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Potential Interactions Involving Inappropriate Medications according to the 2015 Updated Beers Criteria

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Abstract

Objectives: To analyze Potential Drug-Drug Interactions (PDDIs) involving Potentially Inappropriate Medications (PIM) according to the updated Beers criteria and the health conditions associated with these PDDIs and with the use of PIMs.

Design: Population-based cross-sectional study.

Setting: In-home survey conducted by the Elderly Health Surveillance Network of Goiânia, Goiás, Brazil.

Participants: Elderly community-dwelling individuals who answered questions about drugs and presented their respective prescriptions (N=783).

Measurements: PDDIs (identified through Micromedex®) in general and involving PIMs (2015 Updated Beers Criteria), and the associations of PDDIs involving PIMs and the use of PIMs with health conditions.

Results: A total of 2,846 drugs were used, 12.7% of which were PIMs. The prevalence of PIMs used by the elderly was 35.4%. A total of 665 PDDIs were identified, of which 45.1% involved PIMs and 54.9% other drugs. The prevalence of PDDIs involving PIMs among the elderly was 14.8%. A multivariate analysis revealed an association of PMI use with polypharmacy (PR=1.76; 95%CI 1.42-2.19), one/two PDDIs (PR=1.68; 95%CI 1.35-2.11), 3 or more PDDIs (PR=1.86; 95%CI 1.44-2.43), and a poor/bad self-rated health (PR=1.44; 95%CI 1.12-1.86). In addition, the multivariate analysis demonstrated that PDDIs involving PIMs were associated with polypharmacy (PR=4.46; 95%CI 3.12-6.37) and a poor/bad self-rated health (PR=1.93; 95%CI 1.21-3.07).

Conclusion: More than one-third of the elderly individuals use PIMs and half of the identified PDDIs involve PIMs, showing that elderly individuals might be exposed a risk that might exceed the benefits of the drug therapy. The use of PIMs was found to be associated with polypharmacy, the number of PDDIs and a poor self-rated health. Moreover, the PDDIs involving PIMs were associated with polypharmacy and a poor/bad self-rated health.

Keywords: Elderly; Potential Drug-Drug Interactions; Potentially Inappropriate Medications; Polypharmacy

Introduction

Some drugs are considered potentially inappropriate medications (PIMs) for older adults due to a potential inefficacy to achieve the desired therapeutic response, an increased risk of adverse events that exceeds the benefits of the drug, or the existence of a safer therapeutic option [1,2]. Concern over the harmful effects caused by some drugs used by the elderly led to the development of lists of PIMs based on explicit and implicit criteria [1]. The Beers criteria are the most widely used and known worldwide and was updated in 2015 by the American Geriatrics Society.[2] Avoiding

the use of PIMs is an important, simple, and effective strategy for reducing drug therapy-related issues in the elderly [2]. However, the prevalence of the use of these drugs is approximately 40% and is commonly associated with the female gender and the practices of self-medication and polypharmacy [1-3].

The use of many different drugs by elderly patients makes them more susceptible to Potential Drug-Drug Interactions (PDDIs). These interactions might alter the pharmacological activities of the drugs involved, increase or decrease their effects or even cause undesirable clinical consequence relevant to quality of life [4,5]. These consequences can be aggravated by the involvement of one or more PIMs in the PDDI, leading to an elevated risk of complications caused by the use of these drugs [6]. In the 2015 Beers criteria was incorporated into a new area with a PDDI list that should not be overlooked and reinforced the risk of serious harm and PDDI associated with damage to the health of the elderly [2].

Based on the Beers Criteria by the American Geriatrics Society [2], we identified studies that evaluated the use of PIMs by analyzing explicit factors but did not evaluate the PDDIs involving these drugs, which is an essential intrinsic factor for therapeutic success and patient safety. In this context, this study analyzed potential interactions involving medications that are inappropriate for the elderly according to the updated Beers Criteria and the health conditions associated with these PDDIs and the use of PIMs.

Methods

Study Design, Participants, and Data Sources

This cross-sectional population-based study formed part of the in-home survey conducted by the Elderly Health Vigilance Network (EHVN). The sample consisted of 934 elderly (at least 60 years of age) individuals living in the city of Goiânia, Goiás, Brazil. It was approved by the Research Ethics Committee of the Federal University of Goiás.

