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RESEARCH ARTICLE

The "iatrogenic triad": polypharmacy, drug–drug interactions, and potentially inappropriate medications in older adults

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Abstract *Background* The elderly population is often in continuous use of several medications and is more subject to the "iatrogenic triad" of polypharmacy, potentially inappropriate medication use and drug–drug interactions. However, few studies have investigated these three factors concomitantly. *Purpose* To assess the prevalence and inter-relationship of potentially inappropriate medication (PIM) use, polypharmacy and drug–drug interactions in older adults, together with their associated factors. *Setting* city of Juiz de Fora, Brazil. *Methods* a cross-sectional, observational and door-to-door epidemiologic study in community-dwelling older adults was conducted. *Main outcome measure* The primary outcomes were polypharmacy, inappropriate medication use (2012 Beers and 2015 STOPP criteria) and drug–drug interactions. Associated factors were also investigated using bivariate and multivariate analyses. *Results* a total of 368 (92%) older adults were in continuous use of at least one drug. There was a high prevalence of polypharmacy (44.6%), drug–drug interaction (72.3%) and PIMs by Beers (42.1%) and PIMs by STOPP (46.2%). Analysis of the inter-relationship of the criteria (polypharmacy, PIMs STOPP and drug–drug interactions) revealed that 108 (29.3%) of the older adults had all three criteria concomitantly and multivariate analysis showed that frailty and having a caregiver were associated with this "iatrogenic triad". *Conclusion* A high prevalence of iatrogenic effects from drugs was found in the older adults assessed. One in every three elderly participants of the study had all three iatrogenic criteria concomitantly, highlighting the major public health impact of this problem. The results of this study can serve to inform new preventive and educational strategies for health professionals.

Keywords Brazil · Drug interactions · Inappropriate prescribing · Polypharmacy

Impacts on practice

- One in every three older adults has the "iatrogenic triad" in the present study. Health professionals must be aware of this important public health problem.
- Identifying patients at risk for iatrogenic effects is an important step to minimize the adverse events related to inappropriate prescription.
- New preventive and educational strategies are necessary to ensure that health professionals are trained to deal with the "iatrogenic triad".

Introduction

The process of an aging population is a reality in many societies, where an estimated 12% of the world population is elderly [1]. This increase in the elderly population poses new challenges to health care, since this age group has a greater prevalence of chronic-degenerative diseases and is therefore subject to constant use of a high number of drugs [2, 3]. Thus, pharmacological therapy in older adults calls for special care since aging can affect the body's ability to deal with medications owing to changes in kidney, liver

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function, pharmacokinetics and pharmacodynamics of drugs [4].

This factor renders older persons susceptible to adverse effects of medication use [2], where this age group has a higher prevalence of polypharmacy (chronic concomitant use of multiple drugs) [5], potentially inappropriate medication (PIM) use (not indicated based on evidence, increasing risk of adverse reactions compared to younger patients, or not cost effective) [6, 7] and drug–drug interaction (defined as the effect one drug has on another) [8].

Many studies have indicated a high prevalence of iatrogenic effects in elderly patients. An estimated 5–78% of elderly are subject to polypharmacy [9], 13–58% to drug–drug interactions [10] and 2.9–38.5% to inappropriate prescriptions [11], leading to greater health costs, morbidity, hospital admissions and mortality.

However, although numerous studies have investigated aspects related to these iatrogenic effects, few studies have assessed these three aspects (named here as the "iatrogenic triad") concomitantly. Based on the premise that an iatrogenic effect rarely occurs alone, such investigations can contribute by shedding light on the inter-relationship among inappropriate conducts and helping devise public policies and programs aimed at educating health professionals.

Aim of the study

The objective of this study was to assess the prevalence of potentially inappropriate medication use, polypharmacy and drug–drug interactions in older adults, along with their inter-relationship and associated factors.

