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What about the relevance of PIP of psychotropics in older psychiatric inpatients?

Prescriptions potentiellement inappropriées de psychotropes chez le sujet âgé hospitalisé en psychiatrie : le sont-elles vraiment ?

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ABSTRACT

Objective: In 2019, a regional survey of potentially inappropriate prescriptions (PIP) of psychotropic drugs in elderly psychiatric inpatients was carried out highlighting their inappropriate use in this population. The aim of this study was to assess the clinical relevance – defined as the provision of an appropriate and necessary treatment, chosen from other alternatives as being the most likely to produce the expected results for a given patient – of these prescriptions considered inappropriate according to current established criteria.

Material and method: Patients aged over 75, or 64 to 75 and polypathological with at least one PIP of psychotropic drugs or drugs with a high anticholinergic burden, identified by an audit grid established on the basis of STOPP/STARTv2 criteria and the Laroche list on the prescription at 48 h of hospitalization, were included. The weighing of the inappropriateness nature of the prescription (resistance to treatment, period of crisis, comorbidities…) was established by a pharmacist-psychiatrist pair on the entire computerized record of the current episode. The clinical relevance of the PIP and the overall prescription was rated as 0 (irrelevant), 1 (partially relevant) or 2 (relevant).

Results: Thirty-four patients were included. One hundred and twenty-five PIP of psychotropic drugs were noted: 50.4% concerned benzodiazepines and non-benzodiazepines anxiolytics (BZD/Z), 25.6% neuroleptics (NL), 12% antidepressants (ATD) and 12% drugs with a high anticholinergic burden. On one hand, 49.2% of PIP of BZD/Z, 50% of PIP of NL and 20% of PIP of ATD were considered irrelevant. On the other hand, 49.2% of PIP of BZD/Z, 31.3% of PIP of NL and 13.3% of PIP of ATD were considered partially relevant. Furthermore, 1.6% of PIP of BZD/Z, 18.8% of PIP of NL and 66.7% of PIP of ATD were considered relevant. For PIPs of drugs with a high anticholinergic burden, 80% were deemed irrelevant, 13.3% partially relevant and 6.7% relevant. In all, of the 34 drug prescriptions studied, three (8.8%) were considered irrelevant, 11 (32.4%) partially relevant and 20 (58.8%) clinically relevant.

Conclusion: This study highlighted the clinical relevance of more than half the prescriptions considered inappropriate according to current PPI criteria in the elderly. It underlines the interest of a new PPI detection tool for elderly patients with psychiatric disorders.

Objectif: En 2019, l'OMEDIT Pays de Loire a effectué un état des lieux des prescriptions potentiellement inappropriées (PPI) de psychotropes chez le sujet âgé hospitalisé en psychiatrie qui a mis en évidence leur usage inapproprié dans cette population. L'objectif de ce travail est d'évaluer la pertinence clinique, définie comme l'apport d'un traitement approprié, nécessaire et choisi parmi d'autres solutions comme étant le plus à même de produire les résultats attendus pour un patient donné, de ces prescriptions considérées comme inappropriées selon les critères actuels établis.

Matériel et méthode: Les patients âgés de plus de 75 ans ou de 64 à 75 ans et polypathologiques avec au moins une PPI de psychotropes ou de médicaments à charge anticholinergique élevée, identifiée par une grille d'audit établie à partir des critères STOPP/STARTv2 et de la liste de Laroche sur l'ordonnance à 48 heures d'hospitalisation, ont été inclus. La pondération du caractère inapproprié de la prescription (résistance aux traitements, période de crise, comorbidités…) a été établie par un binôme pharmacien-psychiatre sur l'ensemble du dossier informatisé de l'épisode en cours. La pertinence clinique des PPI et de la prescription globale a été cotée 0 (non pertinent), 1 (partiellement pertinent) ou 2 (pertinent).

