Identification of a Set of Patient-Related Features to Foster Safe Prescribing of Specific Antipsychotics in the Elderly With Dementia

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Background: Antipsychotics (APs) are widely used to manage behavioral and psychiatric symptoms in dementia, although with a variety of adverse drug reactions. Therefore, it is important to know which patient-related features should be considered to foster a safe prescribing of these medications.

Objectives: To compile and validate a set of patient-related features (PRFs) to foster safe prescribing of specific APs in the elderly with dementia; and to evaluate the feasibility of using them in clinical practice by analyzing the exhaustiveness of medical records.

Method: A rapid literature review was the starting point, where PRFs were identified through a search in PubMed combined with information from the Summary of Product Characteristics (SmPCs). In the next step, a two-round e-Delphi survey was undertaken, where a total of 450 participants were invited by e-mail, including prescribers and specialists in benefit-risk assessment. Finally, a cross-sectional study was undertaken, where 100 patients were randomly extracted from the psychiatric hospital database. Outcomes were defined as the assessment of the clinical relevance and feasibility of the PRFs, and the level of exhaustiveness of these features in medical records. Data analysis was performed using univariate statistics (IBM SPSS v.23.0).

Results: A total of 92 experts participated in the e-Delphi. Forty-seven PRFs obtained consensus, where 12 were applicable to haloperidol, 14 to olanzapine/risperidone, 13 to quetiapine, and 8 to aripiprazole. Age, comorbidities, and co-medications were rated as important features regardless of the prescribed drug. All PRFs were rated as always or frequently available and, if not, they were easy or partially easy to obtain. Age, comorbidities, and co-medications were always available in the medical records, whereas cognitive status (between 41.4 and 78.8%) or hepatic function (between 17.2 and 30.4%) presented a low-level of exhaustiveness.
Conclusions: Even though a high number of PRFs were rated as clinically relevant, some of them were identified as frequently missing from medical records. This may suggest that medical records should be complemented with other sources (e.g., nursing and pharmacy records) to ensure a safe prescribing of APs.

Keywords: antipsychotics, health care research, prescription, patient safety, cognitive impairment

INTRODUCTION

Antipsychotic (AP) medication is frequently used in several psychiatric conditions, including behavioral and psychiatric symptoms in dementia (BPSD), schizophrenia, and bipolar disorder (1). APs are commonly divided into two groups: typical and atypical. The first group has been on the market since 1950’s and were associated with extrapyramidal symptoms (EPS). Over the years, atypical APs have been widely used compared to the typical group, given their lower risk of EPS (2, 3). However, they have been associated with metabolic syndrome and cardio- and cerebrovascular events (4–6).

Prescribing these medications to older individuals is common, particularly in nursing homes. The use of such medications in this age group is most of the times done off-label, as most of the evidence about their effectiveness and safety was extrapolated from younger adults. They can be used in the elderly to manage psychiatric conditions, including behavioral and psychiatric support systems (e.g., of quality circles, to describe and benchmark differences in practices; and (d) may also be used within clinical decision support systems (12–15). Different indicators may be divided according to different domains, such as safety (prescribing safety indicators) or quality (prescribing quality indicators). The first group has been defined as statements that describe prescribing events that may increase the risk of harm in patients (16). Prescribing safety indicators in mental health have been explored in a recent systematic review, where authors found that presence of PIMs, high risk medications, drug-disease interactions, and drug-related problems are examples of indicators that should be considered. They also found that 15.5% of those indicators were applicable to APs (17). A recent Delphi-study has developed prescribing safety indicators for medications used in mental health disorders, reporting 42 indicators considered to be of high or extreme risk for patient care. These included drug-disease and drug-drug interactions, inadequate monitoring, inappropriate dose, omissions, PIMs, and polypharmacy, most of which were applicable to APs (18).

Even though some studies have been conducted to develop and validate prescribing safety indicators related to mental health, there is still the need to move from a population-based approach to patient-centered care. APs are a good example of a medication class with a wide range of receptor binding affinities, which may contribute to different ADR profile for each drug (19). Therefore, it may be important to know which patient-related features (PRFs) should be taken into account when prescribing specific APs to older patients with dementia. Therefore, our aims were to compile and validate a set of patient-features to foster safe prescribing of APs in older individuals with dementia and to evaluate the level exhaustiveness of such features in medical records of a mental health specialized hospital in Portugal.

MATERIALS AND METHODS

Study Design

This study was divided into three steps: a rapid literature review to identify and compile possible PRFs, i.e., individual characteristics from the patients that may be used to foster safe prescribing of specific APs (e.g., quetiapine, olanzapine/risperidone, haloperidol, and aripiprazole) in the elderly with dementia; a consensus study to select the most clinically relevant PRFs for each drug; and a cross-sectional study where medical records from a Portuguese Psychiatry Hospital were reviewed to access their exhaustiveness regarding the features previously validated among comprehensively and validate PRFs.