The data were collected through visits to the homes of elderly individuals by duly-trained interviewers between December/2009 and April/2010. The parameter details of the sample size calculations and sampling procedures are described in previous publications [7]. Briefly, the sample calculation assumed an expected frequency of 30.0% for all outcomes, 95% confidence intervals, a significance level of 5%, an absolute precision of 5% and a Design Effect of Cluster Sampling (DEF) of 1.8. To cover possible losses, an additional 11% was included, yielding a sample size of 934 elderly individuals. Of this total, 783 responded to questions regarding the use of medication and were included in this study. The elderly was selected by cluster sampling using 912 Census Sectors (CS) from the urban area of the municipality as the primary sampling units. Polypharmacy, Self-Medication and Potentially Inappropriate Medications

During data collection, the elderly individuals were asked about the medications they used daily, with or without prescription, and were requested to show all of the drugs they use and the respective prescriptions. Thus, it was possible to obtain the necessary data on drug use, such as the use of PIMs, polypharmacy, and self-medication, and to analyze PDDIs. To identify PIMs, the updated Beers criteria [2] were applied to the drugs mentioned by the elderly during the survey and the corresponding concentrations and doses. The practice polypharmacy was defined as the concomitant use of at least five drugs [8].

To investigate the practice of self-medication based on the drugs used by the elderly, the individuals were asked who had indicated each of the drugs and to show the prescriptions. All of the drugs taken by the individuals without a current prescription were considered to be due to the practice of self-medication. A prescription with a date older than three months was considered olden.

Potential Drug-Drug Interactions

We used the Micromedex® tool, which is available online with restricted access, to identify PDDIs among the drugs used by the elderly as well as their severity and consequences [9] Regarding severity, the interactions were classified as contraindicated when the simultaneous administration of the drugs was not recommended, severe when the drugs were life-threatening and required immediate medical intervention, moderate when the drugs could worsen the patient's clinical presentation , making it necessary to change the drug therapy, and mild when the patient presented changes in the clinical presentation that did not require changes in drug therapy [9].

Health Status Variables

For the quantification of self-referred diseases, the elderly was given a list of diseases and asked to indicate their diseases that had been diagnosed by their doctors. These diseases were categorized as diabetes, hypertension, obesity, malnutrition, high cholesterol, high triglycerides, osteoporosis, cancer, stroke, myocardial infarction, asthma/bronchitis/respiratory problems, musculoskeletal diseases, depression, memory problems, thyroid disorders, cataracts or other diseases. The number of self-referred chronic diseases was obtained by adding the number of affirmative answers to the above-mentioned question.

To investigate the need for a caregiver, the elderly was asked if they needed someone to help them with their daily activities.

To evaluate hospitalization episodes over the past year, the elderly was asked if they had been admitted to the hospital within the past 12 months. The self-rated health status of the individuals was obtained by asking the elderly to rate their health as excellent/good, regular or poor/bad. In addition, the time-comparative self-rated health status was obtained by asking the individuals the following question: "Compared to one year ago, how would you rate your health in general now?" The answers "somewhat worse" and "much worse" were considered to indicate a worse time-comparative self-rated health status.

Statistical Analysis

The bivariate analysis tested the association between the outcomes variables (use of PIM and PDDIs involving PIMs) and the other study variables by applying Pearson's Chi-squared test. The level of significance adopted was 5%. The outcomes prevalence's for the categories of the other variables of interest was also calculated. A multivariate Poisson regression analysis was performed according to a hierarchic analysis model. The first level included sociodemographic variables (gender, age, civil status and education level), the second level included health variables (polypharmacy, self-medication, PDDIs, number of self-referred diseases, need for caregiver and hospitalization in the past year), and the third level included the worsening time-comparative self-rated health and the self-rated health. All variables that had $p<0.20$ in the bivariate analyzes were included in the multivariate analyzes, and only variables with $p\leq0.05$ remained in the final model.

Results

Of the 934 elderly individuals who participated in the survey, 783 answered all of the questions regarding drugs, showed all of the drugs they used and the respective prescriptions. As a result, these 783 individuals were included in this study, and of these, 65.1% were women, 45.7% were 60 to 69 years of aged, 49.5% were married, and 48.3% had completed primary education (Table 1).

