Title page: Trends in the relationship between the level of drug interactions and sociodemographic, clinical, and functional characteristics in nonagenarians

Short title: Drug interactions in nonagenarians

i. **Word count: 2543**
ii. **Table count: 3**
iii. **Figure count: 0**

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Bullet point summary:

What is already known about drug interaction and hyperpolypharmacy:

- Younger older-adults are more susceptible to drug interaction when with hyperpolypharmacy.
- Adverse effects usually studied with hyperpolypharmacy are dizziness, dyspnea, fatigue, constipation and risk of fall.
- Multiple drug therapy increases the risk of hospitalization and it is associated with reduced physical and cognitive capacity.

What this study adds:

- Nonagenarians with hyperpolypharmacy are even more susceptible to drug interaction.
- All nonagenarians with hyperpolypharmacy presented at least one moderate drug interaction.

- Nonagenarians with major drug interaction reported higher frequency of changes in physical and cognitive performance and depressive symptoms, affecting their quality of life.

ABSTRACT:

Aim: This research aimed to study the association of drug interactions and sociodemographic, clinical, and functional characteristics in nonagenarians with hyperpolypharmacy. **Methods:** This was a secondary analysis of an evaluation performed by the Multiprofessional Care for the Oldest-old Project in 2016, with participants identified with hyperpolypharmacy. **Results:** Results revealed that 69% of 29 participants had at least one major drug interaction, 41% had 10 or more moderate interactions, and 59% had minor interactions. The study revealed significant relationships for major drug interactions with the characteristics of recurrent urinary tract infections, anxiety, and palpitations. The study found near significance for white color, not good general health and appetite, depression, and impaired cognition. For moderate drug interaction, findings showed a relationship near significance for females, perception of not good general health and appetite, hypertension, diabetes, urinary infection, depression scale change, agitation, pain, fatigue, and a fear of falling. For minor drug interactions, the study revealed significant findings for an association with depression, and apathy or sleepiness. There were findings near significance for an association with white color, diabetes, agitation, pain, fatigue, and cough. **Conclusion:** Drug interactions are highly prevalent among nonagenarians with hyperpolypharmacy, with clinical and quality of life impact. Thus they must be constantly evaluated for the presence of drug interactions at all levels of care, whether in primary care or in specialized care. A study with larger sample size and longitudinal contour is proposed to prove the importance of our observations.

Keywords: polymedication, 80+ years old people, side-effects, quality of life.

INTRODUCTION:

Population aging is a global trend. Nonagenarians, individuals aged 90 years or more, have been increasing exponentially in the past decade [1]. Due to their multimorbidities and more advanced age, nonagenarians are more vulnerable than younger older-adults (60-79 years). This vulnerability is due to sociodemographic and clinical characteristics, in addition to physical and cognitive limitations [2]. Multimorbidity is a determining factor in the use of multiple medications, known as polypharmacy (5 or more medications) or hyperpolypharmacy (10 or more medications) [3]. The risk of an adverse event due to drug interactions (DI) increases substantially as multiple drugs are administered simultaneously [4]. These interactions have been studied mainly in young elderly patients and in polypharmacy [5]. However, few have studied the prevalence and consequences of hyperpolypharmacy and drug interactions in nonagenarians. This study aimed to observe the association between drug interactions and sociodemographic, clinical, lifestyle and functional characteristics in nonagenarians with hyperpolypharmacy.

METHODS:

This study was a secondary analysis of a cross-sectional, descriptive, and analytical study. The initial study, the Multiprofessional Care for the Oldest-old Project (Atenção Multiprofissional ao Longevo - AMPAL), done in 2016 by the Institute of Geriatrics and Gerontology of the Pontifical Catholic University of Rio Grande do Sul, evaluated 244 nonagenarians from randomly selected households in Porto Alegre, Brazil. The assessment included the participants' sociodemographic, clinical, lifestyle, and functional characteristics, along with the medications they used. Those participants with hyperpolypharmacy were identified and included in the present analysis. The participants' oral and non-oral medications, including eye drops were evaluated. Exclusion drugs included vitamins, herbal medicines, calcium carbonate, and iron.