Compilation of Different PRFs Regarding AP Prescription for the Elderly With Dementia

Quetiapine, olanzapine/risperidone, haloperidol, and aripiprazole were chosen either based on their consumption pattern in older individuals with dementia or on their innovative mechanism of action, which may be an advantage on the risk benefit ratio when prescribing the drug. A rapid literature review was performed using PubMed (20). Papers describing either PRFs used when prescribing APs or PRFs that should be monitored while using this medication in demented patients were included, considering the drug marketing authorizations of the selected APs. Summary of Product Characteristics (SmPCs)
were used to supplement the results extracted from the rapid literature review. Age, renal and hepatic function, presence of comorbidities, and electrocardiogram results (EKG) were common features for all the selected drugs. PRFs specific for each drug were also extracted and summarized in Table 1.

**Delphi Survey and Participants**

To validate which PRFs would be more suitable to ensure a safe prescription of the previous selected APs in the elderly with dementia, a two-round Delphi survey was undertaken from July to September 2019. This method provides a systematic way to converge the expertise of individuals working in a specific area and gives guidance that is readily applicable to a particular context (21). A total of 450 participants were invited to participate in order to obtain a final sample of 100. Participants should be prescribers (which physicians and pharmacists from countries where this profession is allowed to prescribe) that may have a role in the management of elderly patients with dementia and experiencing BPSD or healthcare professionals specialized in the benefit-risk assessment. The panel size was a convenient sample number that was likely to yield stable results (21).

An initial sample of 38 features (7 for haloperidol, 10 for olanzapine/risperidone, 11 for quetiapine, and 10 for aripiprazole) were presented to the expert panel so they could rate them in terms of: (a) clinical relevance; (b) accessibility, i.e., how often they have access to the selected PRFs and, if needed, how easy it is to obtain them from elsewhere. Rating score were given according to a 5-item Likert scale: very important = 5; important = 3; equivocal = 2; rarely = 1; never = 0.

**Table 1**

| Drug                          | Indicators specific for each of the selected drugs |
|-------------------------------|---------------------------------------------------|
| Haloperidol                   | Aged 65 or older<br>Renal function<br>Hepatic function<br>Comorbidities<br>EKG<br>Concomitant medication<br>Electrolyte disturbances (especially with potassium and magnesium) |
| Olanzapine/risperidone        | Aged 65 or older<br>Renal function<br>Hepatic function<br>Comorbidities<br>EKG<br>Hyperglycaemia/diabetes mellitus<br>BMI > 30 kg/m²<br>Hypercholesterolemia<br>High risk for metabolic syndrome<br>High cardiovascular risk |
| Quetiapine                    | Aged 65 or older<br>Renal function<br>Hepatic function<br>Comorbidities<br>EKG<br>Hypertension<br>High cardiovascular risk<br>High risk for metabolic syndrome<br>Hyperglycaemia/diabetes mellitus<br>Hypercholesterolemia |
| Aripiprazole                  | Aged 65 or older<br>Renal function<br>Hepatic function<br>EKG<br>Sex<br>Smoking habits<br>High cardiovascular risk<br>Hyperglycaemia/diabetes mellitus<br>BMI > 30 kg/m² |

BMI, Body Mass Index; EKG, electrocardiogram.

Consensus Validation

When judging the clinical relevance, a mean score of 2 was used as the cut-off point to be agreed on and 75% as the consensus cut-off (22). In round one, scores ≤ 2 with a ≥ 75% consensus were automatically retained as important PRFs to be considered when prescribing APs for older individuals with dementia, whereas all others were included in round two together with new indicators suggested by the participants on the first round.

**Exhaustiveness of the PRFs in Medical Records of a Portuguese Psychiatric Hospital**

The second part of this study was undertaken at a Portuguese Psychiatry Hospital – Hospital Júlio de Matos, Centro Hospitalar Psiquiátrico de Lisboa – between October and December of 2019. A sample of 100 patients were selected using a systematic method of choosing randomly the first patients of each month hospitalized in the psychogeriatric department between January of 2018 and December of 2019 who met the inclusion criteria (individuals aged 65 or older with dementia diagnosis and prescribed with APs). Data were extracted from medical records, which included sociodemographic information (age, sex, and education level), anthropometric measures (height, weight, and body mass index), clinical and laboratory data (comorbidities, medications, allergies, EKG, Minimal Mental Status – MMS, glycaemia, glycated hemoglobin – HbA1c, urea, creatinine, aspartate transaminase – AST, alanine aminotransferase – ALT, gamma-glutamyltransferase – gamma-GT, cholesterol, HDL, LDL, triglycerides, sodium, potassium, and chloride), and drug-related data (co-medication, antipsychotic used, frequency, route of administration, and safety-related data – previous experience of ADRs).

**Data Analysis**

Statistical analysis was performed using IBM SPSSv.26.0. Descriptive statistics were used for sociodemographic characterization of Delphi participants and to access responses.
obtained as well as to document the exhaustiveness of the PRFs in the medical records. Numerical variables were expressed using central tendency and dispersion measures (either as mean and standard deviations, whichever was applicable), and categorical variables as absolute and relative frequencies.

