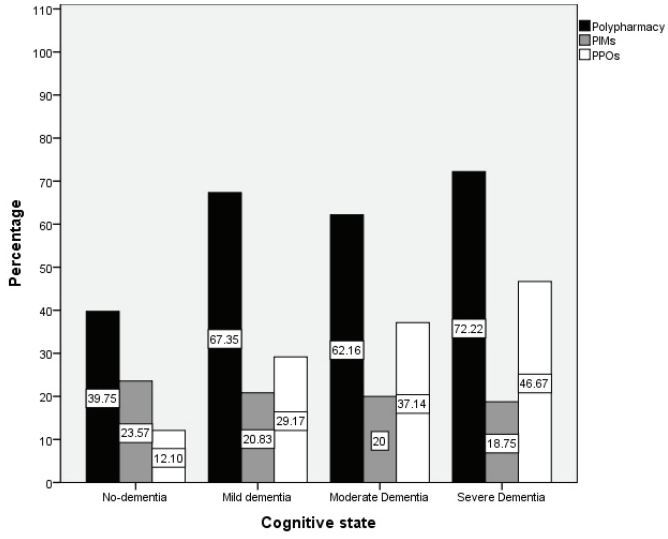

Figure 3. Polypharmacy, PIMs, and PPOs rates according to TIME criteria

PIM: Potentially inappropriate medication, PPOs: Potential prescription omissions

PIM as defined by the TIME criteria. Interestingly, although polypharmacy rate was higher, the frequency of PPOs was also higher in dementia patients. Additionally, PPOs were more widespread in severe stage people with dementia.

Polypharmacy is a common problem in the geriatric population, lead to increase the risk of drug-drug interaction, adverse drug events, and could cause serious medical problems such as hospitalization, increase risk of falls and death. In our study, polypharmacy was more frequent among dementia patients than no-dementia (51.9% versus 48.1%). Other studies using the same definition of polypharmacy have found a comparable, albeit slightly higher, prevalence of 63-69% in Turkish population (22,23). However, these studies were focused on

community dwelling older people or hospitalized patients. A study from Turkey, Bahat et al. (24) reported that polypharmacy rate was 52.5% in a geriatric outpatient clinic. Our results were consistent with similar settings. This study showed that polypharmacy rate was 51.9% in dementia patients. There is a limited information in the literature about polypharmacy rate in Turkish dementia patients. In a recent study from Turkey reported that polypharmacy rate was >65% in Alzheimer dementia patients (25). Other studies from different countries reported that polypharmacy prevalence was 33.5-52.0% in community-dwelling people with dementia (26-28). Our results were similar with the literature.

Gender, education status, chronic diseases frequencies were similar between dementia and no-dementia patients, except depression and urinary incontinence. Charlson comorbidity index score was higher in dementia patients, but that 1-point score difference is due to the dementia disease itself. This study showed that median number of the used drug was higher in dementia patients. We could consider this result as the necessity of the treatment for depression and dementia. Although, the number of the used drug is high in dementia patients, similarity of PIMs ratio, supports our opinion.

Nowadays, adverse drug reactions in older persons and PIMs represent a serious and escalating problem in public health. The explicit and updated screening tools are needed, within this background several criteria have been developed to estimate the appropriateness of some drug. The classification system for medications and their use might differs by countries. Consequently, TIME criteria had been developed for all types of clinical settings in Turkey and validated for European countries (14,15). The PIM prevalence was detected as 21.5% in the whole group and there was no statistically significant difference between no-dementia and dementia patients (23.6% vs 20% respectively) in the present study. Recent trials in Turkey showed significantly high documented PIMs prevalence as 33.3-41.2% detected by START/STOPP and Beer's criteria in older patients (23,24). The prevalence of PIMs among individuals with cognitive impairment or dementia ranged from 10.2-56.4% (28). The PIMs rates that we reported in dementia patients are in the range of other studies in the literature. However, general study population PIMs rates was different from the literature. These results might be related with the study population, screening tool difference or due to the medical trainee. A group of patients admitted after consultation, as well as patients who were followed up in another clinic. This group of patients' medications may have been adjusted before admission to geriatric outpatient clinic. Moreover, the presented study was conducted in a university hospital where provides geriatric education. Due to the trainings