Sociodemographic variables assessed and analyzed in this study included participant sex, education level, marital status, and color. Clinical variables included good general health, appetite, vision, hearing. Certain medical history elements were also considered clinical variables including histories of heart disease, stroke, hypertension, dementia, diabetes, depression, bowel problems, anxiety, respiratory problems, arthrosis, urinary tract infection, thyroid disease, a depression scale change, cognitive impairment (18 points or less up to complete primary school, and 23 for those with more than the primary school at Mini Mental State Examination), and urinary incontinence. Other clinical symptoms evaluated and analyzed in this study included apathetic/sleepy, agitated/hyperactive, dizziness, choking, xerostomia, constipation, diarrhea, pain, dyspnea, palpitation, fatigue, wheezing, cough, history of fall (in the last 6 months) and fear of falling.

The life habits characteristics included activities such as watching TV, domestic activities, reading, caring for plants and animals, listening to the radio, handcrafts activities, physical activity (activity performed at least twice or more weekly), difficulty initiating sleep, restless sleep, sleep without change, normal timed Up and Go (TUG), preserved functional ability, and preserved basic ability. The TUG test measured the time, in seconds, it takes to stand up from a chair, walk three meters, then return and sit in the chair. The test is considered normal if participants spent less than 20 seconds. Functional and basic abilities were assessed according to the participant's degree of difficulty or ease in carrying out each activity. The functional activities assessed included walking 400m or four blocks, climbing 10 steps or a flight of stairs, carrying five-kilogram objects, getting up from a chair without using hands, lowering and standing up to pick up an object on the floor, raise arms above head, touching the back of the head with both hands, picking up a pencil in each hand, grasping objects firmly with both hands [6]. Basic abilities included transferring to a bed or chair and independent bathing, dressing, eating, and toileting. Macedo's criteria [6] was used to score each activity based on the ease or difficulty of performance. who reported ease of performing each activity scored 3, ± easy, 2, difficult 1 and weren't capable 0 points, totaling 27 for those who reported ease in performing all functional activities, reaching 100% of ability (Total points/ 27 times 100), normal if the participant scored 50% or more. The same procedure was performed to calculate the basic abilities, which totaled 15 points, reaching 100% ability, normal if the participant scored 80% or more. This instrument is an adaptation of the functional assessment proposed by Simonsick (2001) [7] and validated in Brazil by Macedo [6].

The prevalence of drug interactions were identified through the website drugs.com and characterized as major, moderate, and minor interactions. The potential interactions of the participants' medications were assessed and listed according to each characterization group. The sociodemographic, life habits, functional abilities, and basic abilities were then analyzed to determine their relationship with the drug interactions. The variables were analyzed by Chi-square so that those with significance levels of $p<0.2$ were classified as near significance and those with $p<0.05$ as statistically significant.

The AMPAL Project was approved by the Research Ethics Committee of PUCRS (CAAE: 55906216.0.0000.5336). All participants were informed of the research aims and assured of the confidentiality of the information collected. Furthermore, the participants voluntarily agreed to participate in the research after reading and signing an informed consent form. For the present analysis researchers received unidentifiable records of the first study. Thus, the confidentiality of the participants' information was preserved.

RESULTS

A total of 29 participants were identified as having hyperpolypharmacy and included in the analysis for this study. Table 1 shows the distribution of sociodemographic and clinical characteristics of participants according to the number of major, moderate, and minor drug interactions noted from participants' medication list. Participants were predominantly female (76%), widowed (69%), white (93%), and lived with a family member (69%). Over half were noted to have low education (55%). Among the 29 participants, 69% (n= 20) were taking medications that had at least one major drug interaction, 41% (n=12) had 10 or more moderate drug interactions, and 59% (n=17) had two or more minor drug interactions.

Analysis revealed that participants with certain characteristics were associated with major drug interactions at an increased frequency compared to those participants with the converse characteristic. These included men (71%, p=0.631), those who were married (100%, p=0.053) those who had other marital status (100%, p=0.053), white color (74%, p=0.089), and those who described the following items as "not good": general health (81%, p=0.119), appetite (83%, p=0.160), vision (71%, p=0.483), and hearing (71%, p=0.550). Health history characteristics noted to have a higher association with major drug interactions included stroke (80%, p=0.498), dementia (100%, p=0.468), diabetes (83%, p=0.375), depression (83%, p=0.160), anxiety (100%, p=0.050), urinary incontinence (73%, p=0.450), and those who had Depression Scale change (72%, p=0.467).

