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Adverse reaction risk score in elderly GerontoNet ADR: Review

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ABSTRACT

OBJECTIVE

To verify the applicability of the GerontoNet ADR risk score in the prevention of adverse reactions in hospitalized elderly patients.

METHODS

A literature review was carried out over a period of ten years in databases such as Google Scholar, Scielo and PubMed on the use of the GerontoNet ADR risk score in validation studies.

RESULTS

Although studies have shown that the GerontoNet score was a good predictor, with satisfactory sensitivity in 4 of the studies, there is a need for further studies that increase specificity.

CONCLUSION

Considering that adverse reactions can be avoided, dispensing them is the best strategy for efficient clinical results and cost reduction, with the participation of the pharmaceutical professional as an ally in care.

DESCRIPTORS

Pharmacovigilance, Adverse reaction in the elderly, Trigger Tools, Risk score, GerontoNet *ADR risk score*, *External validation*.

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INTRODUCTION

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is a harmful, unintentional event that occurs with the use of drugs at the usual doses, whether for therapeutic, prophylactic, or diagnostic purposes[1,2].

Adverse drug reactions (ADRs) are the cause of hospitalizations and complications that affect the patient's quality of life and may lead to death, in addition to hindering diagnosis and treatment. Types of ADRs can be classified according to severity, frequency, or causality[1].

Factors related to age, polymedication, lifestyle habits (such as smoking and alcohol use), and comorbidities interfere in pharmacokinetics, making the individual more susceptible to developing an ADR at a severe level and requiring hospitalization, which, in addition to affecting patient safety, increases hospital costs[2,3].

One strategy to prevent adverse reactions is to identify groups that have a higher risk of suffering an adverse reaction and direct specific resources to this group. When a patient is identified as having a higher risk of developing ADRs, the multidisciplinary team will be more attentive to this patient's therapy[3]. The elderly, for example, are 7 times more likely to develop an ADR that leads to hospitalization associated with an inappropriate prescription[4].

With the aging process and the physiological and pharmacokinetic changes of this process come chronic diseases and with them the use of multiple drugs, often with inappropriate medications, whose risks outweigh the benefits[3]. Complex prescriptions contribute to poor compliance, and medication errors, drug interactions, and adverse reactions that impair the patient's quality of life may occur, which may lead to hospitalizations for iatrogenic diseases and these adverse reactions may lead to complications resulting in death[3,5,6].

The active search for ADRs allows us to collect data, establish the cause, and analyze the probability of an adverse event being related to the drug and leading to hospital complications, which are often underreported[1,8]. The pharmacist has an important role in these interventions to minimize drug-related problems, promoting rational use. To perform the active search and thus recognize and identify possible ADRs, tools such as the so-called Trigger tools may be used[5,7].

The presence of a trigger does not confirm that it is an ADR, but based on this identification, a search may be conducted using some drugs, laboratory test values, or signs and symptoms that may indicate the occurrence of some unexpected event. Subsequently, you can apply causality algorithms that prove the evidence of the adverse reaction and perform a more objective classification[7].

In addition to the active search using triggers, in the practice of care one can identify the possibility of a patient developing an adverse reaction with risk scores. One of these tools is the GerontoNet ADR (Adverse Drug Reaction) score; the use of scores like this can benefit patients who need priority intervention during hospitalization[3,4].

The GerontoNet ADR was developed by the Italian Group of Pharmacoepidemiology in the Elderly (Gruppo Italiano di Farmacoepidemiologia nell'Anziano- GIFA) to identify elderly people at risk of developing an adverse reaction. The group studied consisted of 5,936 elderly patients, with a mean age of 78 (+7.2 years). By means of a form containing some clinical information of the patients and drug history (admission, hospitalization, and discharge), data were collected, and signs of ADR were investigated, being identified in 383 patients. Later, a study was validated in 4 hospitals in Europe, with 483 elderly patients, in which ADRs were identified in 56 patients, having a score of 3-4 as a good cut-off point for risk prediction[3,7].

The score ranges from 0-10 points, assigning different scores according to the presence of 4 or more comorbidities, renal dysfunction, heart failure, liver disease, history of previous ADRs, and polypharmacy from the use of 5 drugs, according to Table 14,7,9. Renal dysfunction was defined by glomerular filtration rate < 60mL/min, by the -CKD-EPI Chronic Kidney Disease Epidemiology Collaboration) equation.

Table 1. GerontoNet Score variables.