To assess the exhaustiveness of data entry, a specific classification was used based in a previous study: high (<1% missing values), medium (missing values between 1 and 15%), and low exhaustiveness (>15% missing values) (23). Anthropometric measures, EKG, MMS, and sociodemographic variables were considered present if described in medical records at the time of admission to the psychogeriatric department. For variables such as comorbidities, co-medications, and AP-related data, high-exhaustiveness was considered if those variables were available in the last update of the medical record. Laboratory values and biomarkers assessment (e.g., blood pressure) were searched for a 6-months period prior to the index date (i.e., date of last medical record update during the study period) and were considered to present high-exhaustiveness if they had at least 3 measurements. For indicators that may result in a final score (e.g., cardio and cerebrovascular risk, frailty/risk of falls) were classified based on the exhaustiveness of the individual data needed to calculate them.

RESULTS

Consensus Results

Participants' Characteristics

From the initial 126 participants who agreed to participate, there were three dropouts from the study and 31 incomplete questionnaires which were excluded. A total of 92 participants were retained, where 53.3% (n = 49) were male and 39.1% (n = 36) belonged to the age group of 30–39 years old. Almost half of the sample (43.5%; n = 40) had a PhD degree and had < 10 years of working experience (43.4%; n = 40). The majority of participants were either psychiatrists (25.0%; n = 23) or internal medicine physicians (25.0; n = 23), followed by pharmacists able to prescribe (15.2%; n = 14), pharmacologists (10.0%; n = 9), gerontologists (9.8%; n = 7), general practitioners (6.5%; n = 6), epidemiologists (5.4%; n = 5), cardiologists (2.2%; n = 2), neurologists (2.2%; n = 2), and palliative care physicians (1.1%; n = 1). Table 2 summarizes the sociodemographic characterization of the panel experts.

PRFs Selected in the Two-Round Delphi Survey

A total of 61 PRFs (13 for haloperidol, 18 for olanzapine/risperidone, 21 for quetiapine, and 20 for aripiprazole) were presented to the expert panel, where 38 were retrieved from the literature and 23 were suggested by the participants after the first round. In the end of the second round, 47 PRFs were retained, where 12 (25.5%) were selected for haloperidol, 14 (29.8%) for olanzapine/risperidone, 13 (27.7%) for quetiapine, and 8 (17.0%) for aripiprazole.

Age, comorbidities, and co-medications were rated as important features for safe prescribing of antipsychotics in the elderly and were found in all the selected drugs. Table 3 summarizes the clinical relevance, availability of specific PRFs in medical records or possibility for obtaining them when not available. All the selected features were either always or frequently available in daily practice and, if not, all of them were easy or partially easy to request.

Exhaustiveness of PRFs in Medical Records

Age, comorbidities, co-medications, and the indication for which the drug was being used presented a high-level exhaustiveness in the medical records independently of the drug used. For haloperidol, electrolyte disturbances and the presence of Parkinson disease were also extensively described in the charts, whereas for olanzapine/risperidone the same result was found for the presence of diabetes. Conversely, hepatic function (haloperidol – 22.2%; olanzapine – 30.4%; risperidone – 17.2%; quetiapine – 30.3%), EKG (haloperidol – 44.4%; quetiapine – 42.4%), cognitive status (haloperidol – 66.7%; olanzapine – 60.9%; risperidone – 41.4%; quetiapine – 78.8%), and weight (olanzapine – 100.0%; risperidone – 100.0%) presented a low-level of exhaustiveness. Renal function (olanzapine – 12.5%; risperidone – 6.9%) and blood pressure (12.1%) presented a medium-level of exhaustiveness. Table 4 summarizes all the results described.
### TABLE 3 | PRFs selected through the Delphi survey for each drug as the most important ones to foster safe prescribing of APs in older individuals.