Table 2. Prevalence of frequently used PIMs and PPOs in the TIME criteria list

		No-dementia (n=160)	Dementia (n=105)
PIMs (TIME to STOP)		(n)	(n)
Proton pump inhibitors		16	6
NSAIDs		8	0
Antipsychotic drugs	Aripiprazole	0	1
	Clonazepam	0	1
	Quetiapine	0	4
Acetylsalicylic acid		5	3
ß blocker		4	0
HMG-CoA inhibitors		2	0
Betahistine		2	3
Piracetam		1	2
Nitrazepam		0	1
Gingko biloba		2	0
Theophylline		0	1
PPOs (TIME to START)			
Oral nutritional support		4	18
Calcium supplement		1	3
Vitamin D		8	8
Vitamin B12		3	1
Depression treatment		3	1
HMG-CoA inhibitors		3	0
Proton pump inhibitors		3	3
Diet fiber		1	2

PIM: Potentially inappropriate medication, PPOs: Potential prescription omissions, NSAID: Non-steroidal anti-inflammatory drugs

Table 3. Cognitive state and polypharmacy, PIMs, and PPOs prevalence according to TIME criteria

	Normal cognitive function (CDR-0)	Dementia CDR-1	Dementia CDR-2	Dementia CDR-3	p
Polypharmacy, n (%)	64 (39.8%)	33 (67.3%)	23 (62.2%)	13 (72.2%)	<0.001
N of drugs, median (IQR)	4 (4)	6 (5)	5 (3)	7 (5)	<0.001
TIME to START, n (%)	19 (12.1%)	14 (29.2%)	13 (37.1%)	7 (46.7%)	<0.001
TIME to STOP, n (%)	37 (23.6%)	10 (20.8%)	7 (20.0%)	3 (18.8%)	0.52

Non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were given as numbers and percentages, PIM: Potentially inappropriate medication, PPOs: Potential prescription omissions

or increased awareness about polypharmacy and PIMs usage could lead to this result. Otherwise, this study showed that most common PIMs were proton pump inhibitors, NSAIDs and acetylsalicylic acid for primary prevention, similar with previous studies (23,24).

Although, several pharmacological therapies are safe in older adults, under-prescription is widespread as ranging from 22-70% (29). However, there is limited evidence of PPOs for dementia patients in the literature, Lombardi et al. (29) showed that dementia is a risk for under prescription. In our study, PPOs was more frequent among dementia patients than no-dementia (34.3% versus 12.1%). Moreover, prevalence of PPOs and lack of oral nutritional supplementation increased with the severity of dementia. This study showed that, oral nutritional supplementation and vitamin D support was the most common PPOs. Studies in the literature have shown that the most common PPOs included calcium-vitamin D supplementation, cardiovascular medications, HMG CoA inhibitors and acetylsalicylic acid (23,29). Our results were similar with the literature. Multi-morbidity, frailty, dementia, living in an institutional setting are related with under treatment. Due to the decreased life expectancy, careful evaluation is important for decision making and treatment goals. However, beneficial effect of preventive treatments should not underestimate in older people. The most important message of this study is that we should suggest oral nutritional supplement and vitamin D for older patients in necessary situations. The diagnosis of dementia should not inhibit us to start preventive or necessary treatments.

Strengths of the current study includes sample size, comparison of dementia and no-dementia patients and using national tools for PIMs and PPOs evaluation. The limitations of this study could be mentioned. The study design was retrospective, and it is not possible to detect causal relationships. Furthermore, a group of patients' medications might be revised in other follow-up clinics before admission to geriatric clinic. This may lead to the fact that we reported different results from the literature. Depression was more common in dementia patients. However, geriatric depression scale scores were lower in dementia patients. This could be due to the communication problems in moderate and severe stages of dementia. Further researches about the effect of polypharmacy and PIM on the general health of older people with and without dementia will guide clinicians in prescription. More details on the causal relationship need to be determined through longitudinal research and interventional research in the future.

Conclusion

Optimal drug treatment for older dementia patients is complex and might lead to inappropriate drug usage or under treatment. Although polypharmacy has been related with concrete adverse outcomes as mortality and morbidity in people with dementia, inappropriate drug usage in older adults could decrease with recently developed national guides and increasing awareness. Despite these encouraging findings, clinicians should remember to provide appropriate and preventive treatments such as nutritional support in necessary situations for older adults.

Ethics

Ethics Committee Approval: The study protocol was approved by Local Ethics Committee (GO 21/755 2021/13-02).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ö., S.C., Concept: C.Ö., M.G.H., Design: C.Ö., M.G.H., Data Collection or Processing: S.C., Analysis or Interpretation: C.Ö., Literature Search: C.Ö., S.C., Writing: C.Ö., M.G.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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