Variables	Total n (%)	Prevalence of PIM use n (%)	PR (95%CI)	*p* value*
Gender				0.196
Male	273 (34.9)	90 (33.0)	1.00	
Female	510 (65.1)	187 (36.7)	1.02 (0.98- 1.06)	
Age (years)				0.203
60 to 69	358 (45.7)	118 (32.9)	1.00	
70 to 79	264 (33.7)	97 (36.7)	1.01 (0.95-1.07)	
≥80	161 (20.6)	62 (38.5)	1.03 (0.97-1.09)	
Civil status				0.714
Married	386 (49.5)	128 (33.2)	1.00 (0.93-1.07)	
Single	75 (9.6)	24 (32.0)	1.00	
Widowed	252 (32.3)	100 (39.7)	0.96 (0.91-1.00)	
Divorced	67 (8.6)	24 (35.8)	0.98 (0.91-1.06)	
Educational level				0.675
Illiterate/never attended school	160 (20.6)	62 (38.7)	1.00	
Complete/incomplete primary education	375 (48.3)	132 (35.2)	1.02 (0.96-1.08)	
Complete/incomplete secondary education	164 (21.1)	52 (31.7)	1.04 (0.97- 1.11)	
Complete/incomplete higher education	77 (10.0)	28 (36.4)	1.01 (0.93-1.10)	
Polypharmacy				<0.001
Yes	207 (26.4)	123 (59.4)	1.23 (1.17-1.29)	
No	576 (73.6)	154 (26.7)	1.00	
Self-medication				0.502
Yes	280 (35.8)	106 (37.8)	1.02 (0.98-1.06)	
No	503 (64.2)	171 (34.0)	1.00	
Potential drug-drug interactions				<0.001

No	494 (63.1)	124 (25.1)	0.81 (0.74- 0.89)	
1 and 2	210 (26.8)	95 (45.2)	1.00	
≥3	79 (10.1)	58 (73.4)	1.13 (1.07- 1.18)	
Number of self-referred diseases				<0.001
1 and 2	195 (25.3)	46 (23.6)	1.00	
3 and 4	258 (33.4)	88 (34.1)	1.06 (1.01-1.11)	
≥5	319 (41.3)	141 (44.2)	1.13 (1.07- 1.18)	
Need for caregiver				0.051
Yes	334 (43.9)	132 (39.5)	1.04 (1.01-1.08)	
No	426 (56.1)	138 (32.4)	1.00	
Hospitalization within the past year				0.002
Yes	186 (26.0)	81 (43.5)	1.07 (1.01-1.12)	
No	529 (74.0)	171 (32.3)	1.00	
Worsening time-comparative self-rated health status				0.050
Yes	239 (31.9)	95 (39.7)	1.04 (1.00-1.09)	
No	511 (68.1)	163 (31.9)	1.00	
Self-rated health status				<0.001
Excellent/good	305 (40.6)	81 (26.6)	1.00	
Regular	350 (46.5)	133 (38.0)	1.11 (1.03-1.20)	
Poor/bad	97 (12.9)	53 (54.6)	1.19 (1.10-1.28)	
PIMs=potentially inappropriate medications; **PR: prevalence ratio; 95%CI: confidence interval 95%; *p=Pearson's Chi-squared test				

Table 1: Prevalence of the Use of Potentially Inappropriate Medications by the Elderly According to Sociodemographic and Health Variables.

These individuals used 2,846 drugs (mean of 3.63 drugs/elderly individual), and 12.7% of these drugs were PIMs, accounting for a group of 35 different drugs. The prevalence of PIM use among the elderly was 35.4% (277). Among all of the drugs used by the elderly, 665 PDDIs were observed. Of these, 45.1% (300) involved PIMs and 54.9% (365) other drugs, and 10.7% (32) of the interactions were between two PIMs. Moreover, 14.8% (116) of the elderly were exposed to PDDIs involving PIMs, and 4.0% (31) were exposed to at least three PDDIs involving PIMs. The investigation of the severity of these PDDIs revealed that 32.1% were severe, 64.6% were moderate, and 3.4% were mild. The PIMs most commonly involved in the PDDIs were diclofenac, amiodarone, digoxin, nifedipine and amitriptyline; in fact, these five drugs were found to be responsible for 73.7% of the PDDIs involving PIMs.