Ethics approval

The study was approved by the Research Ethics Committee of the Federal University of Juiz da Fora and all participants signed a consent term.

Method

A cross-sectional, observational epidemiologic study was conducted by door-to-door survey in the city of Juiz de Fora, Minas Gerais state, Brazil. Juiz de Fora has a population of 516,247 (2010 Demographic Census de 2010), 13.6% of whom are elderly [12]. For the present study, a representative population in the Northern area of Juiz de Fora, a more populous region of the city with greater socioeconomic diversity [13], was assessed comprising a total of 106,355 residents, 10.68% of whom were elderly [14].

Participants

The study sample included older adults (60 years or older according to the WHO concept for developing countries) who agreed to take part in the study and were present during the three attempts to collect data (made on different days and at different times). Participants scoring below the minimum on the Mini-Mental State Examination (MMSE) according to the cut-off scores suggested by the local government (25 points for those with four or more years of education and 18 points for those with less than 4 years of education) [15], were only eligible to take part if another person (informant) in the household answered the questions on their behalf, else the subject was excluded.

Participants were selected in two ways: (a) all participants (n = 462) in the study by Cruz et al. [16] were included, the addresses of whom were drawn from the original survey database. These participants were selected by multistage stratified random cluster sampling in which primary sampling units were the census sectors, as described in more detail in a previous publication [16]; (b) new subjects were recruited for the sample to offset the loss of panel members from the original population surveyed (change of address and inability to track new address, away on long trips, long hospital admissions and transfer to nursing home). These extra individuals were indicated by neighbors where data was being collected and subsequently asked by the research team to take part in the study. Thus, the final sample comprised 248 elderly from the 2010 survey plus 175 elderly recruited for the sample during the present study, giving a total of 423 participants.

Procedures and instruments

The data collection stage was performed door-to-door (at elderly persons' homes) between October 2014 and March 2015, and the average time required for application of the questionnaire was 1 h. The questionnaire was filled out by previously trained researchers conducting the interview.

The present study employed the following instruments:

- Demographic and socioeconomic profile: age, gender, ethnicity, socioeconomic status, educational level, among others;
- Cognitive assessment by applying the Mini-Mental State Examination (MMSE) as outlined above;
- Edmonton Frail Scale (EFS): this scale was validated in Brazil [17]. The EFS covers 9 domains comprising 11 items and has a maximum score of 17 points, with

higher scores indicating greater degrees of frailty. Frailty can by classified according to score obtained into: not frail, vulnerable or frail;

- Health profile: this section was applied to assess the use of health services by the elderly person, self-reported health and vision, use of glasses/contact lenses, presence of health insurance, current or past health problems, hospitalization in the past year and if the person has a caregiver;
- History of falls: through the question "Have you had any falls in the past year?". If the respondent stated "yes", the next question was "how many?" where the number of falls reported by the elderly person was then recorded;
- Patient Health Questionnaire (PHQ-4): a widely used screening instrument for depression and anxiety in different healthcare and community settings [18]. The PHQ-4 comprises two questions assessing anxiety (questions 1 and 2) and two questions assessing depression (questions 3 and 4);
- Lawton & Brody scale [19] (1969): this scale was employed to assess functional status for performing instrumental activities of daily living (IADLs);
- Anthropometric measures: weight, height and BMI;
- Use of Medications: through the question "Are you in continuous use of any drugs?". If the respondent stated "no", the interviewers skipped to the next section; if the respondent answered "yes", then they were asked "how many?" and the number of drugs reported by the respondent was recorded. Respondents were then asked to show the boxes or blister packs of the drugs used continuously to allow completion of a table with the following information: name of active pharmaceutical ingredient, whether the box or blister pack was shown, whether the drug was generic, drug dosage, time using this drug, and the therapeutic regimen. "Continuous use" was defined to the patient as "a medication which you need to take everyday, or almost everyday and that you use it in an uninterrupted way (with no specific date to stop)".