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Résultats: Trente-quatre patients ont été inclus. Cent vingt-cinq PPI de psychotropes ont été notées : 50,4 % concernaient les benzodiazépines et apparentés (BZD/Z), 25,6 % les neuroleptiques (NL), 12 % les antidépresseurs (ATD) et 12 % les médicaments à charge anticholinergique élevée. D'une part, 49,2 % des PPI de BZD/Z, 50 % des PPI de NL et 20 % des PPI d'ATD étaient considérées non pertinentes ; 49,2 % des PPI de BZD/Z, 31,3 % des PPI de NL et 13,3 % des PPI d'ATD étaient estimées partiellement pertinentes. D'autre part, 1,6 % des PPI de BZD/Z, 18,8 % des PPI de NL et 66,7 % des PPI d'ATD étaient jugées pertinentes. Pour les PPI de médicaments avec charge anticholinergique élevée : 80 % étaient jugées non pertinentes, 13,3 % partiellement pertinentes et 6,7 % pertinentes. Au total, sur les 34 prescriptions médicamenteuses étudiées, 3 (8,8 %) étaient jugées non pertinentes, 11 (32,4 %) partiellement pertinentes et 20 (58,8 %) pertinentes cliniquement.
Conclusion: Ce travail a permis de mettre en lumière une pertinence clinique pour plus de la moitié des prescriptions considérées comme inappropriées selon les critères actuels de PPI chez le sujet âgé. Il souligne l'intérêt d'un nouvel outil de détection de PPI chez le sujet âgé atteint d'un trouble psychiatrique.

1. Introduction

In France on January 1st, 2024, individuals aged over 65 represent 22% of the population [1]. Within this elderly population, the prevalence of psychiatric disorders has already reached over 17%, notably with a high prevalence of depressive and anxiety disorders [2]. The elderly, defined by the World Health Organization as being over 75 years old or over 65 with at least 3 chronic pathologies, are at high risk of experiencing adverse drug events. Indeed, managing elderly individuals can be complex due to frequent polypharmacy, multiple pathologies, and physiological changes in the body related to aging, which can lead to pharmacokinetic and pharmacodynamic modifications of the medication [3]. Considering the patient's vulnerability factors, biological data, the risk of drug interactions, and contraindications related to existing comorbidities is important.

To assist in prescribing medications for elderly individuals, tools have been created by expert groups from various disciplines including geriatrics, psychiatry, and pharmacology. In France, the use of REMEDIES criteria [4] and the STOPP/STARTv2 list adapted to French [5] is common. These tools help avoid potentially inappropriate prescriptions, defined as prescriptions where the benefit/risk ratio is unfavorable for a specific patient compared to other therapeutic alternatives. Providing assistance in prescribing psychotropic drugs is a significant aspect of these tools. Psychotropic drugs pose a high iatrogenic risk, and they have numerous adverse effects [6–11]. These risks are also linked to the anticholinergic burden of many psychotropic medications, which can be evaluated using scales such as the anticholinergic cognitive burden (ACB) scale [12] assessing central anticholinergic impact of drugs and the anticholinergic impregnation score (AIS) [13] evaluating peripheral anticholinergic burden.

In the Pays de la Loire region, an assessment of potentially inappropriate prescriptions (PIPs) of psychotropic drugs in elderly hospitalized patients in psychiatry was conducted in 2019. The study of prescriptions 48 hours after admission in 347 patients from 7 different institutions revealed over 90% of inappropriate benzodiazepines and related drugs prescriptions, 56% of patients with un recommended psychotropic drug combinations, and 11% of high anticholinergic burden psychotropic drug prescriptions [14]. Misuse of psychotropic drugs in this population was highlighted. However, it became evident that this assessment also shed light on the limitations of current PIP criteria in the context of psychiatric hospitalization for acute disorders. Clinical relevance of these PIPs was not considered in this work. In a complex setting of treating an elderly patient with a psychiatric disorder, resistant to first-line treatments or non-pharmacological alternatives, or at risk of self-harm or aggression, some of these supposedly inappropriate prescriptions may ultimately be justified.

Our objective is to study the clinical relevance of potentially inappropriate prescriptions of psychotropic drugs in elderly patients hospitalized in psychiatry.