| Indicators | Panel survey score (mean ± SD) |
|------------|-------------------------------|
|            | Clinical relevance¹ | Feasibility* | Availability when asked² |
| **Haloperidol** | | | |
| Age | 1.05 ± 0.7 | 1.25 ± 0.76 | 1.10 ± 0.39 |
| Hepatic function | 2.00 ± 0.9 | 1.73 ± 0.80 | 1.81 ± 0.72 |
| Comorbidities | 1.50 ± 0.6 | 1.48 ± 0.59 | 1.73 ± 0.54 |
| EKG | 1.60 ± 0.6 | 1.94 ± 0.77 | 2.16 ± 0.76 |
| Electrolyte disturbances | 1.90 ± 0.9 | 1.20 ± 0.86 | 1.91 ± 0.74 |
| Co-medications | 1.30 ± 0.7 | 1.41 ± 0.81 | 1.78 ± 0.76 |
| Labeled indication | 1.50 ± 0.7 | 1.27 ± 0.54 | 1.67 ± 0.87 |
| Frailty/Risk of falls | 1.60 ± 0.7 | 1.77 ± 0.76 | 1.91 ± 0.85 |
| Previous ADRs | 1.40 ± 0.5 | 1.92 ± 0.78 | 2.24 ± 1.06 |
| Cognitive status | 1.80 ± 0.8 | 1.66 ± 0.57 | 1.97 ± 0.78 |
| Benefit-risk ratio assessment | 1.30 ± 0.5 | 1.51 ± 0.64 | 1.92 ± 0.89 |
| Presence of Parkinson Disease | 2.00 ± 0.80 | 1.89 ± 0.77 | 1.75 ± 0.74 |
| **Olanzapine/risperidone** | | | |
| Age | 1.03 ± 0.24 | 1.03 ± 0.24 | 1.06 ± 0.33 |
| Renal function | 1.78 ± 0.58 | 1.78 ± 0.58 | 1.63 ± 0.69 |
| Hepatic function | 1.90 ± 0.67 | 1.90 ± 0.97 | 1.67 ± 0.67 |
| Comorbidities | 1.40 ± 0.54 | 1.40 ± 0.54 | 1.63 ± 0.51 |
| Co-medications | 1.50 ± 0.79 | 1.50 ± 0.79 | 1.70 ± 0.51 |
| Hyperglycaemia/diabetes mellitus | 1.76 ± 0.55 | 1.76 ± 0.55 | 1.59 ± 0.54 |
| Weight | 2.16 ± 0.95 | 2.16 ± 0.95 | 1.80 ± 0.65 |
| Cardiovascular risk | 2.03 ± 0.68 | 2.03 ± 0.68 | 1.97 ± 0.72 |
| Labeled indication | 1.56 ± 0.87 | 1.56 ± 0.87 | 1.58 ± 0.76 |
| Frailty/Risk of falls | 1.82 ± 0.91 | 1.82 ± 0.91 | 1.84 ± 0.82 |
| Previous ADRs | 1.94 ± 0.94 | 1.94 ± 0.94 | 2.06 ± 0.77 |
| Cognitive status | 1.71 ± 0.80 | 1.71 ± 0.80 | 1.63 ± 0.66 |
| Benefit-risk ratio assessment | 1.64 ± 0.77 | 1.64 ± 0.77 | 1.68 ± 0.77 |
| Cerebrovascular risk | 1.93 ± 0.48 | 1.93 ± 0.48 | 1.87 ± 0.89 |
| **Quetiapine** | | | |
| Age | 1.60 ± 0.80 | 1.15 ± 0.35 | 1.06 ± 0.33 |
| Hepatic function | 1.90 ± 0.80 | 1.69 ± 0.68 | 1.64 ± 0.61 |
| Comorbidities | 1.50 ± 0.60 | 1.41 ± 0.63 | 1.49 ± 0.50 |
| EKG | 2.00 ± 0.70 | 2.10 ± 0.74 | 1.77 ± 0.62 |
| Co-medication | 1.40 ± 0.50 | 1.44 ± 0.70 | 1.64 ± 0.51 |
| Cardiovascular risk | 1.90 ± 0.70 | 2.20 ± 1.00 | 1.94 ± 0.68 |
| Blood pressure | 2.00 ± 0.80 | 1.46 ± 0.60 | 1.25 ± 0.61 |
| Labeled indication | 1.50 ± 0.60 | 1.49 ± 0.61 | 1.59 ± 0.81 |
| Frailty/Risk of falls | 1.60 ± 0.70 | 1.79 ± 0.75 | 1.71 ± 0.74 |
| Previous ADRs | 1.60 ± 0.80 | 1.82 ± 0.72 | 1.92 ± 0.81 |
| Cognitive status | 1.70 ± 0.80 | 1.65 ± 0.61 | 1.68 ± 0.74 |
| Benefit-risk ratio assessment | 1.50 ± 0.70 | 1.59 ± 0.63 | 1.67 ± 0.81 |
| Cerebrovascular risk | 1.80 ± 0.80 | 1.89 ± 0.82 | 1.93 ± 0.92 |

(Continued)

### TABLE 3 | Continued

| Indicators | Panel survey score (mean ± SD) |
|------------|-------------------------------|
|            | Clinical relevance¹ | Feasibility* | Availability when asked² |
| **Aripiprazole** | | | |
| Age | 1.60 ± 0.80 | 1.12 ± 0.31 | 1.03 ± 0.24 |
| Comorbidities | 1.60 ± 0.80 | 1.49 ± 0.55 | 1.68 ± 0.57 |
| Co-medications | 1.60 ± 0.70 | 1.69 ± 0.95 | 1.69 ± 0.95 |
| Cardiovascular risk | 2.00 ± 0.80 | 2.20 ± 1.00 | 1.99 ± 0.79 |
| Labeled indication | 1.60 ± 0.70 | 1.77 ± 1.03 | 1.77 ± 0.98 |
| Benefit-risk ratio assessment | 1.50 ± 0.70 | 1.71 ± 1.01 | 1.96 ± 0.98 |
| Cerebrovascular risk | 1.90 ± 0.70 | 2.01 ± 0.99 | 1.82 ± 0.93 |
| Clinical response and tolerability to previous APs | 1.60 ± 0.70 | 2.04 ± 0.99 | 2.16 ± 0.91 |