Primary outcomes

After tabulating the drugs used by the elderly participants, the following classification was applied:

Polypharmacy

Defined as concomitant use of five drugs or more [20], polypharmacy is associated with increased risk and severity of adverse reactions to drugs, and promotion of drug–drug interactions, cumulative toxicity, medication errors, poor adherence to treatment and increased morbi-mortality [10]. In the present study, only "continuous use" drugs were included in the polypharmacy criteria. Acute use of antibiotics, creams and injectables was not considered. Creams and patches were considered only if they were for "continuous use" and prescribed by a doctor for a chronic disease.

Drug–drug interaction

Drug–drug interaction is a specific type of adverse drug event; it occurs when the effect of one drug is changed by the presence of another drug, resulting in increased toxicity or reduction [21]. In the present study, the presence or absence of drug interactions was determined using the Drug Interaction Checker software program (http://reference.medscape.com/drug-interactionchecker). The program also enabled interactions to be classified into mild, moderate and severe. Moderate and severe interactions can require specific medical intervention to prevent the exacerbation of previously existing medical conditions and reduce the chance of severe adverse effects, respectively [22, 23].

Potentially inappropriate medications

The 2012 Beers [24] and 2015 STOPP [25] criteria were used to classify the medications as potentially inappropriate.

The version of the Beers criteria published in 2012 [24] is divided into three lists: the first list contains medications or classes of medications that should be avoided by elderly patients, their potential risks and some of their concentrations. The second list contains medications that should be avoided according to disease diagnosis, while the third contains medications or classes of medications to be used with caution.

Recently, the second version of the STOPP and START criteria were developed and validated by O'Mahony et al. [25], enabling more comprehensive identification of potentially inappropriate medications which can have severe deleterious effects on the health and well-being of elderly patients in most clinical situations. This new criteria was developed to be added to the list devised by Gallagher et al. [26].

Statistical analysis

The data collected were tabulated and analyzed using the Statistical Package for Social Sciences® (SPSS) version 21.0 software. The data were initially submitted to descriptive analysis to give measures of absolute (prevalence) and relative frequency of each categorical variable and measures of central tendency (mean, median and

mode) and dispersion (standard deviation and variance) for continuous variables. Inferential analysis was then carried out.

After investigating for PIMs using both tools, there was a significant overlapping between criteria. Therefore, we decided to include only STOPP criteria in the analysis of the "iatrogenic triad" (inappropriate prescribing, drug–drug interactions and polypharmacy), since this criterion identified more PIM and was newer.

Chi square tests were performed to evaluate the factors associated with the "iatrogenic triad". Then, binary logistic regression models were conducted using the "iatrogenic triad" (presence or not) as dependent variable. Factors that showed p values <0.10 in the bivariate tests were included as independent variables in the binary logistic regression. The Hosmer–Lemeshow test and Nagelkerke R Square were used for model fitting. A level of significance of $p < 0.05$ was adopted with a 95% confidence interval.

Results

Of the 423 older adults interviewed, 23 were excluded for low MMSE score (indicating possible cognitive impairment) and in the absence of another person (informant) in the home to answer on their behalf. No patient refused to participate or refused to sign the consent term. Of the 400 participants analyzed in the study, 32 (8.0%) were not in use of any drugs, i.e. 368 older adults (92.0%) were in continuous use of at least one drug.

The general characteristics of the whole sample are given in Table 1. Participants were predominantly female (64.5%), married (55.8%), non-white ethnicity (54.5%), with low income (≤R$1685.00/US$421.00 per month) (70.8%), low educated (0–4 years education) (74.1%), independent (84.5%) and with a mean age of 73.8 (8.0) years.