The most frequent PDDIs involving PIMs were between amiodarone and losartan (12, moderate), digoxin and spironolactone (8, severe), digoxin and furosemide (8, moderate), amiodarone and digoxin (6, severe) and atenolol and nifedipine (6, moderate). The most common effects of these PDDIs were an increase in the exposure to or toxicity of one of the drugs (33.0%), a reduction in the effect of one of the drugs involved in the interaction (29.5%), risk of bleeding (6.9%) and cardiotoxicity and/or QT interval prolongation (6.6%).

We observed associations for the use of PIMs with the practice of polypharmacy (prevalence ratio [PR]= 1.23; confidence interval [95%CI] 1.17-1.29) , the presence of three or more PDDIs (PR= 1.13; 95%CI 1.07-1.18), self-referral of at least five diseases (PR= 1.13; 95%CI 1.07-1.18), episodes of hospitalization within the past year (PR= 1.07; 95%CI 1.01-1.12) and a poor/bad self-rated health status (PR= 1.19; 95%CI 1.10-1.28) (Table 1). The variables polypharmacy (PR=1.76; 95%CI 1.42-2.19), one/two PDDIs (PR=1.68; 95%CI 1.35-2.11), three or more PDDIs (PR=1.86; 95%CI 1.44-2.43), and a poor/bad self-rated health

status (PR=1.44; 95%CI 1.12-1.86) remained in the final multivariate analysis model and were associated with PIM use (Table 3).

The PDDIs involving PIMs were associated with the practice of polypharmacy (PR=4.90; 95%CI 3.47- 6.91), self-referral of at least five diseases (PR= 2.83; 95%CI 1.63-4.91), episodes of hospitalization within the past year (PR= 1.46; 95%CI 1.01-2.10) and a poor/bad self-rated health status (PR= 2.91; 95%CI 1.80-4.73) (Table 2). The variables polypharmacy (PR=4.46; 95%CI 3.12-6.37) and a poor/bad self-rated health status (PR=1.93; 95%CI 1.21-3.07) remained in the final multivariate analysis model and were associated with PDDIs involving PIMs (Table 3).

Variables	Total n (%)	Prevalence of PDDIs involving PIM n (%)	PR (95%CI)	*p* value*
Gender				0.467
Male	273 (34.9)	37 (13.6)	1.00	
Female	510 (65.1)	79 (15.4)	1.14 (0.75- 1.64)	
Age (years)				0.285
60 to 69	358 (45.7)	46 (12.8)	1.00	
70 to 79	264 (33.7)	41 (15.5)	1.20 (0.81- 1.78)	
≥80	161 (20.6)	29 (18.0)	1.40 (0.91- 2.14)	
Civil status				0.538
Married	386 (49.5)	54 (14.0)	1.00	
Single	75 (9.6)	9 (12.0)	0.85 (0.44-1.66)	
Widowed	252 (32.3)	44 (17.5)	1.24 (0.86- 1.79)	
Divorced	67 (8.6)	9 (13.4)	0.96 (0.49- 1.85)	
Educational level				0.617
Illiterate/never attended school	160 (20.6)	22 (13.7)	1.00	
Complete/incomplete primary education	375 (48.3)	56 (14.9)	1.08 (0.68-1.71)	
Complete/incomplete secondary education	164 (21.1)	29 (17.7)	1.28 (0.77- 2.14)	
Complete/incomplete higher education	77 (10.0)	9 (11.7)	0.85 (0.41- 1.75)	