ADRs, Adverse Drug Reactions; ApS, Antipsychotics; EKG, Electrocardiogram. ¹ Rating scale: 1—Very important; 2—Important; 3—Equivocal; 4—Less important; 5—Not important. * Feasibility in clinical practice means how often do healthcare professionals, namely prescribers, have access to the selected indicators in their daily practice; rating scale: 1—Always; 2—Frequently; 3—Sometimes; 4—Rarely; 5—Never. ² Rating scale: 1—Very easy; 2—Partially easy; 3—Equivocal; 4—Partially difficult; 5—Difficult.

**DISCUSSION**

**Main Findings**

In this study, we found that 47 of the initial 61 PRFs were retained as relevant in clinical practice to safely prescribe an AP to an older individual with dementia. Of those indicators, most of them were specific for the selected drugs, and participants reported that all of them were always or frequently available in the medical records. If not available, all of them were easy or partially easy to request. When evaluating their exhaustiveness in the medical records, we found that age, comorbidities, and co-medications were always available, whereas cognitive status or hepatic function presented a low-level of exhaustiveness.

To ensure safe prescribing of APs in the elderly, it is important to consider not only drug-related issues, but also patient-related features. As most other psychotropic drugs, APs are known to have different mechanisms of action, given their binding affinity to specific receptors, which may lead to different ADRs. For instance, haloperidol is known to cause QT-prolongation or parkinsonism, whereas olanzapine and risperidone are known to be associated with metabolic syndrome (24, 25). For this reason, data on EKG, glycemia, cholesterol, and other laboratory values should be available in order not only to monitor patients already instituted therapy, but also to make sure that the AP being prescribed for the first time will not increase the risk of ADRs. We found that EKG was an important feature when prescribing haloperidol or quetiapine, even though a low-level of exhaustiveness was obtained, albeit reported as easy to request. Similar results were found for olanzapine and risperidone when evaluating the presence of hyperglycaemia, hypercholesterolemia, and weight. This indicates that prescribers...
TABLE 4 | Exhaustiveness of PRFs selected through the Delphi survey in medical records of older individuals with dementia.

| Indicators                        | Exhaustiveness of medical records | n   | %  | Description* |
|-----------------------------------|-----------------------------------|-----|----|--------------|
|                                   |                                   |     |    |              |
| **Haloperidol (n = 9)**           |                                   |     |    |              |
| Age                               | 0                                 | 0.0 | High |              |
| Hepatic function                  | 2                                 | 22.2| Low  |              |
| Comorbidities                     | 0                                 | 0.0 | High |              |
| EKG                               | 4                                 | 44.4| Low  |              |
| Electrolyte disturbances          | 0                                 | 0.0 | High |              |
| Co-medications                    | 0                                 | 0.0 | High |              |
| Labeled indication                | 0                                 | 0.0 | High |              |
| Frailty/risk of falls             | n/a                               | n/a | n/a  |              |
| Previous ADRs                     | n/a                               | n/a | n/a  |              |
| Cognitive status                  | 6                                 | 66.7| Low  |              |
| Benefit-risk ratio assessment     | n/a                               | n/a | n/a  |              |
| Presence of Parkinson Disease     | 0                                 | 0.0 | High |              |
| **Olanzapine (n = 23)**           |                                   |     |    |              |
| Age                               | 0                                 | 0.0 | High |              |
| Renal function                    | 3                                 | 12.5| Medium|              |
| Hepatic function                  | 7                                 | 30.4| Low  |              |
| Comorbidities                     | 0                                 | 0.0 | High |              |
| Co-medications                    | 0                                 | 0.0 | High |              |
| Presence of hyperglycaemia        | 6                                 | 26.1| Low  |              |
| Presence of diabetes mellitus     | 0                                 | 0.0 | High |              |
| Weight                            | 23                                | 100.0| Low |              |
| Cardiovascular risk               | n/a                               | n/a | n/a  |              |
| Labeled indication                | 0                                 | 0.0 | High |              |
| Frailty/Risk of falls             | n/a                               | n/a | n/a  |              |
| Previous ADRs                     | n/a                               | n/a | n/a  |              |
| Cognitive status                  | 14                                | 60.9| Low  |              |
| Benefit-risk ratio assessment     | n/a                               | n/a | n/a  |              |
| Cerebrovascular risk              | n/a                               | n/a | n/a  |              |
| **Risperidone (n = 29)**          |                                   |     |    |              |
| Age                               | 0                                 | 0.0 | High |              |
| Renal function                    | 2                                 | 6.9 | Medium|              |
| Hepatic function                  | 5                                 | 17.2| Low  |              |
| Comorbidities                     | 0                                 | 0.0 | High |              |
| Co-medications                    | 0                                 | 0.0 | High |              |
| Presence of hyperglycaemia        | 3                                 | 10.3| Medium|              |
| Presence of diabetes mellitus     | 0                                 | 0.0 | High |              |
| Weight                            | 29                                | 100.0| Low |              |
| Cardiovascular risk               | n/a                               | n/a | n/a  |              |
| Labeled indication                | 0                                 | 0.0 | High |              |
| Frailty/Risk of falls             | n/a                               | n/a | n/a  |              |
| Previous ADRs                     | n/a                               | n/a | n/a  |              |
| Cognitive status                  | 12                                | 41.4| Low  |              |
| Benefit-risk ratio assessment     | n/a                               | n/a | n/a  |              |
| Cerebrovascular risk              | n/a                               | n/a | n/a  |              |
| **Quetiapine (n = 33)**           |                                   |     |    |              |
| Age                               | 0                                 | 0.0 | High |              |
| Hepatic function                  | 10                                | 30.3| Low  |              |
| Comorbidities                     | 0                                 | 0.0 | High |              |