Regarding drugs used (Table 2), there was a high prevalence of polypharmacy (44.6%) and drug–drug interactions (72.3%) among the patients, where 17.9% of these interactions were classified as severe. The main severe drug–drug interactions found were: amlodipine and simvastatin (10.6%), amiodarone and simvastatin (10.6%), nifedipine and simvastatin (9.0%), quetiapine and levodopa (6.0%), and digoxin and omeprazole (6.0%). Considering all patients, the average number of drug interactions per patient was 3.32 (SD: 4.45) and the mean number of drugs used per patient was 4.46 (SD: 3.10).

A high prevalence of PIMs by Beers (42.1%) and STOPP (46.2%) criteria was found, with mean number of Beers PIMs per patient of 0.52 and STOPP PIMs per patient of 0.57. The five most commonly used PIMs were the same for both Beers and STOPP criteria, namely:

Table 1 Sociodemographic data

	N (%)	Mean (SD)
Gender		
Male	142 (35.5)	
Female	258 (64.5)	
Age		
60–74	231 (57.8)	73.80 (8.019)
≥75	169 (42.3)	
Marital status		
Married	223 (55.8)	
Not married	177 (44.3)	
Color/ethnicity		
White	182 (45.5)	
Non-white	218 (54.5)	
Income classification		
High Income	117 (29.3)	
Low income	283 (70.8)	
Education		
0 to 4 years	292 (74.1)	4.15 (3.14)
5 or more years	102 (25.9)	
Having a caregiver		
Yes	162 (40.5)	
No	238 (59.5)	
Cognitive impairment		
Yes	76 (19)	
No	315 (78.8)	
Hospitalization		
Yes	69 (20.4)	
No	270 (79.6)	
Frailty		
Frail	121 (37.5)	
Vulnerable	75 (22.1)	
Not frail	143 (42.2)	
Self-reported health		
Good	178 (56.5)	
Regular/Poor	137 (43.5)	
Self-reported vision		
Good	142 (45.1)	
Regular/Poor	173 (54.9)	
PHQ 1.2		
Normal	229 (72.7)	
Changed	86 (27.3)	
PHQ 3.4		
Normal	243 (77.1)	
Changed	72 (22.9)	
Functionality		
Independent	338 (84.5)	
Dependent	62 (15.5)	
Fall in the past year		
Yes	141 (35.3)	
No	259 (64.8)	

Table 2 Number of patients with the different combinations of criteria for the "iatrogenic triad"

Combinations of criteria	N (%)
None	69 (18.8)
Only drug interaction	65 (17.7)
Only PIM	26 (7.1)
Interaction + PIM	30 (8.2)
Polipharmacy	1 (0.3)
Polypharmacy + Interaction	63 (17.1)
Polipharmacy + PIM	6 (1.6)
"Iatrogenic triad" (Polypharmacy + Interaction + PIM)	108 (29.3)
Total	368 (100.0)

clonazepam–benzodiazepine (8.69%), amiodarone–antiarrhythmic (4.89%), glibenclamide/glyburide–sulfonylureas (4.62%), methyldopa–alpha-2 adrenergic agonist (4.62%) and bromazepam–benzodiazepine (4.07%).

Analysis of the inter-relationship between the criteria suggestive of iatrogenic effects (polypharmacy, PIM by STOPP and drug–drug interactions) revealed that 108 (29.3%) patients showed the presence of all three criteria (the "iatrogenic triad"); 99 (26.9%) of two criteria, 92 (25.0%) of one criterion and only 69 (18.8%) exhibited none of the criteria.

In the bivariate analysis, hospitalization in the past year ($p = 0.006$), frailty ($p < 0.001$), dependency—Lawton/Brody scale ($p = 0.003$) and having a caregiver ($p < 0.001$) were significant associated with the "iatrogenic triad". Other variables, such as, age ($p = 0.066$) and self-reported health ($p = 0.062$) were marginally non-significant ($p < 0.10$). Ethnicity, marital status, income, self-reported vision perception, BMI, PHQ, education, falls, gender, cognitive impairment, medical appointment and health insurance were not significant ($p > 0.10$).