Characteristics that showed an increased association with moderate drug interactions included women (50%, p=0.108), higher education (54%, p=0.219), widowed (45%, p=0.840), non-white color (50%, p=0.665) and those who described the following items as "not good": general health (56%, p=0.071), appetite (58%, p=0.120), and vision (48%, p=0.250). Associations were also observed in those with good hearing, (47%, p=0.550), history of heart disease (50%, p=0.296), dementia (50%, p=0.665), diabetes (67%, p=0.172), depression (50%, p=0.341), anxiety (57%, p=0.295), respiratory problem (46%, p=0.638), thyroid disease (50%, p=0.385), urinary incontinence (47%, p=0.550), and Depression Scale change (55%, p=0.054).

The study revealed characteristics occurring more frequently with two or more minor drug interactions were women (59%, p=0.631), lower education (69%, p=0.219), married (66%, p=0.617), widowed (60%, p=0.617) and white (63%, p=0.163). Those with good appetite (59%, p=0.637), good vision (62%, p=0.568), not good hearing (64%, p=0.550), history of heart disease (62%, p=0.638), stroke (60%, p=0.671), hypertension (61%, p=0.487), diabetes (83%, p=0.182), depression (83%, p=0.028), bowel problems (61%, p=0.774), arthrosis (60%, p=0.876), thyroid disease (60%, p=0.615), urinary incontinence (60%, p=0.876), and Depression Scale change (61%, p=0.514) all were found to have an increased association with minor drug interactions.

Table 1. Distribution of participants regarding the frequency of drug interactions in relation to sociodemographic and clinical characteristics.

Variables	Major Interaction (1 or more)	p	Moderate Interaction (10 or more)	p	Minor Interaction (2 or more)	p	Total
Total	20(69.0%)		12(41.4%)		17(58.6%)		29(100%)
Sex							
female	15(68.2%)	0.631	**11(50.0%)**	**0.108**	13(59.1%)	0.631	22(75.9%)
male	5(71.4%)		**1(14.3%)**		4(57.1%)		7(24.1%)
Years of study							
up to primary	11(68.8%)	0.648	5(31.3%)	0.219	11(68.8%)	0.219	16(55.2%)
primary or higher	9(69.2%)		7(53.9%)		6(46.2%)		13(44.8%)
Marital status							
Married	**6(100%)**	**0.053**	2(33.3%)	0.840	4(66.7%)	0.617	6(20.7%)
Other	**3(100%)**		1(33.3%)		1(33.3%)		3(10.3%)
Widower	**11(55.0%)**		9(45.0%)		12(60.0%)		20(69.0%)
Color							
White	**20(74.1%)**	**0.089**	11(40.7%)	0.665	**17(63.0%)**	**0.163**	27(93.1%)
Not white	**0(0%)**		1(50.0%)		**0(0%)**		2(6.9%)
Good general health							
Not	**13(81.3%)**	**0.119**	**9(56.3%)**	**0.071**	11(68.8%)	0.219	16(55.2%)
Yes	**7(53.9%)**		**3(23.1%)**		6(46.2%)		13(44.8%)
Appetite							
Not good	**10(83.3%)**	**0.160**	**7(58.3%)**	**0.120**	7(58.3%)	0.637	12(41.4%)
Great or good	**10(58.8%)**		**5(29.4%)**		10(58.8%)		17(58.6%)