(Continued)

TABLE 4 | Continued

| Indicators                        | Exhaustiveness of medical records | n   | %  | Description* |
|-----------------------------------|-----------------------------------|-----|----|--------------|
|                                   |                                   |     |    |              |
| EKG                               | 14                                | 42.4| Low  |              |
| Co-medication                     | 0                                 | 0.0 | High |              |
| Cardiovascular risk               | n/a                               | n/a | n/a  |              |
| Blood pressure                    | 4                                 | 12.1| Medium|              |
| Labeled indication                | 0                                 | 0.0 | High |              |
| Frailty/risk of falls             | n/a                               | n/a | n/a  |              |
| Previous ADRs                     | n/a                               | n/a | n/a  |              |
| Cognitive status                  | 26                                | 78.8| Low  |              |
| Benefit-risk ratio assessment     | n/a                               | n/a | n/a  |              |
| Cerebrovascular risk              | n/a                               | n/a | n/a  |              |
| **Aripiprazole (n = 6)**          |                                   |     |    |              |
| Age                               | 0                                 | 0.0 | High |              |
| Comorbidities                     | 0                                 | 0.0 | High |              |
| Co-medications                    | 0                                 | 0.0 | High |              |
| Cardiovascular risk               | n/a                               | n/a | n/a  |              |
| Labeled indication                | 0                                 | 0.0 | High |              |
| Benefit-risk ratio assessment     | n/a                               | n/a | n/a  |              |
| Cerebrovascular risk              | n/a                               | n/a | n/a  |              |

EKG, electrocardiogram; n/a, not available.

* High exhaustiveness: <1% missing values; medium exhaustiveness: between 1 and 15%; low exhaustiveness: >15% missing values.

Know what is important to consider when prescribing these drugs, but data may not be fully available given the organization of the healthcare system. In Portugal, data from in- and out-patient settings are not always integrated, which leads to a different level of exhaustiveness when both settings are compared. Most importantly, this gap makes the data available different for each prescriber, i.e., a general practitioner may have different access to a certain type of indicators in comparison with a psychiatrist.

Another indicator rated as important was cognitive status, which was absent in most medical records. It is known that in patients with cognitive impairment, like demented patients, the assessment of cognitive status is important when prescribing APs (26). These safety issues are crucial when prescribing medications to older adults, especially in patients with psychiatric symptoms where multiple medications may interact with each other, resulting in exacerbation of cognitive impairment.

Even though frailty status, and cardio- and cerebrovascular risk were not available in the medical records, these scores were rated as clinically relevant when prescribing APs to elderly patients with dementia. It is known that these drugs may be associated with an increased risk of cardio- and cerebrovascular events (4–6). These scores sometimes are not available directly in the medical record of the hospital, but nowadays many online calculators are available. Therefore, if the data needed to calculate the scores is available in the medical records, prescribers may be able to calculate them and take these risks into account when prescribing, especially atypical APs (e.g., olanzapine, risperidone, and quetiapine). Another important aspect is the fact that some
PRFs may be available in the nursing records (e.g., blood pressure, weight), which may be missed if prescribers do not look for it when prescribing atypical APs, where the risk of developing metabolic syndrome is high. So, it is important to acknowledge the contribution of different patient information sources to ensure a safe prescribing of such medications (27).

Few studies have evaluated the need to validate prescribing quality and safety indicators, i.e., indicators for evaluating the quality of prescribing (e.g., adherence, presence of polypharmacy), and also the safety when prescribing to older individuals (e.g., presence of drug-drug interactions, concurrent use of more than one AP). One of the aims of developing a set of such indicators was to prevent/minimize the occurrence of ADRs. However, such indicators are mostly population-oriented, and do not consider the need to look for specific features that may be important when prescribing a specific AP, e.g., relevant for haloperidol, but not so important, for instance, for olanzapine. As some of these elder patients may be on more than one AP, a combination of features may need to be accessed prior to a prescription. Moreover, knowing that this population is highly heterogeneous, there may be some patients where specific features may be more important than in others. For instance, in patients with previous history of cardiac arrhythmias, an EKG for evaluating the QT segment may be needed ahead of the prescription, so that prescribers may select among APs that do not increase the risk of heart block.