2. Materials and methods

A retrospective observational monocentric study was conducted in 2022 at a university hospital center with around 3000 beds, including 250 for adult psychiatry.

2.1. Study population

Patients included in the study were elderly patients, defined as being over 75 years old, or aged 65 to 74 with at least 3 documented chronic pathologies, admitted to full hospitalization in the psychiatry department of a university hospital center.

A random list of hospitalization episodes of over 48 hours for patients over 65 years in one of the 5 psychiatry services of the establishment between January 2020 and November 2021 was extracted by the medical information department. Episodes corresponding to the same patient were removed to keep only one episode per patient. Patient records from this list were analyzed randomly with the goal of including at least 30 patients.

2.2. Inclusion criteria

Inclusion criteria:

- patients over 75 years old or patients aged 65 to 74 with at least 3 documented chronic pathologies;
- patients in full hospitalization for at least 48 hours (necessary time for treatment reevaluation by the clinician and within the recommended 72-hour timeframe to apply the STOPP/START criteria);
- patients hospitalized between January 2020 and November 2021;
- patients whose medication prescription was approved by a psychiatrist from the institution;
- patients whose psychotropic drug prescription includes at least one PIP of psychotropics according to the Pays de la Loire regional survey grid [14].

A total of 34 patients were included, and details of the inclusions are provided in Fig. 1.

2.2.1. Audit grid

The audit grid is provided in electronic supplement (Appendix A). Data to establish both a socio-demographic and clinical overview of our population (age, sex, comorbid chronic pathologies, psychiatric pathologies, and their ICD-10 classifications), as well as a description of the prescriptions (number of molecules across all classes, number of background psychotropic treatments, symptomatic treatments, and treatments from each studied class: antidepressants, long half-life benzodiazepines, short half-life benzodiazepines, typical neuroleptics, atypical neuroleptics) were collected. A background treatment was de-

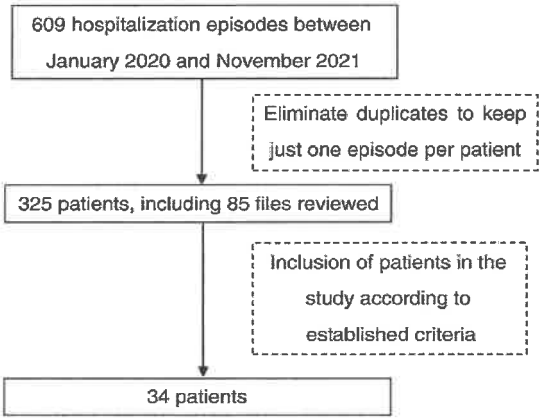

Fig. 1. Flowchart.

fined as a treatment prescribed for more than 3 months to prevent a relapse of the chronic treated pathology, in contrast to symptomatic treatment which addresses symptoms in the short term, for example, during a crisis period.

For patients with two psychotropics from the same class and/or a tricyclic antidepressant and/or a long half-life benzodiazepine, we focused on the concept of pharmacoresistance: absence of resistance for patients who had less than 2 treatment tries for the current episode; resistance if more than 2 treatment lines were attempted.

The study grid was then divided according to the four major classes of PIP of psychotropics studied: (i) antidepressants and antidepressant combinations; (ii) neuroleptics and neuroleptic combinations; (iii) benzodiazepines and related drugs, and their combinations; (iv) treatments known for their anticholinergic properties. Specific details and justifications weighing the inappropriate nature of the prescription were sought. In their absence, the prescription was considered truly inappropriate. These clinical relevance justifications were elaborated by 2 geriatric psychiatrists, in consultation with 1 pharmacist. These could be clinical factors like agitation, suicidal crisis, uncontrolled anxiety, or pharmacological factors like a background treatment recommendation or possibly inadequate dosage for the current condition and severity level.