Vision							
Not good	15(71.4%)	0.483	10(47.6%)	0.250	12(57.1%)	0.568	21(72.4%)
Great or good	5(62.5%)		2(25.0%)		5(62.5%)		8(27.6%)
Hearing							
Not good	10(71. %)	0.550	5(35.7%)	0.550	9(64.3%)	0.550	14(48.3%)
Great or good	10(66.8%)		7(46.7%)		8(53.3%)		15(51.7%)
Heart disease*	11(68.8%)	0.648	8(50.0%)	0.296	10(62.5%)	0.638	16(55.2%)
Stroke *	4(80.0%)	0.498	1(20.0%)	0.293	3(60.0%)	0.671	5(17.2%)
Hypertension*	15(65.2%)	0.375	**8(34.8%)**	**0.172**	14(60.9%)	0.487	23(79.3%)
Dementia*	2(100%)	0.468	1(50.0%)	0.665	1(50.0%)	0.665	2(6.9%)
Diabetes*	5(83.3%)	0.375	**4(66.7%)**	**0.172**	**5(83.3%)**	**0.182**	6(20.7%)
Depression*	**10(83.3%)**	**0.160**	6(50.0%)	0.341	**10(83.3%)**	**0.028**	12(41.4%)
Bowel problem*	**7(53.9%)**	**0.119**	5(38.5%)	0.774	8(61.5%)	0.774	13(44.8%)
Anxiety*	**7(100%)**	**0.050**	4(57.1%)	0.295	4(57.1%)	0.631	7(24.1%)
Respiratory problem*	8(61.5%)	0.353	6(46.2%)	0.638	7(53.9%)	0.638	13(44.8%)
Arthrosis*	10(66.7%)	0.550	6(40.0%)	0.876	9(60.0%)	0.876	15(51.7%)
Urinary infection*	**3(37.5%)**	**0.037**	**1(12.5%)**	**0.060**	4(50.0%)	0.433	8(27.6%)
Thyroid disease*	6(60.0%)	0.364	5(50.0%)	0.385	6(60.0%)	0.615	10(34.5%)
Depression Scale changed	13(72.2%)	0.467	**10(55.6%)**	**0.054**	11(61.1%)	0.514	18(62.1%)
Cognitive impairment	**11(57.9%)**	**0.085**	7(36.8%)	0.385	10(52.6%)	0.309	19(65.5%)
Urine loss	11(73.3%)	0.450	7(46.7%)	0.550	9(60.0%)	0.876	15(51.7%)

* history of

The study analysis also revealed associations between the number of drug interactions and the characteristics of lifestyle and functionality (see Table 2). Those participants who cared for plants or animals (80%, p=0.177), had restless sleep (75%, p=0.636), had difficulty initiating sleep (70%, p=0.636), and who participated in handcraft activities (88%, p=0.192) were found to have a higher frequency of major drug interactions than those with the converse characteristic. Higher frequencies of moderate drug interactions were found in those who practiced reading activities (44%, p=0.486) and handcraft activities (50%, p=0.432). Those who cared for plants or animals (47%, p=0.550), had difficulty falling asleep (50%, p=0.385), and had preserved basic ability (43%, p=0.876) were also associated with more frequent moderate drug interactions. An increase in frequency of minor drug interactions was noted in participants who watched TV (60%, p=0.556), cared for plants and animals (60%, p=0.876), listened to the radio (75%, p=0.047), practiced handcraft activities (63%, p=0.567), had difficulty in initiating sleep (70%, p= 0.310), had restless sleep (75%, p=0.444), and had preserved functional abilities (61%, p=0.514).

Table 2. Distribution of participants regarding the frequency of drug interactions in relation to the characteristics of life habits and functionality

Variables	Major interaction (1+)	p	Moderate interaction 10+	p	Minor interaction (2+)	p	Total
Watching TV	17(68.0%)	0.636	10(40.0%)	0.556	15(60.0%)	0.556	25(86.2%)
Domestic activities	11(64.7%)	0.432	7(41.2%)	0.637	9(52.9%)	0.363	17(58.6%)
Reading	12(66.7%)	0.534	8(44.4%)	0.486	**8(44.4%)**	**0.054**	18(62.1%)
Caring for plants or animals	**12(80.0%)**	**0.177**	7(46.7%)	0.550	9(60.0%)	0.876	15(51.7%)
Listening to the radio	10(62.5%)	0.336	5(31.2%)	0.220	**12(75.0%)**	**0.047**	16(55.2%)
Handcrafts activities	**7(87.5%)**	**0.192**	4(50.0%)	0.433	5(62.5%)	0.568	8(27.6%)
Physical activities	5(55.6%)	0.266	3(33.3%)	0.432	5(55.6%)	0.568	9(31.0%)
Difficulty initiating sleep	7(70.0%)	0.636	5(50.0%)	0.385	**7(70.0%)**	0.309	10(34.5%)
Restless sleep	3(75.0%)	0.636	1(25.0%)	0.444	3(75.0%)	0.444	4(13.8%)
Sleep without change	8(61.5%)	0.353	5(38.5%)	0.774	**5(38.5%)**	**0.047**	13(44.8%)
Normal Timed Up and Go test	8(61.5%)	0.353	5(38.5%)	0.774	7(53.8%)	0.638	13(44.8%)
Preserved functional ability	**10(55.6%)**	**0.053**	6(33.3%)	0.230	11(61.1%)	0.514	18(62.1%)
Preserved basic ability	9(64.3%)	0.450	6(42.9%)	0.876	8(57.1%)	0.876	14(48.3%)
Total	20(68.9%)		12(41.4%)		17(58.6%)		29(100%)