Polypharmacy				<0.001
Yes	207 (26.4)	74 (35.7)	4.90 (3.47- 6.91)	
No	576 (73.6)	22 (3.8)	1.00	
Self-medication				0.597
Yes	280 (35.8)	44 (15.7)	1.09 (0.77- 1.55)	
No	503 (64.2)	72 (14.3)	1.00	
Number of self-referred diseases				<0.001
1 and 2	195 (25.3)	14 (7.2)	1.00	
3 and 4	258 (33.4)	36 (13.9)	1.94 (1.07- 3.50)	
≥ 5	319 (41.3)	65 (20.4)	2.83 (1.63- 4.91)	
Need for caregiver				0.383
Yes	334 (43.9)	53 (15.9)	1.16 (0.82- 1.64)	
No	426 (56.1)	58 (13.6)	1.00	
Hospitalization within the past year				0.043
Yes	186 (26.0)	36 (19.4)	1.46 (1.01- 2.10)	
No	529 (74.0)	70 (13.2)	1.00	
Worsening time-comparative self-rated health status				0.423
Yes	239 (31.9)	39 (16.3)	1.15 (0.80- 1.65)	
No	511 (68.1)	72 (14.1)	1.00	
Self-rated health status				<0.001
Excellent/good	305 (40.6)	28 (9.2)	1.00	

Regular	350 (46.5)	58 (16.6)	1.80 (1.18- 2.75)	
Poor/bad	97 (12.9)	26 (26.8)	2.91 (1.80- 4.73)	
PDDIs= potential drug-drug interactions; PIM=potentially inappropriate medications; **PR: prevalence ratio; 95%CI: confidence interval 95%; *p=Pearson's Chi-squared test				

Table 2: Prevalence of Potential Drug-Drug Interactions Involving Potentially Inappropriate Medications Among the Elderly According to Sociodemographic and Health Variables.

Variables	Adjusted Prevalence Ratio	Adjusted 95%CI	*p* value*
Use of potentially inappropriate medications among the elderly			
1st level			
Polypharmacy			
Yes	1.76	1.42-2.19	<0.001
No	1.00	-	
Potential drug-drug interactions			
No	1.00	-	-
1 and 2	1.68	1.35-2.11	<0.001
≥3	1.86	1.44-2.43	<0.001
2nd level			
Self-rated health status			
Excellent/good	1.00	-	-
Regular	1.17	0.94-1.45	0.146
Poor/bad	1.44	1.12-1.86	0.004
Potential drug-drug interactions with potentially inappropriate medications			
2nd level			
Polypharmacy			
Yes	4.46	3.12 - 6.37	<0.001
No	1.00	-	
3rd level			
Self-rated health status			
Excellent/good	1.00	-	-
Regular	1.61	1.07 – 2.42	0.022
Poor/bad	1.93	1.21 – 3.07	0.005
95%CI: confidence interval; *Multiple hierarchical Poisson regression			

Table 3: Prevalence Ratio (PR) Hierarchically Adjusted for the Use of Potentially Inappropriate Medications by the Elderly and for Potential Drug-Drug Interactions with Potentially Inappropriate Medications.

Discussion

The list of PIMs according to the Beers criteria has been guiding safe drug prescriptions for the elderly population from its first version to the last update [2]. However, the findings of this and other studies reinforce the prevalent use of PIMs by this population, supporting the need to consider the risk of PDDIs involving these drugs [10-12]. The fact that the elderly constitutes the population that most frequently practices polypharmacy and is most susceptible to PDDIs, as well as the with a corresponding imminent risk, should be taken into account [13]. Approximately half of the PDDIs identified involved PIMs. The use of PIMs was strongly associated with a higher amount of PDDIs. Moreover, the most frequent consequence of these interactions was found to be the potentiation of the risks associated with PIM use. These findings confirm the warnings raised by other studies: the drugs defined by the Beers criteria might be toxic or exert adverse effects in the elderly when administered as monotherapies, and these risks might be intensified when these PIMs are involved in interactions with other drugs [2-12].

Some of the elderly individuals were exposed to an even higher risk due to the existence of interactions between the PIMs being used by the individuals. Almost all of these PDDIs potentiated the risk of use of these drugs with severe or even irreversible consequences, such as cardiac arrest [14]. This finding indicates that the health professionals prescribing the drugs and the pharmacists dispensing the drugs are unaware or do not pay attention to the safety issues involving drug use among elderly patients, suggesting a need for more assertive initiatives regarding training and continuing education for health professionals treating this patients [15].