VARIABLES	POINTS
≥ 4 comorbidity	1
Renal insufficiency*	1
Heart failure	1
Liver disease	1
Amount of medication:	
5-7	1
≥ 8	4
Previous adverse reaction	2

Considering that most ADRs are preventable, prevention is the best strategy for efficient clinical results and cost reduction4. In this scenario, the participation and possible intervention of the pharmaceutical professional are numerous7.

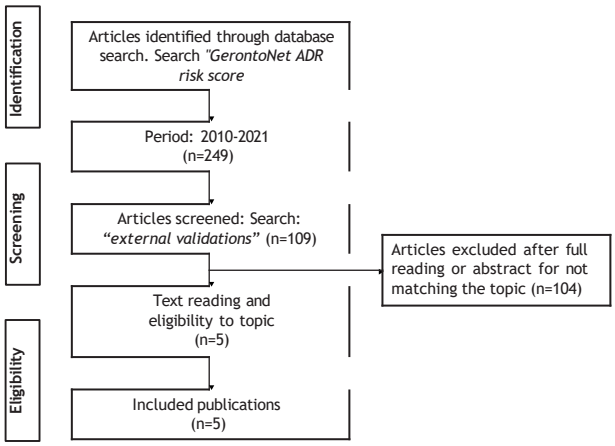
The objective of this study is to verify the applicability of the GerontoNet ADR risk score in the prevention of adverse reactions in elderly hospitalized patients through a literature review of articles that performed validation studies using this tool.

METHODS

This is a systematic literature review. The initial search for theoretical basis was conducted in the Scielo, PubMed and Google Academic databases, according to the keywords: Pharmacovigilance, Adverse reaction in the elderly, Trigger Tools, Risk score, GerontoNet ADR validation in Portuguese, and adverse reactions, elderly, trigger tools, Gerontonet ADR risk score extenal validation, in English.

The collection was performed in the second half of 2022 and studies reporting on the GerontoNet Score were identified, in all languages. Initially, 249 articles were found, and later added the search "external validation", 109 articles were found (Figure 1).

Figure 1. Flowchart of the search and selection of the articles analysed in this study.



After the search, articles that used the Gerontonet ADR risk score in validation studies were identified and selected in the construction of data, excluding 104 articles that did not fit the proposal, after reading the full text or the abstract. The Google Academic database was the only one that presented a search for articles that portrayed the validation of the theme

(5 articles), from publications in 2010, all in English.

The information was collected, evaluating, and comparing the results obtained in the studies between the classification of the score and the data collected, verifying the application of the score to warn about the possibility of some adverse event occurring.

In this study, the Informed Consent Form was waived. A Term of Commitment and Confidentiality will be drawn up, in which the researcher guarantees data confidentiality.

RESULTS

To verify the applicability of the GerontoNet ADR risk score in the prevention of adverse reactions in hospitalized elderly patients, five articles were selected that aimed to validate this tool in patients older than 60 years in hospitalizations.

Table 2 shows the five selected articles and their characteristics, such as authors, study location, results, and comments.

Table 2. Dados, resultados e observações dos artigos selecionados.