Table 3 shows the results of the logistic regression, with the best model created based on associations in the bivariate model. Results revealed that the "iatrogenic triad" was associated with presence of a caregiver (OR 2.22, CI95% = 1.13–4.37, $p = 0.020$) and presence of frailty (OR 2.13, CI95% = 1.01–4.54, $p = 0.049$). Hosmer–Lemeshow test was non-significant, indicating a good fit of the model.

Discussion

The present study identified a high prevalence of medication-related iatrogenic effects in the elderly studied, revealing an important inter-relationship among polypharmacy, inappropriate prescribing and drug–drug interactions.

These results are consistent with other studies finding that polypharmacy was associated with both inappropriate prescribing [27] and drug–drug interactions [28], and inappropriate prescribing was also associated with drug–drug interactions [29]. These results support the premise that a single iatrogenic prescription never comes alone and that, once a medication has been inappropriately prescribed, health professionals should be aware of the possible associated iatrogenic effects.

Although several studies have investigated prescription in older adults, few studies have addressed inappropriate medication use, polypharmacy and drug–drug interactions concomitantly in elderly patients. To our knowledge, this is the first study to assess the inter-relationship and factors associated with this "iatrogenic triad".

A previous study in older adults infected with the HIV virus assessed these three items together and found that 52% of the participants used at least one PIM, 70% had drug–drug interactions with recommendation for change of therapy, and 11% had interactions that should be avoided, while 96% of the participants were in use of five or more drugs [30]. Similarly, a study of elderly nursing home residents in Singapore found polypharmacy and potentially inappropriate medication use in 58.6 and 70.0% of residents, respectively, while 5.8% had risk of drug–drug interactions [31] and a study conducted in Sweden based on a register of elderly patients found a mean of 5.4 drugs per patient, a 17% prevalence of potentially inappropriate medication use and 4% risk of severe drug–drug interactions [32].

However, all these studies were from specific populations and have just reported the percentages of each iatrogenic aspect. In the present study, we are proposing a combination of factors, which we named as the "iatrogenic triad". We believe that this new concept could add further information to the field of inappropriate prescribing, because it can reveal patients at higher risk of adverse effects, which may deserve interventions.

Concerning the factors associated with this triad, only having a caregiver and frailty remained significant. Several studies have already shown that inappropriate prescribing is common in frail elderly [33, 34]. Our study provides further support for this data, showing that frailty is also associated with the "iatrogenic triad". Since frailty identifies a vulnerable group of older people at highest risk of adverse clinical outcomes [34], there is a need for assessing how appropriate a therapy is, valuing factors such as quality of life, functional status and the remaining life expectancy [35].

Other finding of the present study is that "having a caregiver" was associated with the "iatrogenic triad". This relation could be due to the fact that older adults who had a caregiver tend to be more dependent and frail, probably

Table 3 Factors associated with the "iatrogenic triad" through the logistic regression model

"Iatrogenic triad"[a]	OR	P
Having a caregiver		
Yes	2.22 (1.13–4.37)	**0.020**
No	1.00	
Age		
60 to 74	0.91 (0.47–1.74)	0.781
≥75	1.00	
Hospitalization		
Yes	1.30 (0.59–2.87)	0.502
No	1.00	
Functionality		
Independent	0.77 (0.24–2.50)	0.674
Dependent	1.00	
Self-reported health		
Regular/Poor	1.04 (0.51–2.11)	0.897
Good	1.00	
Frailty		
Yes	2.13 (1.01–4.54)	**0.049**
No	1.00	

All significant variables associated with "Iatrogenic Triad" on the bivariate analyses were entered in the model

[a] Hosmer–Lemeshow test: Chi square 4.332, $p = 0.741$, Nagelkerke R Square = 0.110

having more comorbidity, and therefore more indications for medication use, increasing the risk of PIMs and interactions. However, it could also be related to the fact that caregivers on a PIM for a specific condition (e.g., diphenhydramine for sleep, naproxen for pain, fluoxetine for depression) may recognize similar symptoms in the care-recipient and seek similar prescription or over-the-counter therapies [36].