Central and peripheral anticholinergic scores were calculated based on the ACB [12] and AIS [13] scales. A high anticholinergic burden of the overall prescription is considered when the ACB score is equal to or greater than 4 and/or the AIS score is greater than 5. Clinical relevance according to the geriatric psychiatrist who filled out the table was noted on a Likert scale: 0 (no pertinent elements); 1 (prescription with some justifications found but insufficient to explain all the PIPs); 2 (relevant prescription). It was evaluated for each PIP as well as for the overall medical care of the patient.

2.2.2. Data collection procedure

Data collection was performed by a geriatric psychiatrist-pharmacist team. Potential justifications for PIPs were systematically searched for in the entirety of the digital record corresponding to the study episode, using the validated grid (Appendix A).

2.2.3. Statistical analysis

As an exploratory descriptive study without intervention, no comparison, and no a priori hypothesis, it was not possible to calculate a necessary number of patients to include. Recruitment was exhaustive: all patients meeting the inclusion criteria were included. Qualitative variables were described by frequencies and percentages of each modality, and quantitative variables were described by means and standard deviations.

2.2.4. Ethical aspects

Our work was ethically validated by the Nantes Group of Ethics in the Health Domain. Data were anonymized. As each patient admitted to our institution had previously agreed to the use of medical data for research purposes, written consent was not needed for an observational retrospective study categorized outside of the Jardé law.

3. Results

Table 1 describes the population included in the study.
In total, 125 PIPs of psychotropic drugs were identified.

3.1. Antidepressants

Fifteen PIPs concerning antidepressants were found in 13 medication prescriptions. They are described in Fig. 2.

Combinations between a serotonin-norepinephrine reuptake inhibitor (SNRI; 72.8% of combinations) or a selective serotonin reuptake inhibitor (SSRI; 18.2%) and mirtazapine or mianserin were considered relevant in the case of resistant forms of depression and/or psychiatric comorbidities (90.9%).

3.2. Neuroleptics

Thirty-two PIPs of neuroleptics were identified in 19 medication prescriptions. These are detailed in Fig. 3.

Prescribing a neuroleptic such as aripiprazole or amisulpride for patients at risk or with metabolic syndrome was considered relevant as these are molecules with a lower risk of exacerbating or causing it.

A high suicide risk was found in a patient prescribed a neuroleptic other than clozapine or quetiapine in the presence of Parkinson's disease, but it did not justify this PIP. For the other patient, Lewy body dementia was not investigated despite existing prodromes.

Pharmacoresistant forms of the current psychiatric episode (37.5%), stabilizing the condition with combination therapy (37.5%), the presence of psychiatric comorbidities (12.5%), or a suicidal crisis or agita-

Table 1
Socio-demographic and clinical characteristics of included patients (n = 34).

	Included patients
Age (mean, standard deviation, in years)	75.5 (5.6)
Gender (n, %)	
Female	25 (73.5%)
≥ 3 documented chronic pathologies (n, %)	
Yes	28 (82.4%)
Characterized psychiatric disorders[a] (n, %), n = 33	
Depressive episodes (F32)	15 (45.5%)
Recurrent depressive disorders (F33)	5 (15.2%)
Bipolar affective disorders (F31)	8 (24.2%)
Schizophrenia (F20)	3 (9.1%)
Schizoaffective disorders (F25)	1 (3.0%)
Other non-organic psychotic disorders (F28)	1 (3.0%)
Medication management	
Number of medications per patient (mean, standard deviation)	7.9 (3.6)
Number of psychotropics per patient (mean, standard deviation)	2.8 (1.1)
Patients on antidepressants (n, %)	21 (61.8%)
Patients on neuroleptics (n, %)	29 (85.3%)
Patients on benzodiazépines and related drugs (n, %)	29 (85.3%)
Number of maintenance psychotropics per patient (mean, standard deviation)	1.6 (0.9)
Number of symptomatic psychotropics per patient (mean, standard deviation)	1.3 (0.7)
Resistance profile, n = 23	
Non-resistants (n, %)	10 (43.5%)
Resistants (n, %)	13 (56.5%)

[a] ICD-10 classification.