Title	Reference / Authors	Population / Sample	Objectives	Results and observations of the selected studies
Development and Validation of a Score to Assess Risk of Adverse Drug Reactions Among In-Hospital Patients 65 Years or Older: The GerontoNet ADR Risk Score[3].	Onder G. Petrovic M.; Tangiisuran B, et al.	483 patients from 4 University Hospitals in Europe between September and December 2008. The mean age was 80.3 years and they used about 11 medications.	The aim of the study was [1] to develop and [2] validate a practical, efficient and simple method to identify patients at higher risk of ADR in an elderly inpatient population	Applied the risk score, 131 elderly patients scored between 6-7 points and 93 scored 8 or more points, of whom had ADRs 11.5% and 28%, respectively. Further studies are needed to use the tool in other populations and settings, although it has proven useful as an approach in identifying patients at higher risk and who may be targets for ADR. It may assist in reducing drug-related problems in clinical practice interventions.
Application of the GerontoNet ADR Risk Score in a Psychiatric Setting[9].	Gudrun Hefner, Martina Hahn, Sibylle C. Roll, Ansgar Klimke, Christoph Hiemke.	79 patients from a Psychiatric Hospital in Germany from April/2011 to October 2012, 65.8% female and 34.2% male, aged 65-84 years, with a mean of 8 medications.	The objective of this study was [1] to evaluate the clinical applicability of thisscore in the psychiatric setting	After applying the score, the patients had a mean score of 3.7 points, 13 of them with 4 points, 10 elderly with 5 points, 21 with 6 points, and 5 patients with 7 points. The score proved to be a good predictor for psychiatric patients, who are at higher risk for ADR. It is suggested to replace some variables in the GerontoNet risk score for use in the psychiatric setting, as it differs significantly from the one in which the score was originally created. In this study the prescribing of potentially inappropriate medications was identified, ADR presentation was identified, and their severity was classified. The predictive validity of the score was satisfactory, considering that it is based primarily on the number of medications ingested by the patient.
Prediction of ADRs and Estimation of Polypharmacy in Older Patient's Population: Retrospective Study in Russian Gerontology Center[10].	Al-Ragawi A, Zyryanov S, Ushkalova E, Butranova O, Pereverzev A	201 patients from a Russian Gerontology Clinical Research Center between June and December 2017, 74.6% were female. The patients were about 76 years old and used 6-8 medications.	The objective of this study was [1] to review ADRs in patients ≥ 65 years old, based on the GerontoNet risk score, with an emphasis on polypharmacy	In this study, the score was applied in two moments: on admission, in which 44.8% obtained 3 points or more, and during hospitalization, 30.9% of the elderly obtained between 5-7 points and 60.1% more than 8 points.The mean score increased from 2.54 on admission, to 4.79 on hospitalization. 91.0% of the elderly used more than 5 medications during hospitalization. It was identified that, patients with GerontoNet score ≥4 quadruple the risk of ADR exposure, than patients with score between 0-3. The prevalence of polypharmacy (>7 medications) in the study population, raised the score by 4 points, which may have contributed to an inadequate prediction rate. It suggests that ADRs in the elderly may be predicted using the GerontoNet Risk Score as a high-risk group.
Predicting the risk of adverse drug reactions in older inpatients: external validation of the GerontoNet ADR risk score using the CRIME cohort[11].	Petrovic, M., Tangiisuran, B., Rajkumar, C. *et al*	1.075 patients, in the year 2008, with a mean age of 81 years. They used an average of 10 medications. In this study, ADRs were identified and then classified.	The purpose of this study was [1] to externally validate the GerontoNet ADR risk score and [2] to assess its validity in specific subpopulations of elderly hospitalized patients.	Pelo menos 1 RAM foi identificada em 70 pacientes, e foram posteriormente classificadas. O score demonstrou ser uma abordagem prática para identificar subpopulações específicas entre idosos internados com risco aumentado de desenvolver RAM, com uma precisão diagnóstica razoável a boa. O ponto de corte de 4 produziu uma sensibilidade muito boa, porém resultados de baixa especificidade.
The Adverse Drug Reaction Risk in Older Persons (ADRROP) prediction scale: derivation and prospective validation of an ADR risk assessment tool in older multi-morbid patients[12].	O'Mahony, D., O'Connor, M.N., Eustace, J. *et al.*	2.217 patients with acute illness, and among them, 1,687 had risk factors for ADR.	The aim of this study was [1] to derive and [2] validate a new predictive tool to assess ADR Risk in the Elderly (acronym ADRROP).	Of the 1,687 patients, data from 530 patients were used to construct the ADRROP predictive tool, which was then compared with GerontoNet Eight variables were considered as risk factors: female gender, aged > 70 years, estimated glomerular filtration < 30 mLmin, need for assistance for daily activity, ≥ 4 comorbidities, liver disease, presence and number of potentially inappropriate medications defined by STOPP, and fall in the previous year. However, neither the ADRROP scale nor the GerontoNet risk scale predicted the increased likelihood of ADR in the hospitalized elderly.

DISCUSSION

For the validation study of Onder3, data from 483 patients from 4 hospitals in Europe, with a mean age of 80.3 years in the period between September and December 2008, were included. When the score variables were applied, 93 patients scored above 8 points and 131 between 6-7 points, of which 26 (28%) and 15 (11.5%) presented ADRs, respectively.

In Al-Ragawi's study[10], 201 patients were studied, being 150 (74.6%) female and 51 (25.4%) males, from April 2011 to October 2012, with a mean age of 76.1 years. Of these, 46 patients presented with ADR.

The GerontoNet score before admission was 2.54 points on average:

- 111 (55.2%) patients scored between 0-2 points and, 90 (44.8%) patients scored above ≥3 points.

During hospitalization, the mean score increased to 4.79 points.

Regarding the use of medications, the use of 5 or more medications was considered polypharmacy: on admission 36.3% of patients were polymedicated and on hospitalization it in-

creased to 91.0%.