The interactions were frequently classified as severe The constant monitoring of actions that might reduce the risk of unnecessary damage to a patient to an acceptable number must be noted. In the case of drug therapy, the risk-benefit ratio of the drugs and, in particular, the potential for interactions must be well observed and considered at the time of prescription [16], moreover, safer therapeutic alternatives must be considered [2]. Diclofenac, amiodarone, digoxin and nifedipine were found to be responsible for the largest number of moderate and severe PDDIs involving PIMs. PDDIs associated with a risk of bleeding were found for the combination of diclofenac with calcium channel blockers, Ginkgo biloba, and citalopram. According to Shin, et al. [17] the combination of diclofenac with citalopram might cause an increased risk of intracranial bleeding within 30 days. Moreover, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) combined with diuretics and anti-hypertensive agents reduce the efficacy of these drugs, there by resulting in compromised blood pressure control [18].

PDDIs of high clinical significance occur with amiodarone primarily due to its cytochrome P450 and P-glycoprotein inhibitory activities [9-19]. When associated with beta-blockers or calcium channel blockers, as was identified in the present study, amiodarone results in a risk of hypertension and might induce severe bradycardia with a risk of cardiac arrest [20].

Digoxin was associated with several PDDIs, and most of these interactions might increase its serum concentration and toxicity (e.g., when used with diuretics (spironolactone, hydrochlorothiazide (HCTZ), or furosemide), amiodarone or fluoxetine). Effects such as bradycardia and arrhythmia with cardiovascular collapse might also occur when digoxin interacts with carvedilol and calcium [1-21].

Nifedipine, was also associated with several PDDIs, including some serious interactions observed in the study, and with carbamazepine and phenytoin, which are drugs with low therapeutic index inducers of CYP3A4, that reduce nifedipine exposure [9-16]. A poor/bad self-rated health status was associated with PIM use and with the presence of PDDIs involving PIMs. These drugs might have a negative impact on the health of the elderly, as reflected by a worsening of the general health status and a negative assessment. The negative contribution related to the use of PIMs and the PDDIs involving these drugs must be investigated [22,23]. However, in clinical practice, the undesired effects of PIMs and the consequences of PDDIs are rarely investigated; in contrast, the practice of adding one more drug to treat a complaint is more frequent, which further complicates the health status of an elderly patient, particularly when PDDIs are present.

The practice of polypharmacy by the elderly was strongly associated with PIM use. This result is similar to the results reported in the literature [24,25], most likely because a PIM is more likely to be included in a prescription containing many drugs. Bao, et al. [25] also highlighted that this association might lead to disease worsening, hospitalizations, and a higher risk of PDDIs. Moreover, these results draw attention to the importance of promoting treatments not involving drugs, such as a balanced diet and physical exercise, whenever possible; these alternatives should be exhausted before prescribing drugs. Finally, the results underscore the promotion of rational drug use by the elderly.

The results of this study have very clear implications and demonstrate the need to reduce PIMs use. These observations may help health managers and health vigilance managers evaluate the quality and safety of the health assistance provided to the elderly population. Some studies have warned about the importance of reducing the use of these drugs and recommended the implementation of safer therapies or the use of lower doses of these drugs whenever possible.

If a prescription containing PIM with potential for interactions is maintained after a rigorous and individualized analysis, the elderly patient must be monitored for dose adjustment, changes in the dosing schedule, control of serum levels of the drugs, and monitoring of clinical conditions, to enable early detection of signs and symptoms of PDDIs [8-24].

In conclusion, based on the findings of this study, more than one-third of the elderly individuals used PIMs, which exposes them to a risk that might exceed the benefits of the drug therapy. Approximately half of the identified PDDIs involved PIMs, and

half of those PDDIs had the same effects that deemed the drug potentially inappropriate for use by the elderly as a consequence. PIM use was associated with the practice of polypharmacy, the number of PDDIs, and a poor health self-assessment. The risk of use of these drugs and the severity of the PDDIs involving them are well described but, nonetheless, seem to be neglected in clinical practice. These drugs continue to be frequently prescribed for the elderly.

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Conflict of Interests

The authors declare no conflicts of interest.

Author Contributions

All authors participated effectively in the development of the study, such as the study design, data collection, and preparation of the manuscript. All approved the final version of the manuscript, and assume responsibility for the integrity of the results.

Sponsor's Role

The Research Support Foundation of the State of Goiás did not influence the design and performance of the study or the data collection, project management, or data analysis and interpretation. Likewise, it did not influence the study's conclusions, drafting of the manuscript, or choice of journal for publication.

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