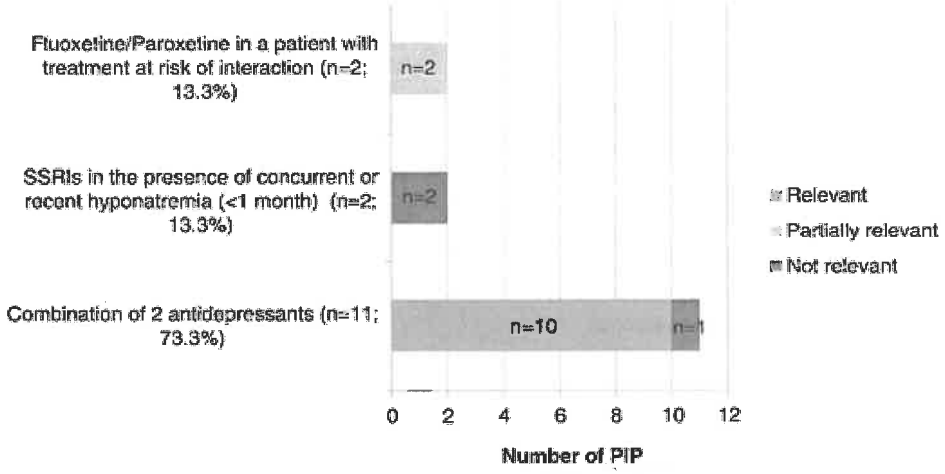

Fig. 2. Description of PPIs (n = 15) from the class of antidepressants (ATD).

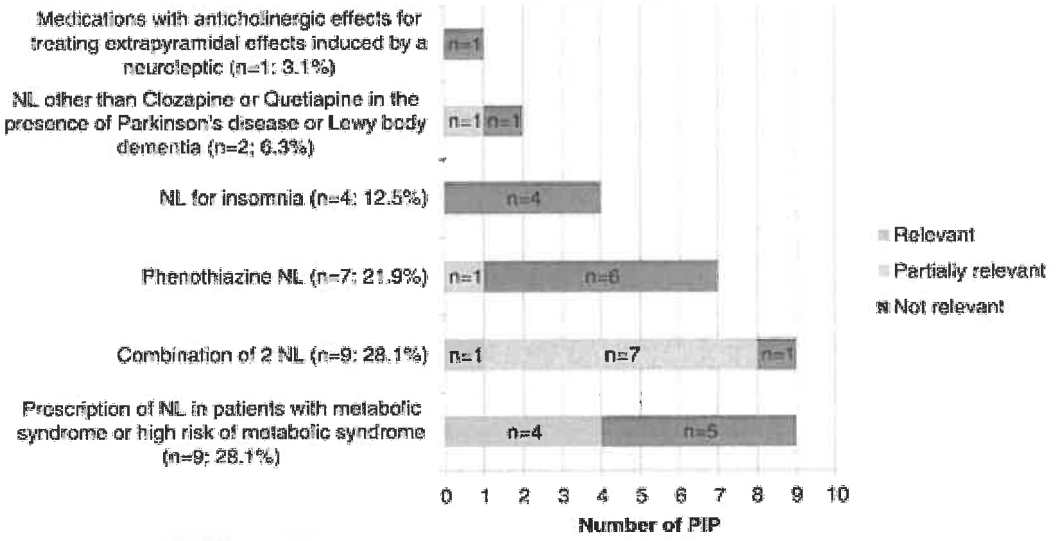

Fig. 3. Description of PPIs (n = 32) from the class of neuroleptics (NL).

tion (12.5%) could partially justify the use of neuroleptic combinations as well as prescription of a phenothiazine neuroleptic.

A patient with psychiatric comorbidities such as anxiety disorders was on a combination of two typical antipsychotics, including occasional loxapine. The lack of optimization of the underlying antidepressant treatment, which is the first-line approach in anxiety disorders, was a criterion for the inappropriate use of a combination of two antipsychotics.