In Petrovic's study[11], 1,075 patients with a mean age of 81.4 years were included. The average was 10 drugs and at least 70 of them presented at least 1 ADR.

The presented ADRs were classified as:

- Type A (dose-dependent and predictable): 50 patients (4.7%), aged <70 or ≥80, low BMI and who had as comorbidity heart failure, diabetes and with a previous history of ADR.
- Probable or definite (classified according to Naranjo's algorithm): 41 patients (3.8%).

In these studies, cutoff point 4 showed good sensitivity, and in the first, the chance of ADR exposure was increased 4x more in those who scored 4 or more points.

In the study by Gudrun[9], with a psychiatric population, the score proved to be a good predictor, highlighting polypharmacy as the most important variable, also suggesting the adaptation of other variables to cover other patient profiles. A total of 79 patients were included, 52 (65.8%) female and 27 (34.2%) males in elderly psychiatric inpatients from April 2011 to October 2012. The patients had a mean age of 73.5 years, used an average of 8.8 medications.

The most frequent diagnoses (ICD-10) were:

- Depressive disorder, with a current major depressive episode, without psychotic symptoms (F33.2) (41.8%).
- Major depressive episode, without psychotic symptoms (F32.2) (12.7%).
- Recurrent major depressive disorder, with psychotic symptoms (F 33.3) (8.9%).
- Recurrent moderate depressive disorder (F33.1) (7.6%).

Applied the score, the following scores were obtained:

- 0 point= 7 patients (8.9%); 1 point =16 patients (20.3%); 2 points =6 patients (7.6%); 3 points = 1 patient (1.3%); 4 points 13 patients (16.5%); 5 points =10 patients (12.7%); 6 points =21 patients (26.6%) and 7 points =5 patients (6.3%).

Inappropriate medication use (IPM) was also identified:

- no IPM, 26 elderly (32.9%); 1 IPM, 35 elderly (44.3%); 2 IPM,15 elderly (19.0%) and 3 IPM, 3 elderly (3.8%).

Regarding ADR presentation and severity:

- No ADR =7 elderly (8.8%); low severity =30 elderly (38.0%); moderate =33 elderly (41.8%) and severe =9 elderly (11.4%).

In O'Mahony et. al.[12] 2,217 patients with acute disease were analysed, among them, 1,687 had risk factors for ADR. Prospectively data from 530 patients to apply the ADRROP predictive scale.

Eight independent risk factors for ADR were identified:

- female sex, age > 70 years, estimated SR < 30 ml/min/1.73 m2, assistance needed for ≥ 1 daily activity, ≥ 4 comorbidities, liver disease, presence and number of potentially inappropriate medications defined by STOPP, and ≥ drop of 1 in the previous year.

According to O'Mahony[12], neither the score nor the other predictive scale was able to predict the increased probability of developing an ADR.

As polypharmacy is an important factor, this study also identified the use of medications clinically classified as inappropriate.

Although there are many risk factors for ADRs, polypharmacy was shown to be an independent risk factor, i.e., the increasing number of drugs prescribed increases susceptibility to adverse reactions, also reflected in the increased score. In the study by Al-Ragawi[10], which compared the score before admission and at hospitalization, an increase in the mean score from 2.54 to 4.79 was noted.

The studies by Gudrun[9] of the identified ADRs 41.8% were classified as moderate and 11.4%, severe; Petrovic[11] classified as predictable in 4.7% of patients and 3.8%, as probable or definite, applying Naranjo's algorithm.

Analysing the profile of the elderly population, the main findings of the selected studies reflect what the literature reports. As expected, the common comorbidities arising from age and the number of medications, often related to an iatrogenic cascade, make the elderly more vulnerable to ADRs. In its current format, the GerontoNet ADR risk score is unlikely to reduce ADR incidence on its own, but it does warn of risk factors that should be considered when prescribing for the elderly.

Although the studies showed that the GerontoNet ADR risk score was a good predictor, with satisfactory sensitivity in 4 of the studies, the need for further studies to increase specificity is noted.

CONCLUSION

Although the studies have shown that the GerontoNet score was a good predictor, with satisfactory sensitivity in 4 of the studies, there is a need for further studies to increase specificity.

The variable related to the number of medications gives greater weight in the score, a common characteristic in the profile of the elderly patient, who is usually polymedicated due to age-related comorbidities.

Identifying risk populations is an important tool for assistance, especially for the elderly, useful in the active search to minimize morbidity and mortality. In this scenario, it is also suggested to replace some variables in the score for application in other environments, a field that allows the intervention of the professional Pharmacist.

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