In regard to the most common severe drug–drug interactions observed in our study, more than 10% of patients presented the interaction between amlodipine and simvastatin, 10% between amiodarone and simvastatin and 9% between nifedipine and simvastatin. All these interactions could significantly increase the blood levels of simvastatin and the risk of side effects such as liver damage and rhabdomyolysis [37]. The interaction between levodopa and quetiapine, found in 6% of participants, could reduce the effectiveness of levodopa and increase the risk of side effects like drowsiness, low blood pressure, dizziness, and lightheadedness [38]. Finally the combination of digoxin and omeprazole, found in 6% of participants, may increase the effects of digoxin, which could cause arrhythmias and digitalis toxicity [39]. The health professional that work with older adults should be aware of these interactions and monitor these patients.

Finally, our study underscores the fact that one in every three community dwelling older adults exhibited all three iatrogenic criteria concomitantly, highlighting the major public health impact of this problem. The fact that the elderly population is a major user of health services and that monthly expenditure on medications can represent up to a quarter of the income of this group [40], points to the need for greater education of health professionals involved in elderly patient care, and for policies facilitating access of this population to medications and promoting rational drug use, thereby averting iatrogenic events and consequently greater costs to the health system. Particularly in the Brazilian case, some factors could help to justify these findings, such as the fact that some PIMs are available over-the-counter (Acetylsalicylic acid, Antitussives; expectorants; mucolytics; antihistamine-decongestant) and that at least one out of four medications available free of charge to the population are included in the Beers criteria as PIM [41].

These results can serve to inform new preventive and educational strategies to ensure that health professionals are trained to deal with the "iatrogenic triad" as a whole rather than each factor separately. Thus, by considering the multiplicity of factors that, not just alone but in conjunction, cause adverse event in elderly patients, iatrogenic events can be more effectively prevented. In the region in which the present study was conducted (Juiz de Fora, Brazil), there are few interventions to minimize the "iatrogenic triad". There is no routine assessment of inappropriate prescribing or polypharmacy in these family medical clinics. Some settings have clinical pharmacists who are responsible for delivering medications free of charge for the community. However, interventions such as annual medication reviews are very scarce. We believe our study could alert healthcare professionals and managers to promote continuing medical education and the use of inappropriate prescription criteria (such as STOPP or Beers), drug–drug interaction softwares or polypharmacy computerized support systems in order to identify wrong patterns and reduce inappropriate prescribing [42].

The present study has the following limitations. First, not all the clinical data on the patients was available, information often required to classify a drug as potentially inappropriate by the STOPP criteria (e.g. serum creatinine, estimated glomerular filtration rate, preserved systolic ventricular function), where this may have led to underestimation of the results of this analysis, since these drugs were not considered PIM. Second, the study was conducted in a Brazilian city, where this may limit the generalization of its results. Third, most participants were women (64.5%). The possible reason for this is the feminization of aging and the fact that women usually are responsible for housework, staying at home more frequently. Third, the

2012 Beers criteria were employed for this study [24] although updated criteria have recently been published [43]. Future studies should adopt these latest criteria. Finally, we have not followed those patients identified with "severe drug–drug interactions" in order to see if they actually experienced a clinical problem/symptom as a result of this interaction.

Nonetheless, the present study has several strengths. The study involved a representative sample of the community, reducing selection bias and assessed three iatrogenic-related aspects which although common, have rarely been assessed together.

Conclusion

One in every three community-dwelling older adults had the "iatrogenic triad" concomitantly (potentially inappropriate medication use, polypharmacy and drug–drug interactions). Further studies investigating these three factors should be conducted to gather evidence that can guide the decision-making of doctors prescribing to this age group.

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Conflicts of interest None.

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