Impact on Practice

To the authors' best knowledge, this is one of the few studies validating patient-related features that may contribute to a safer prescribing pattern of specific APs, like haloperidol, olanzapine, risperidone, quetiapine, and aripiprazole. Current prescribing culture is more focused on effectiveness rather than safety, which in older patients with dementia may increase their odds of experiencing ADRs. Even though prescribers have identified a set of patient-related features with clinical relevance, a low-level of exhaustiveness in our country was found which may be a reality in other countries with a similar healthcare system. This may show the current need not only to integrate the different healthcare software, but also to unify the entire healthcare setting in order to optimize patient medications, especially psychotrophic drugs. Future work will include the development of an algorithm to be integrated in a digital tool or app, that may be able to include all these important variables in order to ensure safe prescribing of APs in this population group.

LIMITATIONS

Some limitations have been identified and are worth acknowledging. First, selection bias may be present in both samples (expert panel and in-hospital patients). However, we believe that in the sample retrieved from the hospital this bias may be reduced, given that we used a quasi-random methodology and patients were extracted from a specialized hospital in psychiatric illness, which may contribute to a more homogeneous distribution of patients' characteristics. Secondly, misclassification bias may be present given that most information was retrieved from medical charts of different physicians. We believe that this bias was minimized given that the authors have coded the variables according to a pre-defined dataset, which may have contributed to a more homogeneous coding system. Finally, this data may not be generalized for a larger population.

CONCLUSIONS

To conclude, this study has validated a set of patient-related features, like age, comorbidities, co-medications, renal and hepatic function, and cognitive status as relevant items to consider in daily practice when prescribing specific APs to older individuals with dementia. All of them always or frequently were available in medical records and, when absent, considered easy to request. However, a low-level of exhaustiveness was found in medical records for certain features, such as cognitive status, hepatic function, and weight. Future work will focus on the development of drug-specific algorithms to be included in a digital platform or app to foster safe prescribing of such medications in older individuals with dementia.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Egas Moniz (658/2018) and the Ethics Committee of Centro Hospitalar Psiquiátrico de Lisboa (0019/2019). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FA, HL, and JA conceived and designed the study. CB, JA, and JG collected, analyzed, and interpreted the data. JA prepared the manuscript. All the authors have critically reviewed the manuscript until its final version.

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REFERENCES

1. Behrman S, Burgess J, Topiwala A. Prescribing antipsychotics in older people: a mini-review. Maturitas. (2018) 116:8–10. doi: 10.1016/j.maturitas.2018.06.015

2. Gareni P, Segura-Garcia C, Manfredi V, Bruni A, Ciambrone P, Cerminara G, et al. Use of atypical antipsychotics in the elderly: a clinical review. Clin Interv Aging. (2014) 9:1363–73. doi: 10.2147/CIA.S63942

3. Shin JY, Choi NK, Lee J, Seong JM, Park MJ, Lee S, et al. Risk of ischemic stroke associated with the use of antipsychotic drugs in elderly patients: a retrospective cohort study in Korea. PLoS ONE. (2015) 10:e0119931. doi: 10.1371/journal.pone.0119931

4. Jackson J, VanderWeele T, Viswanathan A, Blacker D, Schneeweiss S. The explanatory role of stroke as a mediator of the mortality risk difference between older adults who initiate first- versus second-generation antipsychotic drugs. Am J Epidemiol. (2014) 180:847–52. doi: 10.1093/aje/kwu210

5. Jones ME, Campbell G, Patel D, Brunner E, Shatapathy CC, Murray-Thomas T, et al. Risk of mortality (including sudden cardiac death) and major cardiovascular events in users of olanzapine and other antipsychotics: a study with the general practice research database. Cardiovasc Psychiatr Neurol. (2013) 2013:647476. doi: 10.1155/2013/647476

6. Wang P, Schneeweiss S, Avorn J, Fischer M, Mogun H, Solomon D, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med. (2005) 22:2335–41. doi: 10.1056/NEJMoa0502827

7. Jalenques I, Ortega V, Legrand G, Auclair C. Prescription and surveillance at-antipsychotiques chez les patients âgés souffrant de schizophrenie: pratiques des psychiatres et leurs determinants. L’Encéphale. (2015) 42:124–9. doi: 10.1016/j.encep.2015.05.004

8. Sink K, Holden K, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA. (2005) 5:596–608. doi: 10.1001/jama.293.5.596

