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Characteristics of Pharmacist's interventions triggered by prescribing errors related to computerized physician order entry in French hospitals: a cross-sectional observational study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-045778
Article Type:	Original research
Date Submitted by the Author:	12-Oct-2020
Complete List of Authors:	Videau, Manon; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes; CHU Grenoble Alpes, Pharmacie Charpiat, Bruno; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes; Hopital de la Croix-Rousse, Pharmacie Vermorel, Céline; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes Bosson, J.L; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes Conort, Ornella; Hopital Cochin, Pharmacie Bedouch, Pierrick; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes; CHU Grenoble Alpes, Pharmacie
Keywords:	Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

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3 **Characteristics of Pharmacist's interventions triggered by prescribing errors related to**
4 **computerized physician order entry in French hospitals: a cross-sectional observational study**
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27 **Keywords:** drug related problem, prescribing error, pharmacist intervention, computerized physician
28 order entry (CPOE)
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31 Abstract: 290/300 words

32 Main text: 2581/4000 words
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Abstract

Objectives

Computerized physician order entry (CPOE) systems facilitate the review of medication orders by pharmacists. Reports have emerged that show conception flaws or the misuse of CPOE systems generate prescribing errors. We aimed to characterize pharmacist interventions (PIs) triggered by prescribing errors identified as system-related errors (SREs) in French hospitals.

Design

This was a cross-sectional observational study based on PIs prospectively documented in the Act-IP© observatory database from January 2014 to December 2018.

Setting

PISREs from 319 French computerized healthcare facilities were analyzed.

Participants

Among the 319 French hospitals, 232 (72.7%), involving 652 (51%) pharmacists, performed SRE interventions.

Results

Among the 331,678 PIs recorded, 27,058 were qualified as due to SREs (8.2%). The main drug-related problems associated with PISREs were suprathereapeutic (27.5%) and subtherapeutic dosage (17.2%), non-conformity with guidelines/contraindications (22.4%), and improper administration (17.9%). The PI prescriber acceptance rate was 78.9% for SREs versus 67.6% for other types of errors. Concerning the certification status of CPOE systems, the PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems. The PISRE ratio for senior pharmacists was 9.2% and that for pharmacy residents 5.4%. Concerning prescriptions made by graduate prescribers and those made by residents, the PISRE ratio was 8.4 % and 7.8%, respectively.

Conclusion

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3 Computer-related prescribing errors are common. The PI acceptance rate by prescribers was higher than
4 that observed for PIs that were not CPOE related. This suggests that physicians consider the potential
5 clinical consequences of SREs for patients to be more frequently serious than interventions unrelated to
6 CPOE. CPOE medication review requires continual pharmacist diligence to catch these errors. The
7 significantly lower PISRE ratio for certified software should prompt patient safety agencies to undertake
8 studies to identify the safest software and discard software that is potentially dangerous.
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Article Summary

Strengths and limitations of this study

- This study provides an overview of prescribing issues related to the use of CPOE systems at the national level.
- Beyond this large register of prescribing problems related to CPOE use, this is the first study to evaluate pharmacist interventions in daily practice for such a large sample of interventions, pharmacists, and hospitals.
- This study focuses on declarative data based on interventions performed by hospital pharmacists.
- These pharmacist interventions highlight prescription problems, but they are not exhaustive.

1. Introduction

Every day, numerous hospitalized patients are subject to drug-related problems (DRPs), resulting in suboptimal therapy, suffering, and decreased quality of life, as well as high healthcare costs for society [1, 2]. Computerized physician order entry (CPOE) systems, along with clinical decision support systems, improve the safety, quality, and value of patient care [3]. According to a meta-analysis, CPOE systems have reduced hospital medication errors by approximately 12.5% [10.6-14.4%][4]. However, CPOE systems also have the potential to introduce or contribute to errors. Indeed, new mechanisms that lead to prescription errors have been identified with CPOE: wrong patient selection, failure to report drug allergies, incorrect entry or wrong selection of medication, dose, route, or time of administration, and confusing free-text comments [5-10].

In France, as in other countries, various incentives and requirements have been put in place to encourage computerized drug prescribing, such as France's "Digital Hospital" program [11]. Since the 2000s, prescribing errors associated with the use of CPOE have been slowly coming to light as healthcare has become increasingly computerized [9]. Compared to handwritten prescriptions, the analysis of electronic prescriptions requires a particular effort on the part of pharmacists and other health professionals to detect errors [9]. System-related errors (SREs) are defined as those in which the electronic prescribing system functionality or design contributed to the error, with little possibility that another cause, such as lack of knowledge, produced the error. For example, an order for an inappropriate drug located on a drop-down menu next to a likely drug selection is a system-related error [12].

A pharmacist intervention (PI) due to a SRE is defined as any PI resulting from the identification of a prescribing error by a pharmacist that would probably not have occurred in the context of a handwritten prescription and of which at least one cause is related to the use of a computer (software system configuration issue, software functionality issue, or software misuse) [13-16].

Most studies concerning PIs triggered by system-related prescribing errors were conducted within a single hospital [17-19]. As a result, it is not possible to assess the extent of prescribing errors related to electronic systems or draw conclusions about subsequent PIs at a national level.

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3 In 2003, the French Society of Clinical Pharmacy (SFPC) developed and validated a tool for classifying
4 and documenting clinical PIs [20]. This tool allows the reporting of DRPs and PIs performed during the
5 daily review of medication orders [24]. In 2006, a website, Act-IP©, was created with the objectives to
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7 (a) create a documentation system that is freely accessible to any pharmacist, through the French Society
8 of Clinical Pharmacy Web site (<http://www.actip.sfpc.eu/actip/index/ficheip/>) and (b) pool the data
9 recorded by all pharmacists to conduct epidemiological studies concerning DRPs detected by
10 pharmacists [21]. The pooling of PIs constitutes an observatory of clinical pharmacy practices, called
11 the “Act-IP© Observatory”.

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21 The aim of this study was to characterize PIs triggered due to SREs in French hospitals between 2014
22 and 2018. Our secondary objective was to determine the physician acceptance rate and its frequency
23 according to the certification status (certified versus non-certified) of the CPOE systems.
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28 **2. Methods**

29 *2.1. Study design*

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32 This was a cross-sectional observational study using PIs prospectively documented in the Act-IP©
33 observatory over a five-year period from January 1, 2014 to December 31, 2018. The main outcome was
34 a PI due to a SRE (PISRE) reported by French hospital pharmacists on the Act-IP© observatory. Ethical
35 approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-
36 Ferrand, IRB 5891).
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43 *2.2. Data sources*