The associations between clinical symptoms and adverse effects in health and the number of major, moderate and minor drug interactions can be seen in Table 3. Participants who had a higher frequency of major drug interactions were those with dizziness (75%, p=0.353), choking (82%, p=0.228), xerostomia (81%, p=0.119), diarrhea (83%, p=0.375), palpitation (100%, p=0.050), fatigue (88%, p=0.192), cough (86%, p=0.068), and fear of falling (71%, p=0.568). Those who reported feeling apathetic or sleepy (44%, p=0.568), agitated or hyperactive (75%, p=0.178), and those who reported dizziness (50%, p=0.296), choking (46%, p=0.514), xerostomia (50%, p=0.296), pain (58%, p=0.063), sleepiness (50%, p=0.487), dyspnea (50%, p=0.363), palpitation (57%, p=0.295), fatigue (63%, p=0.158), cough (43%, p=0.876) and fear of falling (53%, p=0.131) all presented with a higher frequency of moderate drug interactions. Minor drug interactions were noted more frequently in participants who felt apathetic or sleepy (89%, p=0.032), and who reported dizziness (63%, p=0.638), xerostomia (63%, p=0.638), choking (73%, p=0.208), constipation (65%, p=0.341), pain (75%, p=0.184), palpitation (71%, p=0.369)**,** fatigue (88%, p=0.060), wheezing (75%, p=0.250), cough (71%, p=0.176) and history of fall (69%, p=0.219).

Table 3. Distribution of participants regarding the frequency of drug interactions in relation with characteristics of symptoms and adverse events in health

Variables	Major Interaction (1+)	p	Moderate Interaction 10+	p	Minor Interaction (2+)	p	Total
Apathetic/Sleepy	6(66.7%)	0.591	4(44.4%)	0.568	**8(88.9%)**	**0.032**	9(31.0%)
Agitated/hyperactive	2(50.0%)	0.364	**3(75.0%)**	**0.178**	**1(25.0%)**	**0.178**	4(13.8%)
Dizziness	12(75.0%)	0.353	8(50.0%)	0.296	10(62.5%)	0.638	16(55.1%)
Choking	9(81.8%)	0.228	5(45.4%)	0.514	8(72.7%)	0.208	11(37.9%)
Xerostomia	**13(81.2%)**	**0.119**	8(50.0%)	0.296	10(62.5%)	0.638	16(55.2%)
Constipation	11(64.7%)	0.432	7(41.1%)	0.637	11(64.7%)	0.341	17(58.6%)
Diarrhea	5(83.3%)	0.375	2(33.3%)	0.513	3(50.0%)	0.487	6(20.7%)
Pain	8(66.7%)	0.613	**7(58.3%)**	**0.063**	**9(75.0%)**	**0.184**	12(46.1%)
Dyspnea	9(64.3%)	0.450	7(50.0%)	0.362	8(57.1%)	0.876	14(48.3%)
Palpitation	**7(100%)**	**0.050**	4(57.1%)	0.295	5(71.4%)	0.369	7(24.1%)
Fatigue	**7(87.5%)**	**0.192**	**5(62.5%)**	**0.158**	**7(87.5%)**	**0.060**	8(27.6%)
Wheezing	5(62.5%)	0.483	2(25.0%)	0.250	6(75.0%)	0.250	8(27.6%)
Cough	**12(85.7%)**	**0.068**	6(42.9%)	0.876	**10(71.4%)**	**0.176**	14(48.3%)
History of fall	10(62.5%)	0.336	6(37.5%)	0.638	11(68.7%)	0.219	16(55.2%)
Fear of Falling	12(70.6%)	0.568	**9(52.9%)**	**0.131**	9(52.9%)	0.363	17(58.6%)
Total	20(68.9%)		12(41.4%)		17(58.6%)		29(100%)