9. Brahma D, Wahlang J, Marak M, Ch Sangma M. Adverse drug reactions in the elderly. J Pharmacol Pharmacother. (2013) 2:91. doi: 10.4103/0976-500X.110872

10. Albert S, Colombi A, Hanlon J. Potentially inappropriate medications and risk of hospitalization in retirees. Drugs Aging. (2010) 5:407–15. doi: 10.2165/11315990-000000000-00000

11. Huang CH, Umegaki H, Watanabe Y, Kamitani H, Asai A, Kanda S, et al. Potentially inappropriate medications according to STOPP criteria and risk of hospitalization and mortality in elderly patients receiving home-based medical services. PLoS ONE. (2019) 2:e0211947. doi: 10.1371/journal.pone.0211947

12. Brimelow R, Wollin J, Byrne G, Dissanayaka N. Prescribing of psychotropic drugs and indicators for use in residential aged care and residents with dementia. Int Psychogeriatr. (2018) 31:837–47. doi: 10.1017/S1041610218001229

13. Brett J, Zoega H, Buckley N, Daniels B, Elshaug A, Pearson SA. Choosing wisely? Quantifying the extent of three low value psychotropic prescribing practices in Australia. BMC Health Serv Res. (2018) 18:1009. doi: 10.1186/s12913-018-3811-5

14. Paton C, Lelliott P. The use of prescribing indicators to measure the quality of care in psychiatric inpatients. Qual Saf Health Care. (2004) 13:40–5. doi: 10.1136/qshc.2003.006338

15. Ofori-Asenso R, Behlakova P, Pollock A. Prescribing indicators at primary healthcare centers within the WHO Africanregion: a systematic analysis (1995–2015). BMC Public Health. (2016) 16:724. doi: 10.1186/s12889-016-3428-8

16. Spencer R, Bell B, Avery A, Gooley G, Campbell S. Identification of an updated set of prescribing-safety indicators for GPs. Br J Gen Pract. (2014) 62:e181–90. doi: 10.3399/bjgp14X677806

17. Khawagi W, Steinke D, Nguyen J, Keers R. Identifying potential prescribing safety indicators related to mental health disorders and medications: a systematic review. PLoS ONE. (2019) 14:e0217406. doi: 10.1371/journal.pone.0217406

18. Khawagi W, Steinke D, Nguyen J, Pontefract S, Keers R. Development of prescribing safety indicators related to mental health disorders and medications: modified e-Delphi study. Br J Clin Pharmacol. (2020). doi: 10.1111/bcp.14391. [Epub ahead of print].

19. Aguiar J, Alves da Costa F, Egberts T, Leufkens H, Souverein P. The association between receptor binding affinity and metabolic side effect profile of antipsychotics and major cardio- and cerebrovascular events: a case/non-case study using VigiBase. Eur Neuropsychopharmacol. (2020) 35:30–8. doi: 10.1016/j.euroence.2020.03.022

20. Garrity C, Garthlehrer G, Kamel C, King VJ, Nussbaumer-Streit B, Stevens A, et al. Cochrane Rapid Reviews. Interim Guildance from the Cochrane Rapid Reviews Methods Group. (2020). p. 1–2.

21. Kim SO, Jang S, Kim CM, Kim YR, Sohn H. Consensus validated list of potentially inappropriate medication for the elderly and their prevalence in South Korea. Int J Gerontol. (2015) 9:136–41. doi: 10.1016/j.ijge.2015.05.013

22. Keeney S, Hasson F, McKenna H. Consulting the oracle: ten lessons from using the Delphi technique in nursing research. J Adv Nurs. (2006) 2:205–12. doi: 10.1111/j.1365-2648.2006.03716.x

23. Verdasca J, Alves da Costa F, Ramos C, Murteira R, Miranda A. The South region cancer registry: an evaluation of its exhaustiveness in a cohort of lung cancer patients: exhaustiveness of cancer registry in Portugal. Thoracic Cancer. (2018) 10:330–4. doi: 10.1111/1759-7714.12915

24. Huffman J, Stern T. QTc prolongation and the use of antipsychotics: a case discussion. Prim Care Companion J Clin Psychiatry. (2003) 5:67–81. doi: 10.4088/PCC.v05n0605

25. Mittal D, Li C, Viverito K, Williams J, Landes R, Thapa P, et al. Monitoring for metabolic side effects among outpatients with dementia receiving antipsychotics. Psychiatr Serv. (2014) 65:1147–53. doi: 10.1176/appi.ps.201300317

26. Livingston G, Walker A, Katona C, Cooper C. Antipsychotics and cognitive decline in Alzheimer’s disease: the LASER-Alzheimer’s disease longitudinal study. J Neurol Neurosurg Psychiatr. (2007) 78:25–9. doi: 10.1136/jnnp.2006.094342

27. Oliveira J, Cabral A, Lavrador M, Costa F, Almeida F, Macedo A, et al. Contribution of different patient information sources to create the best possible medication history. Acta Médica Port. (2020) 6:384–9. doi: 10.20344/amp.12082

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.