3.3. Benzodiazepines and related drugs

Sixty-three PPIs of benzodiazepines and related drugs (BZD/Z) were found in 26 medication prescriptions (Fig. 4).

The only PIP deemed relevant was the absence of a gradual decrease in BZD due to the need for rapid cessation in a patient with respiratory insufficiency.

A suicidal crisis or major uncontrolled anxiety despite appropriate background treatment (37.5%), a suicidal crisis or major uncontrolled anxiety with temporarily inappropriate background treatment (25%), a prior trial of a short half-life benzodiazepine (25%) partially justified prescriptions of long half-life molecules.

A suicidal crisis or unbalanced depression as well as an age below 85 years (threshold for which we considered an unfavorable risk/benefit ratio regardless of clinical presentation) partially justified prescriptions at doses higher than those recommended.

Factors mitigating the inappropriate nature of prescriptions lasting more than 4 weeks were partially balanced pathology due to benzodiazepine use (29.4%), a reassessment of the prescription every 2 months (52.9%), and the absence of treatment-attributable adverse effects (82.4%).

3.4. Psychotropics with high anticholinergic burden

Fifteen PIPs of drugs with anticholinergic properties were identified in 12 patients. Ten affected patients had major neurocognitive disorders or delirium syndrome. Except for one ongoing antipsychotic medication switch, none of the prescriptions were considered clinically relevant.

Regarding the 34 prescriptions:

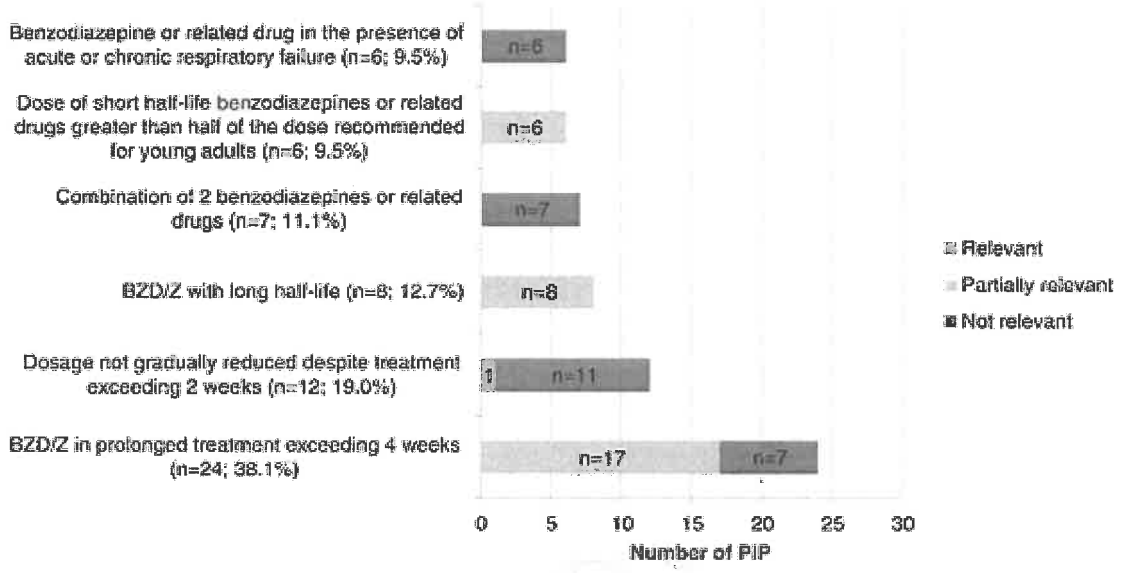

Fig. 4. Description of PPIs (n = 63) from the class of benzodiazepines and related drugs.

- six (17.6%) had a significant central anticholinergic burden, of which 2 had a PIP of psychotropics with anticholinergic effects;
- five (14.7%) had a significant peripheral anticholinergic burden, of which 3 had a PIP of psychotropics with anticholinergic effects.

3.5. *Overall clinical relevance rating*

The overall clinical relevance rating of the prescriptions is presented in Fig. 5.

4. Discussion

Almost 60% of potentially inappropriate prescriptions were deemed clinically relevant in this study. This study is the first to evaluate the inappropriate nature of psychotropic prescriptions based on potential clinical relevance in the context of acute admission in psychiatry, assessed by a psychiatrist specializing in elderly care and a pharmacist.

The results are relatively reliable considering the population studied is comparable to the general elderly population and those in other studies, and the PIP rates are similar to those found in the OMEDIT audit (n = 347) [14]. The dual assessment by a psychiatrist specialized in elderly care and a clinical pharmacist enabled an in-depth analysis of patient records.

The class most affected by potentially inappropriate prescriptions with relevance was antidepressants, especially due to the interest in antidepressant combination therapies in the elderly. For severe treatment-resistant depression and/or patients with psychiatric comorbidities like sleep disorders or anxiety, which was the case for 90% of patients in our study, the combination of an SSRI or SNRI with an alpha-2 antagonist like mirtazapine can be effective in clinical practice. Study by Charpeaud et al. suggests a beneficial association significantly improving clinical outcomes and remission rates of treatment-resistant depression under such combination therapies [15]. Recommendations by Kok and Reynolds also support this approach [16]. The combination of an antidepressant with lithium treatment or a neuroleptic like aripiprazole

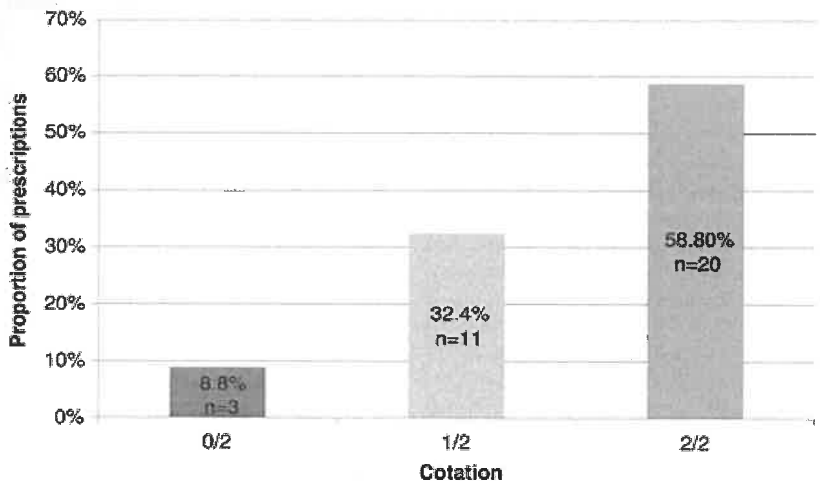

Fig. 5. Overall relevance rating of prescriptions (n = 34).

is also recommended for treatment-resistant depressions [17], although this was less common in our study. Nasal Esketamine is a more recent augmentation therapy in treatment-resistant depression, showing potential benefits in adults but limited data in the elderly. In the absence of contraindications, especially vascular ones, this could be a possible strategy [18]. The use of non-pharmacological alternatives like electroconvulsive therapy or rTMS is still inadequately accessible despite good evidence and safety levels in this population.

Approximately one-third of PIPs were deemed partially relevant by the study psychiatrists, including a considerable number of antipsychotic combinations in an elderly psychiatric population often resistant to several lines of treatment. As Humaraut et al. suggest, limiting the use of these neuroleptic combinations in acute crisis situations can be challenging [19]. However, it is important to note the lack of reassessment for patients stabilized on these treatments. Even if the pathology is stable, aging patients require treatment adjustments. The elderly become more sensitive to neuroleptics, and decreasing dopamine receptor counts imply reduced neuroleptic dosing in the elderly despite disease balance [20]. Intramuscular lorazepam is now indicated in cases of agitation or acute anxiety, potentially reducing the need for neuroleptics in these situations [21].

Using a neuroleptic other than clozapine or quetiapine is contraindicated in Parkinson's disease or Lewy body dementia. For a patient in this situation, prodromal symptoms of Lewy body dementia were present in the medical record without an explicit diagnostic evaluation at the time of hospitalization, emphasizing the importance of identifying these conditions in this context. Depressive or psychotic symptoms can be prodromal signs of Lewy body dementia, necessitating the exploration of associated symptoms and neuroimaging to optimize medication management [22]. In the second patient, olanzapine at a dose of 5 mg was prescribed alongside occasional loxapine, in a context of high self-aggression risk. Suicidal crisis should never justify the prescription of a neuroleptic other than those recommended for Parkinson's disease due to the risk of worsening motor symptoms [23].

Regarding benzodiazepines, PIPs involving long half-life molecules were considered partially relevant. The half-life of benzodiazepines is prolonged in the elderly due to increased body fat mass and often impaired renal function [24]. The extended sedative effect of a long half-life benzodiazepine increases the risk of falls. Their use may be appropriate in cases of suicide crisis in a patient with well-adjusted background treatment and for a short period. Indeed, in cases of high suicide risk, a long half-life benzodiazepine minimizes the risk of rebound effects and offers more effective coverage. An anxiety disorder resistant to conventional background treatments and psychotherapy could also justify the use of a longer half-life benzodiazepine, albeit at a low dosage and with the aim of improving quality of life. Tolerance assessment is always necessary. Indeed, even though the vulnerability and treatment tolerance of patients with a PIP of benzodiazepines in our study were often evaluated, this does not justify their prescriptions. In vulnerable patients, a prescription initially deemed appropriate may quickly become inappropriate, urging caution [25]. These indications of crises could justify a benzodiazepine prescription at a dosage higher than half the recommended adult amount. Some prescriptions of benzodiazepines over an extended period ($>$ 4 weeks) and/or without dose reduction after 2 weeks of treatment could be justified by the time needed to stabilize a psychotic state, acute delusion, manic phase, or severe depression, typically exceeding 15 days.

Finally, for some PIPs, no justification was found. Examples include SSRIs prescribed concurrently with hyponatremia, problematic due to possible neurological consequences, particularly impacting attention and balance, increasing fall risk [11,26].

BZD/Zs are the most common class of psychotropics represented in clinically irrelevant PIPs in our study and in the literature [6,19,27]. Misuse may be due to overconsumption in anxiety disorders and mood disorders [28,29]. The work of Manthey et al. shows discrepancies between recommendations and actual practices, with 82.5% of patients (n = 2852) included consuming benzodiazepines for longer periods than recommended, for indications like chronic sleep disorders, pain, or depressive disorders [29]. Deprescribing benzodiazepines seems crucial in this context, especially considering no long-term benefits have been proven.

The rate of inappropriate prescriptions of psychotropics with a high anticholinergic burden correlates with that found in the French literature [30]. In our study, the prescription of 2 psychotropics with anticholinergic effects did not significantly increase the overall anticholinergic burden of the prescription. In another study, Mukku et al. found that nearly half of the elderly patients included (n = 129) had a high anticholinergic burden (ACB score $>$ 3) due to high psychotropic consumption [31]. Grossi et al.'s work shows that the risk of confusion and major neurocognitive disorders is amplified by the frequent use of high anticholinergic burden treatments (score $\geq$ 4 based on the ACB scale), even in patients with intact cognitive function at treatment initiation [32].

This study has several limitations: a limited sample size, the retrospective nature of the study, evaluation at 72 hours and not at the end of hospitalization, the lack of a double psychiatrist evaluation of each dossier, and the adopted criteria lacking expert consensus validation. The prescription justification was not discussed with the prescriber, who remains free and responsible for their choices. Nonetheless, this work advocates for a specialized approach in elderly psychiatry, adopting a rigorous and nuanced approach to prescriptions, considering benefit-risk balance, patient examination, PIP criteria, justification search when criteria are not met, and the implementation of an appropriate monitoring strategy. It necessitates multidisciplinary reflections on adapting PIP criteria for psychiatric units and developing practical tools based on national expert recommendations in elderly psychiatry.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.encep.2024.04.005.

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