DISCUSSION:

This work aimed to better understand characteristics associated with hyperpolypharmacy in nonagenarians. Among the twenty-nine participants identified with hyperpolypharmacy for this study, sociodemographic, clinical, life habits, functional ability characteristics and drug interaction data were analyzed. The results revealed that certain characteristics were associated with minor, moderate, and/or major drug interactions more frequently than other characteristics.

Based on the findings of this study, certain sociodemographic and health history characteristics may be associated with drug interactions found in hyperpolypharmacy. Incidences of major drug interactions were significantly associated with marital status in general, whether married, other, or widowed. By grouping the marital status into two categories, non-widowed and widowed, those who were non-widowed had a significantly ($p=0.017$) higher incidence of major drug interactions than widowed. Major and minor drug interactions were noted to be higher in those of white color with a finding near significance ($p=0.089$ and $p=0.163$ respectively). However, there were only 2 non-white participants in the study. There were associated findings near significance ($p=0.119$) for major interactions and moderate interactions ($p=0.071$) in those who reported their health as not good. Those who reported their appetite as not good also had increased frequency of major drug interactions near significance ($p=0.160$) and moderate drug interactions near significance ($p=0.120$) when compared to those who reported their appetite as good. Clinical problems and health history found to be statistically significantly associated with increased major drug interactions included anxiety and history of urinary infection. Depression, bowel problems, and cognitive impairment were also noted to have increased frequency of major drug interactions near significance compared to those who do not have those problems. Depression was also a statistically significant ($p=0.028$) characteristic associated with minor drug interactions. Other characteristics with an association near significance related to moderate drug interactions included female, hypertension, diabetes, urinary infection, and a Depression Scale change.

Several life habits and functional abilities were found to be associated with increased frequency of drug interactions. Participants who listened to the radio and those who had no change in sleep were found to have a statistically significant ($p=0.047$ and $p=0.047$ for both characteristics) association with minor interactions. For those who had an increase in medications with major interactions, the findings were near significance for the characteristics of caring for plants and animals (0.177) and performing handcraft activities ($p=0.192$). Those participants with preserved functional ability also had an association near significance ($p=0.53$) in major interactions.

This study revealed increased association between participant symptoms and drug interactions. Participants who had apathy or sleepiness were found to have a statistically significant ($p=0.032$) association with incidences of minor interactions. Those with complaints of palpitation had a statistically significant ($p=0.050$) association with major interactions. For those with moderate drug interactions, there was near significance of association with agitation ($p=0.178$), pain ($p=0.063$), fatigue ($p=0.158$), and fear of falling ($p=0.131$).

The participant sample was a limitation of this study as it was relatively small for generalizability of results. However, due to the few studies available that evaluate the consequences of hyperpolypharmacy in this population, the information learned in this study can be helpful to gain further insight. Future studies with larger sample sizes as well as longitudinal studies are needed to expand on these findings.

CONCLUSIONS:

In conclusion, this study revealed demographic, clinical, and functional characteristics that may be associated with increased frequency of minor, moderate, and major drug interactions in nonagenarians. Nonagenarians are a vulnerable population due to these characteristics and hyperpolypharmacy. Hyperpolypharmacy may contribute to increased symptomatology due to medication side effects and

interactions. Clinical pharmacists are in an ideal position to recognize hyperpolypharmacy in this population and use interventions that identify and minimize drug-related problems, thus highlighting this important role.
Therefore, drug interaction besides being very frequent, was also related to factors referent to the quality of life of the participants. Thus, nonagenarians with hyperpolypharmacy must be constantly evaluated for the presence of drug interactions at all levels of care, whether in primary care or in specialized care. A study with a larger sample size and longitudinal outline is proposed to prove the importance of our observations.

ACKNOWLEDGEMENTS:

The present work was carried out with the support of the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - Financing Code 001.

CONFLICT OF INTEREST STATEMENT:

All authors declare no conflicts of interest.

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