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45 The data comes from the Act-IP© Observatory. Based on the SFPC criteria, using the report form
46 developed and validated for routine documentation of the PIs, Act-IP© users completed the online report
47 form notifying the date, type of DRP, PI, type of drug involved (according to the ATC (Anatomical
48 Therapeutic Chemical) classification), acceptance of the intervention by the prescriber, and free-text
49 details of the context. Ten categories were determined for DRPs and seven for PIs (Appendix 1). A PI
50 was considered to be “accepted” if the physician took it into account and modified the prescription as
51 suggested by the pharmacist or “refused” if the prescription remained unchanged, including cases of
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3 expressed refusal by the prescriber. If acceptance of the intervention was impossible to ascertain (i.e.
4 discharged patients or those transferred to another ward before acceptance), the PI was noted as “not
5 assessable”. The pharmacist’s academic background, hospital characteristics, and software used were
6 documented online by the pharmacist when he/she registered onto the Act-IP© website. Since July 2013,
7 pharmacists have been able to indicate whether the DRP was “related to the electronic system” or not
8 for each registered PI. For the purpose of this study, DRPs identified as “related to the electronic system”
9 were considered to be PISREs.
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18 French law made the certification of CPOE systems mandatory on December 29, 2011. However, two
19 decrees abolished this obligation in 2017. Certification is now based on the sole initiative of the software
20 developer. Forty-eight hospital CPOE software packages are currently certified by the agency for patient
21 safety [Haute Autorité de Santé (HAS)] [22]. For our analysis, PIRSEs were classified according to the
22 HAS status of the CPOE system (certified versus not certified).
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30 2.3. Analysis

31 The PISRE ratio was estimated relative to the total number of PIs. Proportions were compared using the
32 chi-square test. PISREs coded as “refused” or “not assessable” were combined and compared to the
33 accepted PISREs. Probability values < 0.001 were considered to be statistically significant. Statistical
34 analyses were performed using Stata 13 (Stata Corporation, College Station, Texas, USA). Several
35 qualitative examples are given to illustrate PISREs.
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43 4. Results

44 From January 2014 to December 2018, 331,678 PIs were entered into the Act-IP© observatory. Among
45 them, 27,058 (8.2%) were indicated to be system-related prescribing errors (Figure 1).
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50 Over the study period, 1,219 pharmacists from 319 hospitals recorded PIs in the Act-IP© observatory
51 database. The geographical location of the hospitals involved is shown in Figure 2. Among them, 232
52 (72.7%), involving 652 (51%) pharmacists, performed SRE interventions. Among the 319 hospitals, 87
53 (27.3%) did not qualify any PIs as being due to a SRE. PIs come from 82 software involving 19 certified
54 systems.
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3 The characteristics of the PISREs are summarized in Table 1. The most commonly identified type of
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The characteristics of the PISREs are summarized in Table 1. The most commonly identified type of
DRP was “supratherapeutic dosage”, followed by “non-conformity with guidelines/contraindications”
and “improper administration”. Among the 27,058 PISREs, 78.9% (n = 21,356) were accepted. The
PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p-value < 0.001).
Table 2 presents examples of drug-related problems classified as being triggered by prescribing errors
due to the CPOE system.

5. Discussion

This study provides an overview of prescription problems related to CPOE system used in French
hospitals. It provides insights into the main situations and medications involved in computer-related
prescribing problems detected by pharmacists by providing a broad description of PIs performed during
the daily review of routine medication orders. One strength of this study is that it is based on a large
number of hospitals scattered throughout France, as no prior study of such extent evaluating PIs in daily
practice has been published.

5.1. PISRE rate

Our PISRE rate (8.2%) is within the range reported by Korb-Savoldelli et al. [19]. They analyzed peer-
reviewed studies (n = 14) that quantitatively reported medication-prescription errors related to CPOE.
The prevalence of CPOE system-related medication errors relative to all prescription medication errors
ranged from 6.1 to 77.7% (median = 26.1% [IQR:17.6–42,1]) and was less than 6.3% relative to the
number of prescriptions reviewed. Ours is the first large-scale descriptive study using an observatory
hospital pharmacy practice database to study computer-related prescribing errors.

5.2. DRPs induced by CPOE

The main category of DRPs identified as PISREs were supratherapeutic (27.5%, 7,436) and
subtherapeutic dosage (17.2%, 4,646), non-conformity to guidelines/hospitals' drug formularies (22.4%,
6,069) (i.e. medication selection non-compliant with the hospital drug formulary), and improper
administration (17.9%, 4,838) (i.e. incorrect or no formulation, wrong timing). According to Korb-
Savoldelli et al., all studies reported “wrong dose” and “wrong drug” errors [19], with the “wrong dose”

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3 error being that most frequently reported (from 7 to 67.4%, median = 31.5% [IQR:20.5–44.5]). Many of
4 the prescription errors due to CPOE systems can have serious consequences for patients, depending on
5 the clinical circumstances. Although some of are unlikely to occur (e.g. IV ketoprofen 150 ampoules/day
6 instead of 150 mg/d), they nevertheless illustrate flaws in certain CPOE systems [23]. However, our
7 data do not allow the discrimination between software errors, connection problems, and human error.
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13 14 15 *5.3. CPOE systems*

16 The proportion of PIs triggered by software-related prescription errors was higher for non-certified
17 (9.4%) than certified software (5.5%). In France, certification tests produced by the HAS are intended
18 to technically assess the functionality of the software in various situations, as the CPOE evaluation
19 methodology simulates various clinical scenarios [24]. French regulations do not require CPOE
20 developers to carry out usability studies before the systems are marketed. Nevertheless, despite the
21 limitations of this type of certification criteria, which have already been highlighted [25], our results
22 show that prescribing with CPOE-certified systems results in fewer prescription errors than prescribing
23 with non-certified software. These results are consistent with those of other studies, i.e. all software is
24 not equal and some is safer than others [26-28].
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36 37 *5.4. Prescribers*

38 The PISRE ratio was higher for prescriptions made by graduate prescribers (8.4%) than medical
39 residents (7.8%) (p-value < 0.001). This finding is, at first glance, counterintuitive, as one would expect
40 that a prescriber who has been practicing for several years in the same health facility would make fewer
41 CPOE-related prescription errors with the software than a resident who has only been using the software
42 for a few months. Observational studies show that medical residents make most prescriptions and
43 transcribe them to the software prescription instructions of senior prescribers during the medical
44 examination [29]. It is thus possible that, in some hospitals, senior physicians are only occasional users
45 of the prescription software. According to Nerich et al., the occasional use of software (< 1 prescription
46 per day) is a risk factor for prescription error (OR = 3.85, 95% CI [2.08-7.14]) [30]. Tolley described
47 how a junior doctor remarked that there was no one he could ask for help with using the ePrescribing
48 system, as he was “the most experienced person on this floor with regards to the ePrescribing system”.
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3 She also described how one consultant admitted she had not “learnt how to prescribe properly” because
4 she did not “use the system often enough and regularly enough to know the quirks and tweaks”. This
5 consultant relied on her junior staff to prescribe on the system [31].
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10 *5.5. Act-IP© Pharmacist’ users*

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12 The PISRE ratio for senior pharmacists (9.2%) was higher than that of pharmacy residents (5.4%). This
13 is consistent with the results of a study performed in a UK teaching hospital showing that the likelihood
14 of senior pharmacists identifying errors was greater than that of junior pharmacists [32] and in
15 accordance with our expectations. A study concerning French pharmacy students showed that they trust
16 the contribution of computerization to healthcare without critical analysis. This results in overconfidence
17 in the computer tool, perceived to be reliable, and makes users less willing to search for the errors
18 produced by this tool [33]. They are therefore not aware that the review of computerized prescription
19 orders requires additional effort to identify prescription errors. This is the consequence of the lack of
20 teaching/training about this subject in French pharmacy schools. This situation contrasts strikingly with
21 the content of the curricula taught in the United Kingdom and USA, for example [34,35].
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34 *5.6. Prescriber Acceptance rate*

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36 The rate of acceptance of PISREs by prescribers was 78.9% versus 67.6% for other PIs. This suggests
37 that prescribers recognize the relevance of such interventions due to the potential clinical consequences
38 of such prescription errors. This rate varies from 65.9 to 92% in studies of drug errors induced by
39 computerized prescription [10, 14], suggesting that physicians consider the potential clinical
40 consequences of SRE to patients to be more frequently serious than interventions unrelated to CPOE. In
41 light of our findings, a CPOE-related prescription error is a factor that favors acceptance of the
42 PI. These points warrant further studies.
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51 *5.7. Limits*

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53 Our study had several limitations. First, it focused on declarative data based on interventions performed
54 by hospital pharmacists. These PIs highlight prescription problems, but are not exhaustive. However,
55 the large sample size probably provides a relatively precise vision of the problem at the national level.
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3 Second, several pharmacists analyzing the same drug prescriptions may not all track down the same
4 problems. For example, the mean percentage of detected prescribing errors was 59% in a study involving
5 57 hospital pharmacies, with a broad range of 7 to 88% between pharmacies [36]. In the absence of
6 specific studies to determine the performance of pharmacists in detecting prescription errors induced by
7 CPOE-system flaws and misuse, we are reduced to simply assuming that such variation may be
8 observed. In addition, there are various definitions of PISREs in the literature [13-16]. This suggests
9 that there is a certain level of subjectivity when a pharmacist characterizes a PI as being related to a
10 computer-generated prescription. Among hospitals that entered the PIs on Act-IP©, 87 never qualified
11 a PI as being a SRE. There are two possible explanations for this observation. The first, and relatively
12 unlikely, is that the software is near perfect and that there was no misuse by prescribers. For example,
13 the absence of PISREs for these hospitals could result from the absence of computer-related errors due
14 to the use of high-performance software and/or appropriately trained prescribers. The second possibility
15 is that pharmacists do not establish a link between certain prescription errors and misuse of the
16 prescription software and/or its design flaws. Conversely, a high rate of PISREs for a given hospital
17 may result from software conception flaws and/or misuse of the software by prescribers and pharmacists
18 who are very aware of the role of CPOE-systems in generating prescription errors. Regardless of the
19 considered scenario, it is important to remember that differences in PISRE rates may also be due to the
20 quality of the training provided. Studies have shown that insufficient training on an ePrescribing system
21 can contribute to errors [37, 38]. Tolley illustrated how pharmacists did not receive any formal training
22 about the system after starting at a hospital trust and observed that no formal training was offered when
23 pharmacists changed roles. It has been shown that training plays a role in the users' experience but there
24 is a lack of published research in this area [31]. Thus, further research is warranted to lift the veil on
25 these unknowns.

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52 Our results highlight that prescribing problems related to computer software are common in France.
53 This is a concern that affects most (if not all) CPOE systems currently being used and therefore all
54 hospitals, to varying degrees. Identifying the most dangerous software appears to be a priority to
55 improve the quality and safety of patient care.

6. Conclusion

Computer-related prescribing errors are common, with wrong dose being the most frequent type of error. Such errors concern all drug classes and have potentially serious adverse clinical consequences if they are not intercepted by pharmacists when performing their daily medication review. The message appears to be well received by prescribers who agree to change their prescription more frequently than for PIs not related to CPOE use. CPOE medication review requires additional pharmacist diligence to catch such errors. As the PISRE ratio is significantly lower for certified software, patient safety agencies should undertake studies to identify the safest software so as to discard software that is potentially dangerous.

Author contributions

Manon Videau and Bruno Charpiat designed the study, performed the statistical analyses, interpreted the results, and wrote the first version of the manuscript. Céline Vermorel contributed to the design of the study, performed the statistical analyses, and revised the manuscript. Jean-Luc Bosson contributed to the design of the study and revised the manuscript. Ornella Conort contributed substantially to the interpretation of the data and contributed to the revision of the manuscript. Pierrick Bedouch designed the study, performed the statistical analyses, interpreted the results, and revised the manuscript.

Acknowledgements

The authors would like to thank the team of THEMAS and VIP working group for assistance in this project. We thank the clinical pharmacists of the SFPC Act-IP© group who participated in the data collection.

Members of the working group “Valorization of Pharmaceutical Interventions/ Valorisation des Interventions Pharmaceutiques – Act-IP©” of the French Society for Clinical Pharmacy: Pierrick Bedouch (Grenoble), Magalie Bourdelin (Villefranche-sur-Saone), Bruno Charpiat (Lyon), Ornella Conort (Paris), Julien Gravoulet (Leyr), Audrey Janoly-Dumenil (Lyon), Michel Juste (Epernay), and Céline Mongaret (Reims).

Clinical pharmacists of the SFPC Act-IP© group who participated in the data collection: S. Abkhtaoui-Couriat (Corbie), B. Allard-Latour (Saint-Genis-Laval), C. Andrieu (Saint-Etienne), X. Armoiry (Lyon), E. Armoiry (Villeurbanne), D. Attivi (Neufchâteau), L. Audibert (Alix), A. Barbet (Amiens), M. Bascoulergue (Aulnay sous bois), C. Basselin (Saint-Genis-Laval), F. Baud (Paris), P. Bedouch (Grenoble), M. Belhout (Amiens), S. Benhaoua (Saint Denis), J. Beny (Alix), S. Berthet (Lyon), J. Berthou (Besancon), D. Bichard (Besancon), A.C. Blandin (Besancon), E. Blondel (Aix les Bains), S. Bonn Loue (Luneville), A. Bonvin (Lyon), F. Bouchand (Garches), P. Bouniot (Francheville), M. Bourdelin (Besancon), C. Bouret (Lyon), L. Bourguignon (Lyon), C. Bourne (Saint-Egrève), M. Bouteille (Lyon), J. Burdin (Lyon), C. Bureau (Alix), C. Bureau (Villeurbanne), M. Burgin (Luneville), M. Buyse (Paris), E. Cabaret (Hyerres), D. Cabelguenne (Pierre Benite), C. Capele (Saint André lez Lille), D. Carli (Vienne), I. Carpentier (Saint-Genis-Laval), E. Chambrey (Rang-du-Fliers), S. Chantel (Pierre Benite), N. Charhon (Vienne), B. Charpiat (Lyon), M. Chaumont (Le Chesnay), K. Civiletti (Martigues), B. Clerc (Besancon), M. Cleve (Vienne), R. Colomb (Saint-Etienne), C. Combe (Saint-Etienne), O. Conort (Paris), R. Contreras (Besancon), S. Crepin (Limoges), M. Creusat-Aube (Illkirch-Graffenstaden), A. Cuoq (Lyon), C. Decourcelle (Lomme), T. Delanoy (Vienne), C. Derharoutunian (Vienne), A. Deronze (Lyon); M. Desseignet (Lyon), S. Diallo (Le Chesnay), L. Dietrich (Strasbourg), A. Dory (Strasbourg), J. Dos-Reis (Paris), N. Duarte (Draveil), M.O. Duzanski (Strasbourg), L. Escofier (Mayenne), F. Fabre (Clermont-Ferrand), S.

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11 Chesnay), M. Le Duff (Rennes), R. Lecointre (Saint-Etienne), J. Lecompte (Grasse), M. Lefebvre
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15 Etienne), D. Matanza (Francheville), V. Mermet (Saint-Genis-Laval), C. Mouchoux (Villeurbanne), Y.
16 Nivoix (Strasbourg), A. Orly (Paris), E. Orng (Lyon), A. Oufella (Aulnay Sous Bois), I. Paillole
17 (Toulouse), D. Pallot (Saint Denis), A. Papon (Lyon), L. Parnet (Paris), M. Paysant (Saint-Genis-
18 Laval), E. Perrier-Cornet (Illkirch-Graffenstaden), S. Perrin (Besancon), D. Peynaud (Lyon), B.N.
19 Pham (Vienne), D. Piney (Luneville), A. Pohyer (Montpellier), C. Porot (Besancon), J. Pouzoulet
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21 (Besancon), C. Remonnay (Besancon), M. Remy (Ho-Chi-Minh Ville), M. Rhalimi (Chaumont-en-
22 Vexin), C. Rioufol (Pierre Benite), A. Robelet (Paris), S. Roche (Epernay), F.X. Rose (Saint-Avé), R.
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26 Laval), N. Vantard (Lyon), N. Vauvarin (Joigny), S. Vernardet (Annonay), D. Viard (Besancon), C.
27 Vignand (Lyon), C. Villa (Vienne), P. Vonna (Epernay), S. Wacker (Strasbourg), N. Wereszczynski
28 (Grasse), and L. Zerhouni (Paris).

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45 We thank Kévin Mastrotillo, technical consultant of the Act-IP© observatory, for his contribution to the
46 data extraction and data management.

47 48 49 **Funding statement**

50 This research received no specific grant from any funding agency in the public, commercial, or not-for-
51 profit sectors.

52
53
54 This study was supported by The French Society of Clinical Pharmacy, a nonprofit and independent
55 foundation for clinical pharmacy research and development.

56 57 58 **Statement on conflicts of interest**

59 The authors declare that they have no conflicts of interest.
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3 **Patient consent for publication**

4 Not required
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7 **Ethical approval**

8 Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne,
9 Clermont-Ferrand, IRB 5891).
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3 **Summary table**
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5 Table 1. Characteristics of Act-IP© observatory PISREs and PIs between 2014 to 2018.
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8 Table 2. Examples of PISREs and drug-by-drug related problems (N = 27,822).
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Summary Figures

Figure 1. Flowchart, PISRE selection in Act-IP© observatory (extraction on 11th February 2019)

Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018

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Table 1. Characteristics of all Act-IP© observatory PISREs and PIs between 2014 to 2018.

Characteristics	PISRE	PI total	ratio	
	(N = 27,058)	(N = 331,678)	%	p-value
Drug related problem				
Supratherapeutic dosage	7,436	72,912	10.2	
Non-conformity with guidelines/hospital formulary	6,069	86,072	7.1	
Improper administration	4,838	49,184	9.8	
Subtherapeutic dosage	4,646	29,105	16.0	
Untreated indication	2,366	30,138	7.9	
Drug without indication	1,302	27,690	4.7	
Drug interaction	161	18,267	0.9	
Drug monitoring	111	10,303	1.1	
Adverse drug reaction	65	5,854	1.1	
Failure to receive drug	64	2,153	3.0	
Type of intervention				
Dose adjustment	7,447	89,390	8.3	
Drug switch	6,649	85,033	7.8	
Drug discontinuation	5,220	62,715	8.3	
Optimization of administration	4,123	32,558	12.7	
Addition of new drug	3,228	34,198	9.4	
Change of administration route	213	6,978	3.1	
Drug monitoring	178	20,806	0.9	
Prescriber Acceptance				
Interventions accepted	21,356	227,223	9.4	< 0.001*

Interventions not accepted	3,068	51,957	5.9	
Not assessable	2,634	52,498	5.0	
Prescriber's status				
Senior	15,152	180,863	8.4	< 0.001
Resident	11,765	150,136	7.8	
Midwife**	141	679	20.8	
Pharmacist's status				
Senior	21,271	231,519	9.2	< 0.001
Resident	4,640	86,728	5.4	
Not assessable**	1,147	13,431	8.5	
CPOE system status				
Not certified	21,385	226,878	9.4	< 0.001
Certified	5,549	101,516	5.5	
Not assessable**	124	3,284	3.8	
Total	27,058	331,678	8.2	

PI: pharmacist's intervention, PISRE: pharmacist's intervention identified as due to a system-related error, CPOE: computerized prescriber order entry

**Not accepted and not assessable interventions have been regrouped for chi-square test; **excluded from the chi-square analysis*

Table 2. Examples of PISRE and drug by drug-related problems (N = 27,822)

Drug-related problem	Number of drugs involved – n (%)	Most frequent drug (generic name) (n)	Examples
Supratherapeutic dosage	7,571 (27.2)	Paracetamol (1,043), tramadol (223), pantoprazole (212), enoxaparin (204)	“Duplicate prescription: 1 in predefined protocol and 1 outside predefined protocol = 8 g of paracetamol per day”
Non-conformity to guidelines/contraindication	6,212 (22.3)	Alfuzosin (515), dutasteride (493), silodosin (469), paracetamol (460), tamsulosin (373)	“prescription of dutasteride, which is not in the hospital drug formulary, with a risk of treatment omission”
Improper administration	4,972 (17.9)	Paracetamol (277), levothyroxine (130), pregabalin (130), methylprednisolone (124)	“selection of IV terbutaline for administration by aerosol”
Subtherapeutic dosage	4,738 (17.0)	Enoxaparin (965), heparin (450), tinzaparin (186), paracetamol (140), macrogol (105),	“Enoxaparin 4000 UI/0.4 ml prescription: 1 IU instead of 1 syringe”
Untreated indication	2,441 (8.8)	acetylsalicylic acid (82), pregabalin (80), paracetamol (74), tinzaparin (69), bisoprolol (69), enoxaparin (68),	“prescription of pregabalin not renewed (hospital stay longer than the duration of the prescription)”

1 2 3 4 5 6 7 8 9 10 11 12 13 14	Drug without indication	1,340 (4.8)	Pantoprazole (66), amoxicillin and beta-lactamase inhibitor (44), cholecalciferol (40), ceftriaxone (34), enoxaparin (30)	“duplicate prescription of pantoprazole per os and IV by two prescribers”
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	Drug interaction	262 (0.9)	Amiodarone (27), fluindione (9), levothyroxine (9)	“cordarone and escitalopram combination contra-indicated: risk of “torsade de pointes” not modified during drug interaction alert with Clinical Decision Support System (CDSS)”
30 31 32 33 34 35	Drug monitoring	124 (0.4)	Fluindione (25), polystyrene sulfonate (8), paracetamol (4)	
36 37 38 39 40 41 42 43 44	Adverse drug reaction	70 (0.3)	Polystyrene sulfonate (11), furosemide (6), atorvastatin (4), tramadol (3), macrogol (3)	“increased risk of adverse reactions by the combination of atorvastatin and fenofibrate”
45 46 47 48 49 50 51 52 53	Failure to receive drug	92 (0.3)	Esomeprazole (3), cholecalciferol (3), acetylsalicylic acid (3), furosemide (3)	“Prescription of furosemide not appearing on the nursing plan”

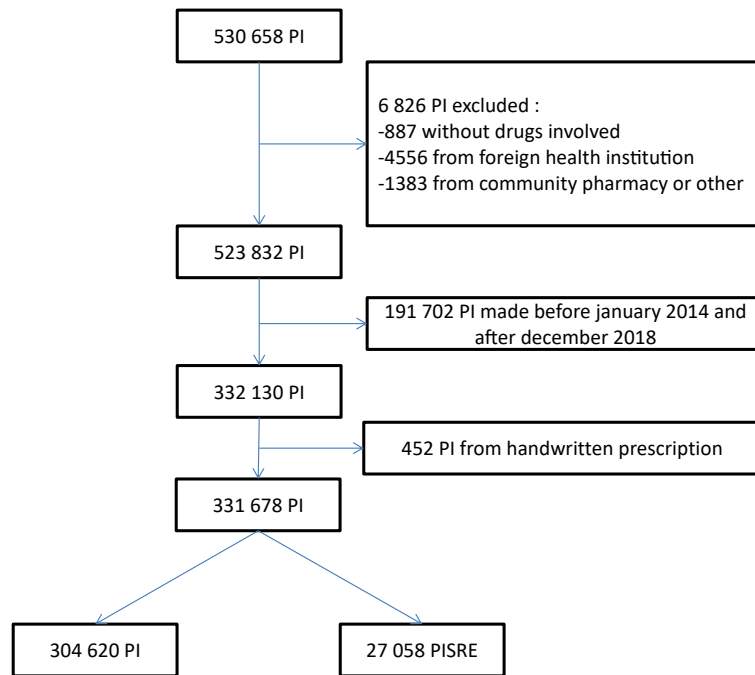
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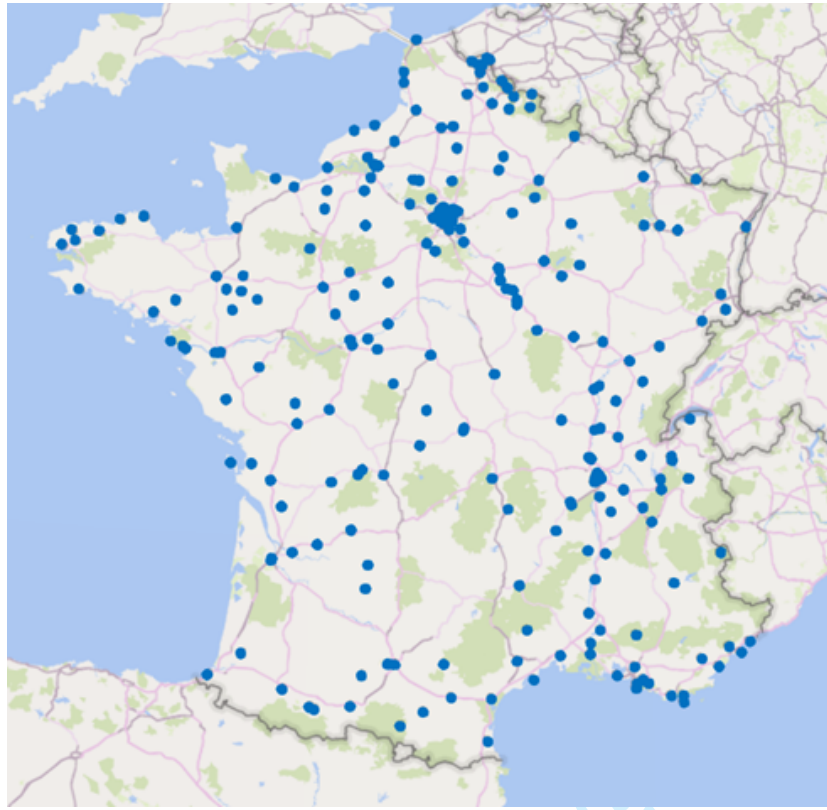
Figure 1. Flowchart, PISRE selection in Act-IP© observatory (extraction on 11th February 2019)



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Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018



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Appendix 1. The Pharmacist intervention form

PHARMACIST INTERVENTION FORM📅 **DATE:** / /📁 **INTERVENTION N°:**🏢 **CENTER N°:****PATIENT:**

Last name:

First name:

Age: years / Weight: Kg

Sex: M F**Hospital ward:**

- Psychiatry
 Acute care
 Long term care
 Rehabilitation ward

1- DRUG RELATED PROBLEM (1 choice):

- 1 Non conformity to guidelines or contra-indication
2 Untreated indication
3 Subtherapeutic dosage
4 Supratherapeutic dosage
5 Drug without indication
6 Drug interaction
 To be taken into account
 Use with caution
 Combination to be avoided
 Combination contra-indicated
 Documented but not in VIDAL®
7 Adverse drug reaction
8 Improper administration
9 Failure to receive drug
10 Drug monitoring

2- INTERVENTION (1 choice):

- 1 Addition of a new drug
2 Drug discontinuation
3 Drug switch
4 Change of administration route
5 Drug monitoring
6 Administration modalities optimisation
7 Dose adjustment

DRUG NAME (INN):**3- DRUG CLASSIFICATION (ATC):**

- A Alimentary tract & metabolism
 B Blood & blood forming organs
 C Cardiovascular system
 D Dermatological
 G Genito urinary system & sex hormones
 H Systemic hormonal preparations
 J Anti-infective for systemic use
 L Anti-neoplastic & immunomodulating agents
 M Musculo-skeletal system
 N Nervous system
 P Antiparasitic products
 R Respiratory system
 S Sensory organs
 V Various

4- INTERVENTION FOLLOW-UP:

- Accepted
 Non accepted
 Non assessable

DETAILS ⇒ If necessary, give details on any aspects of the detected DRP and describe the intervention, precisely**Context****Problem****Intervention**

BMJ Open

Characteristics of Pharmacist's interventions triggered by prescribing errors related to computerized physician order entry in French hospitals: a cross-sectional observational study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-045778.R1
Article Type:	Original research
Date Submitted by the Author:	26-Jul-2021
Complete List of Authors:	Videau, Manon; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes; CHU Grenoble Alpes, Pharmacie Charpiat, Bruno; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes; Hopital de la Croix-Rousse, Pharmacie Vermorel, Céline; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes Bosson, J.L; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes Conort, Ornella; Hopital Cochin, Pharmacie Bedouch, Pierrick; TIMC-IMAG, CNRS-UMR 5525/ThEMAS/Université Grenoble Alpes; CHU Grenoble Alpes, Pharmacie
Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Health informatics, Health services research, Pharmacology and therapeutics
Keywords:	Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

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3 **Characteristics of Pharmacist’s interventions triggered by prescribing errors related to**
4 **computerized physician order entry in French hospitals: a cross-sectional observational study**
5

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15 members in acknowledgments)
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33 **Keywords:** drug related problem, prescribing error, pharmacist intervention, computerized physician
34 order entry (CPOE)
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39 Abstract: 305/300 words

40 Main text: 2785/4000 words
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Abstract

Objectives

Computerized physician order entry (CPOE) systems facilitate the review of medication orders by pharmacists. Reports have emerged that show conception flaws or the misuse of CPOE systems generate prescribing errors. We aimed to characterize pharmacist interventions (PIs) triggered by prescribing errors identified as system-related errors (SREs) in French hospitals.

Design

This was a cross-sectional observational study based on PIs prospectively documented in the Act-IP© observatory database from January 2014 to December 2018.

Setting

PISREs from 319 French computerized healthcare facilities were analyzed.

Participants

Among the 319 French hospitals, 232 (72.7%) performed SRE interventions, involving 652 (51%) pharmacists.

Results

Among the 331,678 PIs recorded, 27,058 were qualified as due to SREs (8.2%). The main drug-related problems associated with PISREs were suprathereapeutic (27.5%) and subtherapeutic dosage (17.2%), non-conformity with guidelines/contraindications (22.4%), and improper administration (17.9%). The PI prescriber acceptance rate was 78.9% for SREs versus 67.6% for other types of errors. The PISRE ratio was estimated relative to the total number of PIs. Concerning the certification status of CPOE systems, the PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p -value <0.001). The PISRE ratio for senior pharmacists was 9.2% and that for pharmacy residents 5.4% (p -value <0.001). Concerning prescriptions made by graduate prescribers and those made by residents, the PISRE ratio was 8.4 % and 7.8%, respectively (p -value <0.001).

Conclusion

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3 Computer-related prescribing errors are common. The PI acceptance rate by prescribers was higher than
4 that observed for PIs that were not CPOE related. This suggests that physicians consider the potential
5 clinical consequences of SREs for patients to be more frequently serious than interventions unrelated to
6 CPOE. CPOE medication review requires continual pharmacist diligence to catch these errors. The
7 significantly lower PISRE ratio for certified software should prompt patient safety agencies to undertake
8 studies to identify the safest software and discard software that is potentially dangerous.
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For peer review only

Article Summary

Strengths and limitations of this study

- This study provides an overview of prescribing issues related to the use of CPOE systems at the national level.
- Beyond this large register of prescribing problems related to CPOE use, this is the first study to evaluate pharmacist interventions in daily practice for such a large sample of interventions, pharmacists, and hospitals.
- This study focuses on declarative data based on interventions performed by hospital pharmacists.
- These pharmacist interventions highlight prescription problems, but they are not exhaustive.

1. Introduction

Every day, numerous hospitalized patients are subject to drug-related problems (DRPs), resulting in suboptimal therapy, suffering, and decreased quality of life, as well as high healthcare costs for society [1, 2]. Computerized physician order entry (CPOE) systems, along with clinical decision support systems, improve the safety, quality, and value of patient care [3]. According to a meta-analysis, CPOE systems have reduced hospital medication errors by approximately 12.5% IC95% [10.6-14.4%] [4]. However, CPOE systems also have the potential to introduce or contribute to errors. Indeed, new mechanisms that lead to prescription errors have been identified with CPOE: wrong patient selection, failure to report drug allergies, incorrect entry or wrong selection of medication, dose, route, or time of administration, and confusing free-text comments [5-10].

In France, as in other countries, various incentives and requirements have been put in place to encourage computerized drug prescribing, such as France's "Digital Hospital" program [11]. Since the 2000s, prescribing errors associated with the use of CPOE have been slowly coming to light as healthcare has become increasingly computerized [9]. Compared to handwritten prescriptions, the analysis of electronic prescriptions requires a particular effort on the part of pharmacists and other health professionals to detect errors [9]. System-related errors (SREs) are defined as those in which the electronic prescribing system functionality or design contributed to the error, with little possibility that another cause, such as lack of knowledge, produced the error. For example, an order for an inappropriate drug located on a drop-down menu next to a likely drug selection is a system-related error [12].

A pharmacist intervention (PI) due to a SRE is defined as any PI resulting from the identification of a prescribing error by a pharmacist that would probably not have occurred in the context of a handwritten prescription and of which at least one cause is related to the use of a computer (software system configuration issue, software functionality issue, or software misuse) [13-16].

Most studies concerning PIs triggered by system-related prescribing errors were conducted within a single hospital [17-19]. As a result, it is not possible to assess the extent of prescribing errors related to electronic systems or draw conclusions about subsequent PIs at a national level.

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3 In 2003, the French Society of Clinical Pharmacy (SFPC) developed and validated a tool for classifying
4 and documenting clinical PIs [20]. This tool allows the reporting of DRPs and PIs performed during the
5 daily review of medication orders [21]. In 2006, a website, Act-IP©, was created with the objectives to
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7 (a) create a documentation system that is freely accessible to any pharmacist, through the French Society
8 of Clinical Pharmacy Web site (<http://www.actip.sfpc.eu/actip/index/ficheip/>) and (b) pool the data
9 recorded by all pharmacists to conduct epidemiological studies concerning DRPs detected by
10 pharmacists [22]. The data recording is on a voluntary basis. The pooling of PIs constitutes an
11 observatory of clinical pharmacy practices, called the “Act-IP© Observatory”.

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21 The aim of this study was to characterize PIs triggered due to SREs in French hospitals between 2014
22 and 2018. Our secondary objective was to determine the physician acceptance rate and its frequency
23 according to the certification status (certified versus non-certified) of the CPOE systems.

28 **2. Methods**

29 *2.1. Study design*

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32 This was a cross-sectional observational study using PIs prospectively documented in the Act-IP©
33 observatory over a five-year period from January 1, 2014 to December 31, 2018. The main outcome was
34 a PI due to a SRE (PISRE) reported by French hospital pharmacists on the Act-IP© observatory. Ethical
35 approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-
36 Ferrand, IRB 5891).

43 *2.2. Data sources*

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46 The data comes from the Act-IP© Observatory. Based on the SFPC criteria, using the report form
47 developed and validated for routine documentation of the PIs, Act-IP© users completed the online report
48 form notifying the date, type of DRP, PI, type of drug involved (according to the ATC (Anatomical
49 Therapeutic Chemical) classification), acceptance of the intervention by the prescriber, and free-text
50 details of the context. Ten categories were determined for DRPs and seven for PIs (Appendix 1). A PI
51 was considered to be “accepted” if the physician took it into account and modified the prescription as
52 suggested by the pharmacist or “refused” if the prescription remained unchanged, including cases of
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3 expressed refusal by the prescriber. If acceptance of the intervention was impossible to ascertain (i.e.
4 discharged patients or those transferred to another ward before acceptance), the PI was noted as “not
5 assessable”. The pharmacist’s academic background, hospital characteristics, and software used were
6 documented online by the pharmacist when he/she registered onto the Act-IP© website. To be registered
7 onto the Act-IP© website, pharmacists had prior to accept terms and conditions and allowed the use of
8 their data for analysis. Since July 2013, pharmacists have been able to indicate whether the DRP was
9 “related to the electronic system” or not for each registered PI. For the purpose of this study, DRPs
10 identified as “related to the electronic system” were considered to be PISREs.

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12 French law made the certification of CPOE systems mandatory on December 29, 2011. However, two
13 decrees abolished this obligation in 2017. Certification is now based on the sole initiative of the software
14 developer. Forty-eight hospital CPOE software packages are currently certified by the agency for patient
15 safety [Haute Autorité de Santé (HAS)] [23]. For our analysis, PIRSEs were classified according to the
16 HAS status of the CPOE system (certified versus not certified).

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2.3. Analysis

The PISRE ratio was estimated relative to the total number of PIs. Proportions were compared using the
chi-square test. PISREs coded as “refused” or “not assessable” were combined and compared to the
accepted PISREs. Probability values < 0.001 were considered to be statistically significant. Statistical
analyses were performed using Stata 13 (Stata Corporation, College Station, Texas, USA). Several
qualitative examples are given to illustrate PISREs.

4. Results

From January 2014 to December 2018, 331,678 PIs were entered into the Act-IP© observatory. Among
them, 27,058 (8.2%) were indicated to be system-related prescribing errors (Figure 1).

Over the study period, 1,219 pharmacists from 319 hospitals recorded PIs in the Act-IP© observatory
database. The geographical location of the hospitals involved is shown in Figure 2. Among them, 232
(72.7%), involving 652 (51%) pharmacists, performed SRE interventions. Among the 319 hospitals, 87

(27.3%) did not qualify any PIs as being due to a SRE. PIs come from 82 software involving 19 certified systems.

The characteristics of the PISREs are summarized in Table 1. The most commonly identified type of DRP was “supratherapeutic dosage”, followed by “non-conformity with guidelines/contraindications” and “improper administration”. Among the 27,058 PISREs, 78.9% (n = 21,356) were accepted. The PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p-value < 0.001). Appendix 2 presents examples of drug-related problems classified as being triggered by prescribing errors due to the CPOE system. For example: Prescription errors can be the same whether they are handwritten prescriptions or computer-assisted prescriptions. Indeed, the combination of amiodarone and escitalopram can appear on handwritten prescription because of prescriber’s lack of knowledge. With CPOE, Clinical Decision Support System (CDSS) tool can alert on drug-drug interaction. However, high frequency of alerts and dozens of daily interruptions for clinicians are responsible of "alert fatigue" and practitioners override alerts [24]. We can also find duplicate orders, meaning the same drug is prescribed twice. With predefined order set, it is common to have 8 grams of paracetamol per day prescribed. Duplication errors are partially explained by the fact that many screens are required to view patient medications, making intrinsically difficult to spot duplicates [25].

5. Discussion

This study provides an overview of prescription problems related to CPOE systems used in French hospitals. It provides insights into the main situations and medications involved in computer-related prescribing problems detected by pharmacists by providing a broad description of PIs performed during the daily review of routine medication orders. Thus one strength of this study is that it is based on a large number of hospitals scattered throughout France, as no prior study of such extent evaluating PIs in daily practice has been published.

5.1. PISRE rate

Our PISRE rate (8.2%) is within the range reported by Korb-Savoldelli et al. [19]. They analyzed peer-reviewed studies (n = 14) that quantitatively reported medication-prescription errors related to CPOE.

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3 The prevalence of CPOE system-related medication errors relative to all prescription medication errors
4 ranged from 6.1 to 77.7% (median = 26.1% [IQR:17.6–42,1]) and was less than 6.3% relative to the
5 number of prescriptions reviewed. Ours is the first large-scale descriptive study using an observatory
6 hospital pharmacy practice database to study computer-related prescribing errors.
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11 12 *5.2. DRPs induced by CPOE*

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14 The main category of DRPs identified as PISREs were suprathereapeutic (27.5%, 7,436) and
15 subtherapeutic dosage (17.2%, 4,646), non-conformity to guidelines/hospitals' drug formularies (22.4%,
16 6,069) (i.e. medication selection non-compliant with the hospital drug formulary), and improper
17 administration (17.9%, 4,838) (i.e. incorrect or no formulation, wrong timing). According to Korb-
18 Savoldelli et al., all studies reported “wrong dose” and “wrong drug” errors [19], with the “wrong dose”
19 error being that most frequently reported (from 7 to 67.4%, median = 31.5% [IQR:20.5–44.5]). Many of
20 the prescription errors due to CPOE systems can have serious consequences for patients, depending on
21 the clinical circumstances. Although some of are unlikely to occur (e.g. IV ketoprofen 150 ampoules/day
22 instead of 150 mg/d), they nevertheless illustrate flaws in certain CPOE systems [26]. However, our
23 data do not allow the discrimination between software errors, connection problems, and human error.
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36 *5.3. CPOE systems*

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38 The proportion of PIs triggered by software-related prescription errors was higher for non-certified
39 (9.4%) than certified software (5.5%). In France, certification tests produced by the HAS are intended
40 to technically assess the functionality of the software in various situations, as the CPOE evaluation
41 methodology simulates various clinical scenarios [27]. French regulations do not require CPOE
42 developers to carry out usability studies before the systems are marketed. Nevertheless, despite the
43 limitations of this type of certification criteria, which have already been highlighted [28], our results
44 show that prescribing with CPOE-certified systems results in fewer prescription errors than prescribing
45 with non-certified software. These results are consistent with those of other studies, i.e. all software is
46 not equal and some is safer than others [29-31].
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58 *5.4. Prescribers*

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3 The PISRE ratio was higher for prescriptions made by graduate prescribers (8.4%) than medical
4 residents (7.8%) (p-value < 0.001). This finding is, at first glance, counterintuitive, as one would expect
5 that a prescriber who has been practicing for several years in the same health facility would make fewer
6 CPOE-related prescription errors with the software than a resident who has only been using the software
7 for a few months. Observational studies show that medical residents make most prescriptions and
8 transcribe them to the software prescription instructions of senior prescribers during the medical
9 examination [32]. It is thus possible that, in some hospitals, senior physicians are only occasional users
10 of the prescription software. According to Nerich et al., the occasional use of software (< 1 prescription
11 per day) is a risk factor for prescription error (OR = 3.85, 95% CI [2.08-7.14]) [33]. Tolley described
12 how a junior doctor remarked that there was no one he could ask for help with using the ePrescribing
13 system, as he was “the most experienced person on this floor with regards to the ePrescribing system”.
14 She also described how one consultant admitted she had not “learnt how to prescribe properly” because
15 she did not “use the system often enough and regularly enough to know the quirks and tweaks”. This
16 consultant relied on her junior staff to prescribe on the system [34].

33 5.5. Act-IP© Pharmacist' users

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35 The PISRE ratio for senior pharmacists (9.2%) was higher than that of pharmacy residents (5.4%). This
36 is consistent with the results of a study performed in a UK teaching hospital showing that the likelihood
37 of senior pharmacists identifying errors was greater than that of junior pharmacists [35] and in
38 accordance with our expectations. A study concerning French pharmacy students showed that they trust
39 the contribution of computerization to healthcare without critical analysis. This results in overconfidence
40 in the computer tool, perceived to be reliable, and makes users less willing to search for the errors
41 produced by this tool [36]. They are therefore not aware that the review of computerized prescription
42 orders requires additional effort to identify prescription errors. This is the consequence of the lack of
43 teaching/training about this subject in French pharmacy schools. This situation contrasts strikingly with
44 the content of the curricula taught in the United Kingdom and USA, for example [37,38].

57 5.6. Prescriber Acceptance rate

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3 The rate of acceptance of PISREs by prescribers was 78.9% versus 67.6% for other PIs. This suggests
4 that prescribers recognize the relevance of such interventions due to the potential clinical consequences
5 of such prescription errors. This rate varies from 65.9 to 92% in studies of drug errors induced by
6 computerized prescription [10, 14], suggesting that physicians consider the potential clinical
7 consequences of SRE to patients to be more frequently serious than interventions unrelated to CPOE. In
8 light of our findings, a CPOE-related prescription error is a factor that favors acceptance of the
9 PI. These points warrant further studies.
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18 *5.7. Limits*

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20 Our study had several limitations. First, it focused on declarative data based on interventions performed
21 by hospital pharmacists. These data are prospectively enter by pharmacists. There for, these PIs highlight
22 prescription problems, but are not exhaustive. However, as illustrated by publications related to other
23 databases on information technology incidents, despite their limitations, voluntary reports are useful to
24 examine the nature of information technology events [39,40]. And the large sample size probably
25 provides a relatively precise vision of the problem at the national level. Second, several pharmacists
26 analyzing the same drug prescriptions may not all track down the same problems. For example, the mean
27 percentage of detected prescribing errors was 59% in a study involving 57 hospital pharmacies, with a
28 broad range of 7 to 88% between pharmacies [41]. In the absence of specific studies to determine the
29 performance of pharmacists in detecting prescription errors induced by CPOE-system flaws and misuse,
30 we are reduced to simply assuming that such variation may be observed. In addition, there are various
31 definitions of PISREs in the literature [13-16]. This suggests that there is a certain level of subjectivity
32 when a pharmacist characterizes a PI as being related to a computer-generated prescription. Among
33 hospitals that entered the PIs on Act-IP©, 87 never qualified a PI as being a SRE. There are two possible
34 explanations for this observation. The first, and relatively unlikely, is that the software is near perfect
35 and that there was no misuse by prescribers. For example, the absence of PISREs for these hospitals
36 could result from the absence of computer-related errors due to the use of high-performance software
37 and/or appropriately trained prescribers. The second possibility is that pharmacists do not establish a
38 link between certain prescription errors and misuse of the prescription software and/or its design flaws.
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3 Conversely, a high rate of PISREs for a given hospital may result from software conception flaws and/or
4 misuse of the software by prescribers and pharmacists who are very aware of the role of CPOE-systems
5 in generating prescription errors. Regardless of the considered scenario, it is important to remember that
6 differences in PISRE rates may also be due to the quality of the training provided. Studies have shown
7 that insufficient training on an ePrescribing system can contribute to errors [42,43]. Tolley illustrated
8 how pharmacists did not receive any formal training about the system after starting at a hospital trust
9 and observed that no formal training was offered when pharmacists changed roles. It has been shown
10 that training plays a role in the users' experience but there is a lack of published research in this area
11 [34]. Thus, further research is warranted to lift the veil on these unknowns.
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23 Our results highlight that prescribing problems related to computer software are common in France.
24 This is a concern that affects most (if not all) CPOE systems currently being used and therefore all
25 hospitals, to varying degrees. Identifying the most dangerous software appears to be a priority to
26 improve the quality and safety of patient care.
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32 **6. Conclusion**

33 Computer-related prescribing errors are common, with wrong dose being the most frequent type of error.
34 Such errors concern all drug classes and have potentially serious adverse clinical consequences if they
35 are not intercepted by pharmacists when performing their daily medication review. The message appears
36 to be well received by prescribers who agree to change their prescription more frequently than for PIs
37 not related to CPOE use. CPOE medication review requires additional pharmacist diligence to catch
38 such errors. As the PISRE ratio is significantly lower for certified software, patient safety agencies
39 should undertake studies to identify the safest software so as to discard software that is potentially
40 dangerous.
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Author contributions

Manon Videau and Bruno Charpiat designed the study, performed the statistical analyses, interpreted the results, and wrote the first version of the manuscript. Céline Vermorel contributed to the design of the study, performed the statistical analyses, and revised the manuscript. Jean-Luc Bosson contributed to the design of the study and revised the manuscript. Ornella Conort contributed substantially to the interpretation of the data and contributed to the revision of the manuscript. Pierrick Bedouch designed the study, performed the statistical analyses, interpreted the results, and revised the manuscript.

Acknowledgements

The authors would like to thank the team of THEMAS and VIP working group for assistance in this project. We thank the clinical pharmacists of the SFPC Act-IP© group who participated in the data collection.

Members of the working group “Valorization of Pharmaceutical Interventions/ Valorisation des Interventions Pharmaceutiques – Act-IP©” of the French Society for Clinical Pharmacy: Pierrick Bedouch (Grenoble), Magalie Bourdelin (Villefranche-sur-Saone), Bruno Charpiat (Lyon), Ornella Conort (Paris), Julien Gravoulet (Leyr), Audrey Janoly-Dumenil (Lyon), Michel Juste (Epernay), and Céline Mongaret (Reims).

Clinical pharmacists of the SFPC Act-IP© group who participated in the data collection: S. Abkhtaoui-Couriat (Corbie), B. Allard-Latour (Saint-Genis-Laval), C. Andrieu (Saint-Etienne), X. Armoiry (Lyon), E. Armoiry (Villeurbanne), D. Attivi (Neufchâteau), L. Audibert (Alix), A. Barbet (Amiens), M. Bascoulergue (Aulnay sous bois), C. Basselin (Saint-Genis-Laval), F. Baud (Paris), P. Bedouch (Grenoble), M. Belhout (Amiens), S. Benhaoua (Saint Denis), J. Beny (Alix), S. Berthet (Lyon), J. Berthou (Besancon), D. Bichard (Besancon), A.C. Blandin (Besancon), E. Blondel (Aix les Bains), S. Bonn Loue (Luneville), A. Bonvin (Lyon), F. Bouchand (Garches), P. Bouniot (Francheville), M. Bourdelin (Besancon), C. Bouret (Lyon), L. Bourguignon (Lyon), C. Bourne (Saint-Egrève), M. Bouteille (Lyon), J. Burdin (Lyon), C. Bureau (Alix), C. Bureau (Villeurbanne), M. Burgin (Luneville), M. Buyse (Paris), E. Cabaret (Hyerres), D. Cabelguenne (Pierre Benite), C. Capele (Saint André lez Lille), D. Carli (Vienne), I. Carpentier (Saint-Genis-Laval), E. Chambrey (Rang-du-Fliers), S. