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Drug-related problems among older patients: analysis of 8 years of pharmacist's interventions.

Problèmes médicamenteux chez le sujet âgé : Analyse de 8 ans d'interventions pharmaceutiques.

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1 **Introduction**

2 Drug-Related Problems (DRPs) have been defined as « an event or circumstance involving
3 drug therapy that actually or potentially interferes with a desired health outcome » [1]. The
4 risk of DRPs increases with age due to age-related physiological and pathophysiological
5 changes in organ function that affect the pharmacodynamics and pharmacokinetics of drugs
6 [2]. These changes lead to reduced homoeostasis, the presence of co-morbidities,
7 interindividual variability and frailty also associated with DRPs [3]. Increasing age,
8 polypharmacy, increasing complexity of drug therapy and the use of potentially inappropriate
9 drugs in aged people were associated with an increased risk of hospitalization [4–8] Hospital
10 stay and polypharmacy were associated with severe DRPs-related events [9].

11 During their hospital stay, all patients benefit from a medication order review conducted by
12 physicians in collaboration with pharmacists [10,11]. During this process, pharmacists can
13 detect DRPs and formulate pharmacists' interventions (PIs) which will be transmitted to
14 physicians either orally or through the prescribing software. A PI is defined as "any action
15 initiated by a pharmacist directly resulting in a change of the patient's management or
16 therapy" [12]. Literature supports the value-adding role of pharmacists during the medication
17 order review, improving medication adherence, knowledge and appropriateness [10,13,14].
18 When most DRPs can be considered as preventable [15], this collaborative approach
19 contributes to decrease the number of DRPs and to improve patient safety. The relevant
20 detection of DRPs is usually associated with the expertise and the education of both
21 pharmacists and physicians[16,17]. Physicians and pharmacists may have difficulties to deal
22 with patients with specificities that do not fall within the scope of their expertise. Thus,
23 investigating DRPs that have been detected during daily medication order review can helped
24 to identify at-risk population, additional training needs for healthcare professionals and
25 specific quality indicators that can be followed over time.

26 The aim of this study was to quantify and describe DRPs and PIs among older patients in a
27 French teaching hospital between 2008 and 2015. Secondary objectives were to compare
28 DRPs between 18-74 and 75 years and over patients to identify DRPs that are specific to older
29 patients and to compare DRPs in older patients treated in geriatric wards or in general wards.

30 **Methods**

31 **Study Design**

32 An observational study on DRPs and PIs was conducted in the university hospital centre of
33 Lyon – the second biggest in France with 5362 hospital beds – over a 96-month period from
34 1st January 2008 to 31st December 2015. This institution federates 14 hospital centres,
35 including 3 centres providing emergency, medical and surgical services in a wide range of
36 disciplines, 7 specialized centres and 4 geriatric centres. DRPs were identified by the
37 pharmacist during the medication order review which could be performed either in wards or
38 in central pharmacy. Considering the number of centres and the specificities of practices in
39 each centre, medication order review could be done in a very heterogeneous way across wards
40 and time. Clinical specifications and information on treatment regimen could be discussed
41 with physicians during medical tour or by phone. A medication order review with a
42 pharmacist is not conducted on every hospital bed, therefore this study only reflects a part of
43 potential DRPs and PIs. Only DRPs and PIs identified in patient aged 18-74 years (younger
44 patients) and ≥ 75 years (older patients) were included in this analysis. Specific DRPs that
45 involved cancer drugs were excluded from analyses.

46 **DRPs and PIs data**

47 During medication order review, pharmacists assessed the appropriateness of each prescribed
48 medicine according to their expertise and looked for possible drug interactions. Pharmacists
49 had access to electronic medical records, biology, and drug prescriptions. Any identified
50 relevant DRPs lead to a PI which was submitted to the physician. Pharmacist could be a

51 senior or a resident managed by a senior pharmacist. The type of DRPs and PIs was classified
52 according to the SFPC (Société Française de Pharmacie Clinique – The French Society of
53 Clinical Pharmacy) criteria using the report form developed and validated for routine
54 documentation of the PIs [18,19]. Whenever a DRPs was identified, the pharmacist could
55 record their PIs in the Act-IP© database through the online report form
56 (<http://actip.sfpc.eu/actip>) notifying the date, patient characteristics (age, gender), drug
57 involved (classified according to the Anatomical Therapeutic Chemical (ATC) classification
58 of the World Health Organization), ward, DRP description and specific recommendations.
59 Physicians' acceptance is also collected to assess the relevance of PIs and is grouped in 3
60 items: "Accepted" which means that the physician agreed with the PI, "Non-accepted" if the
61 physician refused the PI and "Non-assessable" if the pharmacist didn't have any feedback on
62 the suggested PI (e.g. patient discharged or transferred before considering the PI).

63 **Data analysis**

64 Data were retrospectively retrieved from the Act-IP© database and split into 2 groups:
65 patients aged 18-74 years (younger patients) and patients aged ≥ 75 years (older patients).
66 Database quality controls were performed looking for aberrant entries to ensure that data
67 coding and entry errors were minimal. Continuous variables were expressed as means \pm
68 standard deviation. Categorical variables were expressed in frequencies and percentages.
69 Descriptive statistics were used for characterizing population characteristics, DRPs, PIs and
70 physicians' acceptance. Top 20 of the most frequent DRPs and physicians' acceptance in both
71 older and younger were examined and compared. DRPs and physicians' acceptance
72 proportions between older patients treated in a dedicated geriatric ward or in a general ward
73 were also compared. Proportions were compared using the chi-square test or Fisher's exact
74 test where appropriate for categorical data. The evolution over time of the most frequent
75 DRPs in older patients between 2008 and 2015 presenting most frequent DRPs of each year
76 were also presented. Comparisons between continuous variables were done by using the t-test.

77 A two-tailed $p < 0.01$ was considered statistically significant after a bonferroni correction. Data
78 and figures were managed using Excel 2010™ (Microsoft Corporation, Seattle, WA, USA).
79 Statistical analyses were performed using SPSS (IBM Corp. Released 2012. IBM SPSS
80 Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

81 **Results**

82 Over the 96-month study period, 56223 DRPs were recorded in 7 out of the 14 centres of the
83 teaching hospital: 37167 in patients aged 18 to 74 years (51.3 ± 15.2 years, 31.6% female) and
84 19056 were in patients ≥ 75 years (84.1 ± 5.7 years, 58.0% female).

85 **DRPs and PIs in older patients and comparison with younger patients**

86 The characteristics of the DRPs and PIs are summarized in Table 1. The most common type
87 of DRPs identified by pharmacists was ‘supratherapeutic dosage’ (22.4%), ‘improper
88 administration’ (19.3%) and ‘non-conformity to guidelines/contra-indication’ (19.0%). Non-
89 conformity to guidelines/contra-indication also included non-conformity to drug formulary
90 (54.9% in older patients and 43.8% in younger patients). The PIs were mainly proposals for
91 ‘dose adjustment’ (27.3%), ‘drug discontinuation’ (22.8%) and ‘drug switch’ (17.6%). The
92 types of drugs most frequently implicated in DRPs were: analgesics and antipyretics (12.1%),
93 anti-infectives (9.6%), psycholeptics (9.4%), antithrombotics (7.9%) and drugs for peptic
94 ulcer and reflux disease (5.1%). Table 2 showed the top 20 of DRPs and associated drugs in
95 older patients. The most common DRPs were supratherapeutic dosages with acetaminophen
96 (5.2%) and with related benzodiazepines (4.0%), improper administration of acetaminophen
97 (2.8%), use of trimetazidine without indication (1.4%), indication of vitamin D without
98 treatment (1.2%). Four types of DRPs involved proton pump inhibitors (PPI): improper
99 administration (1.0%), supratherapeutic dosage (0.9%), drug without indication (0.7%) and
100 non-conformity to guidelines (0.6%). In comparison with DRPs recorded for 18-74 years
101 patients, pharmacists identified more ‘non-conformity to guidelines’ (19.0% vs 14.1%,

102 p<0.01), ‘adverse drug reactions’ (7.4% vs 3.8%, p<0.01) and ‘supratherapeutic dosage’
103 (22.4% vs 19.0%, p<0.01) in over 75 years patients (Table 1). ‘Drug switch’ (17.6% vs
104 13.3%, p<0.01) and ‘dose adjustment’ (27.3% vs 24.2%, p<0.01) were most frequently
105 recommended by pharmacists in older patients in comparison with younger patients.
106 However, ‘drug monitoring’ (13.4% vs. 9.7%, p<0.01) was most recommended in younger
107 patients (table 1). Significant differences between older patients and younger patients were
108 shown for every DRPs and associated drugs identified in the top 20 (table 2), except
109 “improper administration associated to proton pump inhibitor”. Fifteen of the 20 identified
110 DRPs were significantly higher in older patients compared to younger patients. DRPs related
111 to PPI were more likely to be observed in younger patients. Supratherapeutic dosage in other
112 opioids (mostly tramadol) was also mainly observed in younger patients.

113 **Physicians’ acceptance of PIs in older patients and comparison with** 114 **younger patients**

115 In older patients, 10886 (57.1%) PIs were accepted by the physicians, 2966 (15.6%) were not
116 accepted and 5204 (27.3%) were considered as non-assessable. Of the 37167 PIs recorded in
117 younger patients, 23905 (64.3%) were accepted by physicians, 6845 (18.4%) were not
118 accepted and 6417 (17.3%) were not assessable (table 1). The most accepted PIs in older
119 patients (table 3) were related to bleedings in patient treated by vitamin K antagonists while
120 the least accepted PIs were related to the use of trimetazidine without indications.

121 **Geriatric wards**

122 In older patient, 7840 (41.2%) PIs were done in geriatric wards (table 1). The most frequent
123 PIs (table 2) were supratherapeutic dosage with acetaminophen (4.8%), improper
124 administration of acetaminophen (3.0%), indication of vitamin D without treatment (2.3%)
125 and a non-conformity to guidelines using drugs from the heparin group (1.8%). In general
126 wards, frequent PIs in older patients were supratherapeutic dosage with hypnotics (5.8%) and

127 with acetaminophen (5.6%) and, improper administration of acetaminophen (2.6%), use of
128 trimetazidine without indication (2.3%). Every DRPs involving a “non-conformity to
129 guidelines” were higher in geriatric wards. Supratherapeutic dosages were mainly
130 significantly detected in general wards. Overall, physicians’ acceptance was significantly
131 higher for PIs realized in geriatric wards than those realized in general wards (respectively
132 62.1% and 53.6%) (table 3).

133 **Evolution of DRPs over time**

134 Except for DRPs related to anilides (acetaminophen), most frequent DRPs detected in 2008
135 gradually decreased until 2015 (i.e supratherapeutic dosage in hypnotics, drug without
136 indication in other medication in cardiology, supratherapeutic dosage in uric acid synthesis
137 inhibitors, adverse drug reaction in vitamin K antagonists) (Fig. 1). Increasing DRPs in 2015
138 included non-conformity to guidelines for osmotically acting laxatives (2.4%),
139 benzodiazepine derivatives (1.4%) and heparin (1.0%), untreated indication for vitamin D and
140 analogues (1.7%), drug without indication for PPI (1.6%).

141 **Discussion**

142 This study was conducted in a multi-centre teaching hospital over an 8-year period. It aimed
143 at quantifying and describing DRPs and PIs among older patients and at giving an insight into
144 the clinical contexts and medications involved in DRPs. DRPs and PIs between younger and
145 older patients were also compared to identify DRPs that are specific to older patients. The
146 description of DRPs in geriatrics allows PIs to be targeted and allows clinical pharmacy
147 activities to be adapted to geriatrics specificities.

148 A substantial number of DRPs was collected with 56223 DRPs recorded in the database. In
149 older patient, 19056 DRPs were recorded and the most frequent DRPs was ‘supratherapeutic
150 dosage’ (22.4%). Accordingly, the main PIs was ‘dose adjustment’ (27.4%). These rates were
151 consistent with Ruiz-Milo et al in their study conducted on patient aged 75 and over [20].

152 Their most common DRPs were ‘unnecessary drug’ (25.3%), ‘supratherapeutic dosage’
153 (24.9%) and ‘need for additional drug’ (24.8%). Their most frequent PIs were ‘dose
154 adjustment’ (29.6%), ‘drug discontinuation’ (27.3%) and ‘addition of a new drug’ (21.9%). In
155 comparison with the present study, more ‘untreated indication’ requiring the ‘addition of a
156 new drug’ were identified by Ruiz-Millo et al. but less ‘improper administration’ requiring an
157 ‘optimization of the administration mode’ were observed. However, the DRPs and PIs
158 classifications were not the same between these 2 studies.

159 No larger study identifying DRPs in older patients has been conducted so far. However a
160 previous study using the same DRPs and PIs classifications and including 34 522 PIs was
161 conducted among patients with no age limit (mean age = 67.9 years, 0-106 years). Although
162 populations differed in age, the distributions of DRPs and PIs were similar [19]. The largest
163 differences observed between these 2 populations regarding DRPs were for ‘adverse drug
164 reaction’ (7.4% in older patient of the present study vs. 4.3% in Bedouch et al. study) and
165 ‘drug interaction’ (8.1% vs. 11.7%). Regarding PI, small differences were observed for ‘drug
166 discontinuation’ (22.8% vs. 20.0%) and ‘dose adjustment’ (27.3% vs. 24.5%). These findings
167 can be explained by the age differences in groups between the two studies. Older patients are
168 more likely to experiment adverse drug reaction and have drugs discontinued or adjusted [2].

169 After exclusion of non-assessable interventions, the physicians’ acceptance rate was 78% both
170 in younger and in older patients (64.3% and 57.1% respectively before exclusions). These
171 encouraging rates are consistent with previous studies that reported rates ranging from 39% to
172 100% [19,21–23] and highlights the relevance of PI.

173 Focusing on the main DRPs associated to a PI, acetaminophen associated with a
174 supratherapeutic dosage was the most frequent. This was mostly explained by overuse of
175 acetaminophen (> 3g daily) in patients weighting less than 50kg and/or presenting altered
176 renal function. Dose adjustment is recommended in the French summary of product
177 characteristics when creatinine clearance < 30mL/min. SiteGPR (www.sitegpr.com), a French
178 website for health professionals to help with prescriptions to chronic kidney disease patients

179 also recommended a dose adjustment when creatinine clearance < 50mL/min. Prescription of
180 2 drugs containing acetaminophen at the same time (e.g. acetaminophen alone and
181 acetaminophen associated with opioids) was also frequently reported. These PIs were in line
182 with the previous study conducted in the same hospital, showing a risk of acetaminophen
183 overuse still significant [24]. Another DRP associated with acetaminophen was an improper
184 administration when the intravenous form was used instead of the oral form while the clinical
185 situation did not require IV administration. It has been shown that there were no benefits
186 using costly intravenous form when oral route is possible [25]. The frequency of this DRP
187 was similar both in geriatric wards and in general wards with similar acceptance rate of the PI.
188 A suprathereapeutic dosage was also associated with tramadol such as: the prescription over
189 the maximum recommended daily dose of 400mg, no dose adjustment regarding body weight
190 loss, the use of a sustained release form or/and an inappropriate dose with altered renal
191 function. Dose adjustment is recommended in the French summary of product characteristics
192 when creatinine clearance < 30mL/min and by SiteGPR, when creatinine clearance <
193 60mL/min. DRPs involving tramadol were not specific to older patients (they were more
194 frequent in younger patient). Renal impairment was involved in other suprathereapeutic dosage
195 of drugs such as fluoroquinolones, uric acid synthesis inhibitors, angiotensin converting
196 enzyme inhibitor and heparin. Physicians' acceptance rates to PIs associated to these
197 suprathereapeutic dosages range from 51.2% to 61.1%. The use of hypnotics (zolpidem,
198 zopiclone) was also associated with suprathereapeutic dosage, especially in general wards.
199 Hypnotics are potentially inappropriate medications associated with a 2.6 fold risk of falls
200 [26] and should be started at half of the usual dose [27]. However, the acceptance rate for this
201 PI was one of the lowest (42.8%). Otherwise, the rate of this DRP gradually decreased over
202 time, showing a possible improvement in the prescription of hypnotics.

203 One of the most frequent DRPs was the use of a "drug without indication" associated to
204 trimetazidine, a drug usually prescribed as a long-term treatment of angina pectoris, and for
205 tinnitus and dizziness. This drug had been in the spotlight of several medical journals before

206 2011 because of serious neurological adverse effects such as extrapyramidal symptoms, gait
207 instability, restless leg syndrome and other related movement disorders. In 2011, the
208 European Medicines Agency made restriction on the use of trimetazidine [28]. PIs were made
209 to reduce the use of this drug which has a negative risk-benefit balance [27]. The acceptance
210 rate of this PI before 2011 was very low but the afterward restriction of use shows that those
211 PIs were yet relevant. After 2011, the rate of this DRP sharply decreased. Another “drug
212 without indication” referred to third generation cephalosporins such as ceftriaxone. PIs were
213 in line with French recommendation and their encouragement to time-
214 limiting initial antibiotic prescriptions [29,30].

215 The most accepted PIs involved vitamin K antagonists and “adverse drug reactions”. This
216 DRP was mostly motivated by a high International Normalized Ratio (INR) associated or not
217 with bleeding events and/or a potential drug-drug interaction with vitamin K antagonists.
218 Warnings had been also made in older patients at risk of falling to prevent from potential
219 adverse drug reactions. The rate of this DRP decreased after 2012 when the first direct
220 thrombin inhibitors and direct factor Xa inhibitors were marketed. The second most accepted
221 PIs involved the calcium/vitamin D supplementation. There are strong recommendations to
222 maintain an optimal blood level of vitamin D [31] and PIs were suggested to reduce the
223 underuse of vitamin D and avoid vitamin D deficiency. The rate of this PI increased after
224 2012 according to the 2012-update of the French GRIIO guidelines [32] and STOPP/START
225 criteria [33].

226 The overuse and misuse of PPI were frequently reported both in older and in younger patients
227 and this finding is consistent with Chau et al [34]. The overuse of PPI has been widely
228 described [35,36] and can be explained by the continuation of PPI after the resolution of the
229 gastric problem [34]. In the past decade, a list of complication associated with long-term use
230 of PPI such as osteoporosis and pulmonary or gastric infections has been reported [37,38] and
231 pharmacists remain especially alert to their use. Increasing rates of DRPs related to PPI over

232 time showed that pharmacists encourage physicians to decrease dosage of PPI or stop PPI
233 when clinical situation is appropriate. Pharmacists could also monitor decrease in vitamin B12
234 and magnesium level in chronic PPI user. Deprescribing algorithm also exists to help
235 reducing PPI safely [39].

236 Drug interaction between fluoroquinolones and divalent cations (magnesium, calcium, iron
237 salts) was often detected in older patients before 2013. Treatment failures and emergence of
238 resistances to fluoroquinolones have been previously described underlying the relevancy of
239 these PIs [40,41]. In Figure 1, escitalopram associated to other drugs involved in long QT
240 syndrome was also a frequent drug interaction detected in older patients and the rate of this PI
241 increased after 2011 and a specific warning from the European and French medicine agencies
242 [42,43].

243 Improper administration of calcium (figure 1) referred to potential drug interaction with other
244 medications and the need to change the time of the drug administration. It also referred to the
245 administration of calcium twice a day instead of once. Improper administration of furosemide
246 referred to an administration in the evening instead of the morning or midday for a better
247 tolerance (potential urge to urinate during the night that increases the risk of falls).

248 Few DRPs were associated with specific geriatric DRPs such as potentially inappropriate
249 medication [27] or STOPP/START criteria [33]. A supratherapeutic dosage of hypnotics,
250 vitamin D supplementation and the misuse of long half-life benzodiazepines were mostly
251 described. Figure 1 also showed a misuse in hydroxyzine mostly before 2013 when the 100-
252 mg tablets were still marketed. However, in this study, a choice was made to associate a
253 problem with a drug to classify DRP. In this context, a same specific geriatric DRP can be
254 coded in different ways in the Act-IP database according to pharmacists' practices. For
255 example, hydroxyzine is not recommended in older patients due to anticholinergic and
256 sedative effect. This can be coded either in "Non-conformity to guidelines/contra-indication"

257 or “Adverse drug reaction” or “Drug without indication“. Guidelines that are more detailed
258 should be written to ensure better coding and to allow more precise analyses of the database.

259 Overall, drug prescription seems appropriate in geriatric wards (more specific geriatric DRPs
260 detected and less supratherapeutic dosage). Physicians’ acceptance is also higher in geriatric
261 wards. Geriatricians and pharmacists share the same objectives regarding the prevention and
262 the detection of DRPs in older patients. Moreover, pharmacists who work in geriatric wards
263 have specific skills and a higher experience in the detection and the prevention of DRPs in
264 older patients. Thus, geriatricians are more likely to consider PIs and these PIs are more likely
265 to be relevant in older patients. The high level of DRPs (58.8%) in older patients treated in
266 general wards, non-specific PIs and lower physicians’ acceptance confirm that patients treated
267 in general wards are a specific at-risk population.

268 Some limitations to this study should be pointed. As reported in previous studies, the Act-IP
269 observatory does not report the total number of medication orders analysed by pharmacist
270 [19]. Thus, it is not possible to calculate the true rate of DRPs. However, there is a general
271 trend to under-declare PIs in geriatric wards where pharmacists are usually well implemented
272 and directly discuss DRPs with physicians. Recommendations made by pharmacists through
273 the prescription software are automatically and prospectively collected whereas suggestions
274 made orally to physicians are less frequently recorded (time consuming). The distribution of
275 PIs can probably differ from one centre to another. Some pharmacists can be more diligent in
276 entering their PIs in the Act-IP observatory, and thus trigger higher frequencies for DRPs they
277 are used to detect. In the context of this study, focus was not only on the drugs or the
278 problems but also on the association of both. This allowed better understanding of the
279 rationale behind each PI. However, it was not possible to understand rationale behind
280 physicians’ refusal of PIs because this information is not collected in the database. It would
281 have been crucial to confirm the relevance of PIs and adjust pharmaceutical
282 recommendations. Lastly, the clinical significance of PIs could not be assessed. However,

283 other similar studies showed clinical significance in older patients in 55,2% to 75.3% of the
284 PIs [44,45].

285 Identifying main DRPs associated to drugs is a helpful way to point out targeted actions such
286 as internal audit on specific prescriptions or drug use. A recent audit on the proper use of
287 fluoroquinolones has been recently conducted in geriatric units [46]. Other examples include
288 specific flyers on the appropriate use of PPI and hydroxyzine have been developed, alerts that
289 have been created in prescription software to encourage the revision of antibiotics
290 prescriptions after 72 hours. The rates of DRPs can be used then as quality indicators and can
291 be followed over time to assess the relevance of the targeting action. Others quality indicators
292 could be followed up such as the rate of the use of long half-life benzodiazepines or
293 acetaminophen, the rate of the vitamin D supplementation when evidence of deficiency or the
294 rate of suprathreshold dosage of allopurinol when altered renal function. Educational
295 interventions to patients, pharmacists and physicians could be developed to manage the use of
296 inappropriate drugs such as long half-life benzodiazepine and hypnotics. In addition,
297 pharmacists can be an effective relay, through their PI, for the dissemination and the reminder
298 of alert letters and recommendations for clinical practices. Older patients treated in general
299 wards are also pointed out as a population at higher risk of DRP. Special attention should be
300 paid to this population by integrating, for example, pharmacists into mobile geriatrics teams
301 or by reinforcing training on the medication management in older patients in general wards
302 (including physicians, pharmacists and nurses).

303

304 **Conclusion**

305 In the present study, DRPs and associated drugs detected in daily practice by pharmacists in
306 both older and younger hospitalized patients in several centers of a large university hospital
307 were reported. In particular, suprathreshold dosages, improper administration and non-

308 conformity to guidelines/contra-indication were described. DRPs associated to a drug in older
309 patients included a suprathereapeutic use of acetaminophen and hypnotics, medication in
310 cardiology used without indication and underuse of vitamin D. Focus on general wards and
311 geriatric wards was also made and a population of older patients at higher risk of DRPs in
312 general wards was confirmed. Describing PIs in older patients allowed us to better understand
313 and improve clinical practice in this very specific population. These findings should be
314 brought to the attention of prescribers to discuss their relevance and design specific training
315 and targeting communication focusing on potentially inappropriate medications and
316 prescriptions in older patients. Common trainings to healthcare workers could be initiated to
317 increase interprofessional collaboration. As the number of older patients treated outside of
318 geriatrics wards is expected to increase, discussion should be initiated to require geriatrics in
319 continuing medical education. This would be a valuable point to reduce DRPs, prevent from
320 potentially significant adverse effects, and thus contribute to the overall safety of ordering
321 processes.

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333 **Declarations**

334 **Ethics approval and consent to participate:** This study has been conducted on retrospective
335 data and therefore did not need to be approved by a research ethics committee (law no. 2017-
336 884, May 9th, 2017). It was conducted in compliance with the data protection legislation (law
337 no. 2004-801, August 6th, 2004).

338 **Consent for publication:** Not applicable.

339 **Availability of data and material:** The data that support the findings of this study are
340 available from the corresponding author, Frédéric Gervais, upon reasonable request.

341 **Competing interests:** Frédéric Gervais, Teddy Novais, Sylvain Goutelle, Mathieu Chappuy,
342 Stephanie Parat , Delphine Cabelguenne and Chistelle Mouchoux declare that they have no
343 conflicts of interest.

344 **Funding:** No sources of funding were used to assist in the preparation of this study

345 **Authors' contributions:** Frédéric Gervais, Teddy Novais and Christelle Mouchoux designed
346 the study and analysed the results. Delphine Cabelguenne retrieved data from the Act-IP
347 database and prepared the dataset. Sylvain Goutelle, Mathieu Chappuy and Sephanie Parat
348 operatively contributed to the research performance. The first draft of the manuscript was
349 written by Frédéric Gervais and Teddy Novais, and all authors commented on previous
350 versions of the manuscript. All authors read and approved the final manuscript.

351

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494 **Table 1** Drugs-related problems characteristics, Pharmacists' interventions, Physicians' acceptance and main
 495 types of drugs involved.

496 Caractéristiques des problèmes médicamenteux, interventions pharmaceutiques, acceptation par les prescripteurs
 497 et principaux types de médicaments impliqués.

| | ≥ 75 years n= 19 056 | [18-75[years n= 37 167 | <i>p</i> |
|--|-------------------------|----------------------------|---------------------|
| Women, n (%) | 11061 (58.0) | 11736 (31.6) | p<0,0001* |
| Age mean ± SD | 84.1 ± 5.7 | 51.3 ± 15.2 | p<0,0001* |
| Geriatric units | 7840 (41.2) | 3130 (8.4) | p<0,0001* |
| Drug-related problems, n (%) | | | p<0,0001* |
| Supratherapeutic dosage | 4263 (22.4) | 7055 (19.0) | |
| Improper administration | 3678 (19.3) | 7910 (21.3) | |
| Non-conformity to guidelines / contra-indication | 3618 (19,0) | 5237 (14.1) | |
| Drug without indication | 2139 (11.2) | 4520 (12.2) | |
| Drug interaction | 1548 (8.1) | 3940 (10.6) | |
| Adverse drug reaction | 1408 (7.4) | 1398 (3.8) | |
| Untreated indication | 908 (4.8) | 2050 (5.5) | |
| Subtherapeutic dosage | 900 (4.7) | 1797 (4.8) | |
| Drug monitoring | 512 (2.7) | 1902 (5.1) | |
| Failure to receive drug | 82 (0.4) | 1353 (3.6) | |
| Pharmacists' Interventions, n (%) | | | p<0,0001* |
| Dose ajustement | 5240 (27.3) | 9103 (24.2) | |
| Drug discontinuation | 3901 (22.8) | 8515 (23.3) | |
| Drug switch | 3812 (17.6) | 5177 (13.2) | |
| Administration mode optimization | 2716 (14.7) | 6229 (16.5) | |
| Drug monitoring | 1880 (9.7) | 4627 (13.4) | |
| Addition of a new drug | 902 (4.3) | 2182 (5.8) | |
| Change of administration route | 605 (3.5) | 1334 (3.6) | |
| Physicians' acceptance, n (%) | | | p<0,0001* |
| Accepted | 10886 (57.1) | 23905 (64.3) | |
| Non-accepted | 2966 (15.6) | 6845 (18.4) | |
| Non-assessable | 5204 (27.3) | 6417 (17.3) | |
| Types of drugs, n (%) | | | |
| Analgesics and antipyretics | 2366 (12.1) | 5073 (13.1) | p<0,0001* |
| Anti-infectives for systemic use | 1778 (9.6) | 3228 (8.6) | 0.552 |
| Psycholeptics | 1617 (9.4) | 4736 (14.0) | p<0,0001* |
| Antithrombotics | 1477 (7.9) | 1533 (4.1) | p<0,0001* |
| Drugs for peptic ulcer and reflux disease | 957 (5.1) | 2835 (7.6) | p<0,0001* |
| Psychoanaleptics | 856 (4.2) | 1225 (3.2) | p<0,0001* |
| Vitamin and mineral supplements | 721 (2.8) | 812 (1.9) | p<0,0001* |
| Renin-angiotensin system blocking drugs | 703 (3.5) | 812 (2.1) | p<0,0001* |
| Cardiac therapy | 696 (4.1) | 420 (1.1) | p<0,0001* |
| Laxatives | 612 (2.7) | 842 (1.9) | p<0,0001* |
| Anti-epileptics | 240 (1.3) | 1266 (3.6) | p<0,0001* |

498 * P-value that remained significant after a Bonferroni correction

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508 **Table 2** Drug-Related Problems and associated drugs mostly reported in older patients compared to younger
 509 patients.

510 **Principaux problèmes médicamenteux associés à un médicament chez les patients âgés comparés aux**
 511 **patients plus jeunes.**

| Drug-related problems | Pharmaco-therapeutic group | ≥ 75 years | | | p^{α} | [18-75] years n= 37 167 | p^{β} |
|---------------------------------|--|--------------------|-------------------------------|------------------------------|---------------------|-------------------------------|---------------------|
| | | Total n= 19 056 | Geriatric wards n= 8667 | General wards n= 10389 | | | |
| Supratherapeutic dosage | Anilides (<i>acetaminophen</i>) | 998 (5.2) | 445 (5.1) | 553 (5.3) | 0.5608 | 1402 (3.8) | p<0,0001* |
| Supratherapeutic dosage | Hypnotics (<i>zolpidem, zopiclone</i>) | 768 (4.0) | 132 (1.5) | 636 (6.1) | p<0,0001* | 521 (1.4) | p<0,0001* |
| Improper administration | Anilides (<i>acetaminophen</i>) | 528 (2.8) | 253 (2.9) | 275 (2.6) | 0.2545 | 855 (2.3) | 0.0013 |
| Drug without indication | Other medication in cardiology (<i>trimetazidine</i>) | 263 (1.4) | 0 (0.0) | 263 (2.5) | NC | 82 (0.2) | p<0,0001* |
| Untreated indication | Vitamin d and analogs | 222 (1.2) | 212 (2.4) | 10 (0.1) | p<0,0001* | 56 (0.1) | p<0,0001* |
| Supratherapeutic dosage | Fluoroquinolones | 213 (1.1) | 41 (0.5) | 172 (1.7) | p<0,0001* | 160 (0.4) | p<0,0001* |
| Non-conformity to guidelines | Heparin | 203 (1.1) | 153 (1.8) | 50 (0.5) | p<0,0001* | 127 (0.3) | p<0,0001* |
| Improper administration | Proton Pump Inhibitor | 183 (1.0) | 84 (1.0) | 99 (1.0) | 0.9087 | 406 (1.1) | 0.1455 |
| Supratherapeutic dosage | Proton Pump Inhibitor | 177 (0.9) | 65 (0.7) | 112 (1.1) | 0.0187 | 417 (1.1) | 0.0393 |
| Adverse drug reaction | Vitamin K antagonists | 176 (0.9) | 4 (0.0) | 172 (1.7) | p<0,0001* | 49 (0.1) | p<0,0001* |
| Improper administration | Osmotically acting laxatives | 159 (0.8) | 97 (1.1) | 62 (0.6) | 0.0063* | 168 (0.4) | p<0,0001* |
| Supratherapeutic dosage | Uric acid synthesis inhibitors | 159 (0.8) | 29 (0.3) | 138 (1.3) | p<0,0001* | 90 (0.2) | p<0,0001* |
| Non-conformity to guidelines | Benzodiazepine derivatives | 145 (0.8) | 109 (1.3) | 36 (0.3) | p<0,0001* | 134 (0.4) | p<0,0001* |
| Non-conformity to guidelines | Osmotically acting laxatives | 142 (0.7) | 128 (1.5) | 14 (0.1) | p<0,0001* | 119 (0.3) | p<0,0001* |
| Drug without indication | Proton Pump Inhibitor | 140 (0.7) | 61 (0.7) | 78 (0.8) | 0.7078 | 632 (1.7) | p<0,0001* |
| Supratherapeutic dosage | Angiotensin converting enzyme inhibitors | 134 (0.7) | 68 (0.8) | 66 (0.6) | 0.2194 | 56 (0.1) | p<0,0001* |
| Supratherapeutic dosage | Other opioids (<i>tramadol</i>) | 133 (0.7) | 13 (0.1) | 120 (1.2) | p<0,0001* | 357 (1.0) | 0.097 |
| Drug without indication | Third generation cephalosporins | 131 (0.7) | 128 (1.5) | 3 (0.0) | p<0,0001* | 23 (0.1) | p<0,0001* |
| Non-conformity to guidelines | Proton Pump Inhibitor | 129 (0.7) | 72 (0.8) | 57 (0.5) | 0.0180 | 447 (1.2) | p<0,0001* |
| Non-conformity to guidelines | Dihydropyridine derivates | 123 (0.6) | 75 (0.9) | 48 (0.5) | 0.0005 | 75 (0.2) | p<0,0001* |

512 * P-value that remained significant after a Bonferroni correction

513 α Comparison between geriatric and general wards in older patients

514 β Comparison between total older patients and younger patients

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517 **Table 3** Physicians' acceptance related to the most frequent DRPs associated to a drug in older patients

| Drug-related problems | Pharmaco-therapeutic group | ≥ 75 years | | | p |
|------------------------------|---|---------------------|--------------------|--------------------|---------------------|
| | | Total | Geriatric wards | General wards | |
| Total | | 10886 (57.1) | 4871 (62.1) | 6015 (53.6) | p<0.0001* |
| Adverse drug reaction | Vitamin K antagonists | 152 (86.3) | 2 (66.7) | 150 (86.7) | 1 |
| Untreated indication | Vitamin d and analogs | 112 (55.2) | 89 (62.2) | 23 (38.3) | 0.148 |
| Non-conformity to guidelines | Dihydropyridine derivates | 83 (67.5) | 58 (82.8) | 25 (47.2) | 0.0006* |
| Improper administration | Proton Pump Inhibitor | 121 (66.1) | 59 (72.8) | 62 (60.8) | 0.441 |
| Supratherapeutic dosage | Anilides (<i>acetaminophen</i>) | 640 (64.1) | 244 (65.2) | 396 (63.5) | 0.791 |
| Supratherapeutic dosage | Other opioids (<i>tramadol</i>) | 85 (63.9) | 7 (70.0) | 78 (63.4) | 0.847 |
| Non-conformity to guidelines | Osmotically acting laxatives | 88 (62.0) | 76 (64.4) | 12 (50.0) | 0.507 |
| Improper administration | Anilides (<i>acetaminophen</i>) | 314 (59.5) | 147 (62.5) | 167 (57.0) | 0.562 |
| Drug without indication | Third generation cephalosporins | 76 (58.0) | 71 (65.7) | 5 (21.7) | p<0.0001* |
| Supratherapeutic dosage | Uric acid synthesis inhibitors | 89 (56.0) | 14 (66.7) | 75 (54.3) | 0.584 |
| Non-conformity to guidelines | Proton Pump Inhibitor | 72 (55.8) | 42 (57.5) | 30 (53.6) | 0.810 |
| Supratherapeutic dosage | Proton Pump Inhibitor | 98 (55.4) | 30 (50.0) | 68 (58.1) | 0.578 |
| Non-conformity to guidelines | Heparin | 112 (55.2) | 89 (62.2) | 23 (38.3) | 0.081 |
| Supratherapeutic dosage | Angiotensin converting enzyme inhibitors | 73 (54.5) | 52 (81.2) | 21 (30.0) | p<0.0001* |
| Improper administration | Osmotically acting laxatives | 86 (54.1) | 51 (64.5) | 35 (43.7) | 0.149 |
| Supratherapeutic dosage | Fluoroquinolones | 109 (51.2) | 22 (64.7) | 87 (48.6) | 0.344 |
| Supratherapeutic dosage | Hypnotics (<i>zolpidem, zopiclone</i>) | 329 (42.8) | 54 (44.6) | 275 (42.5) | 0.785 |
| Non-conformity to guidelines | Benzodiazepine derivatives | 59 (40.7) | 43 (48.3) | 16 (28.6) | 0.119 |
| Drug without indication | Proton Pump Inhibitor | 54 (38.8) | 16 (31.4) | 38 (43.2) | 0.354 |
| Drug without indication | Other medication in cardiology (<i>trimetazidine</i>) | 102 (38.8) | 0 (0.0) | 102 (38.8) | NC |

519 * P-value that remained significant after a Bonferroni correction

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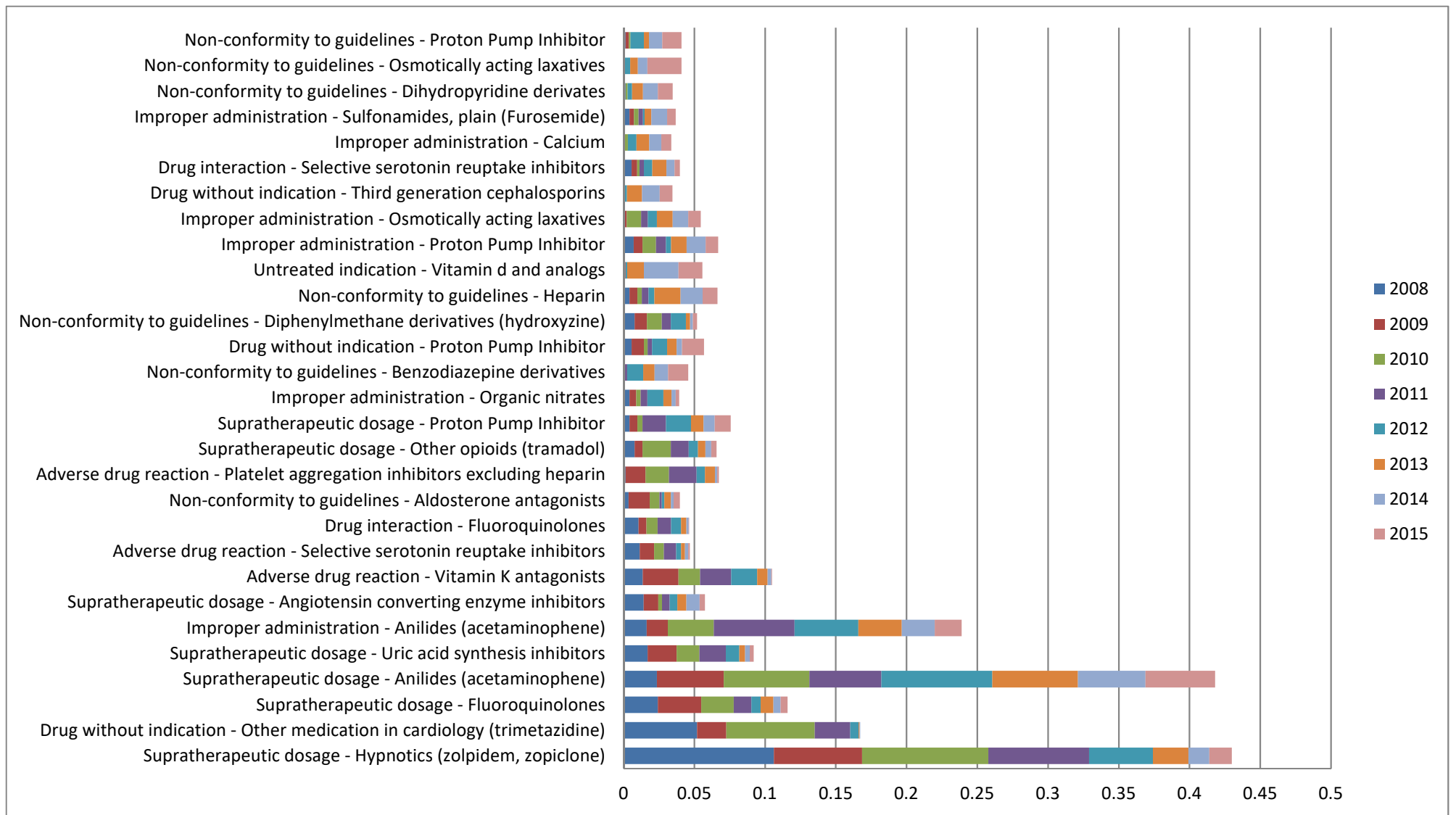


Fig. 1 Evolution of the most frequent DRPs in older patients (%) over time / Evolution des principaux problèmes médicamenteux chez le patient âgé au cours du temps (%)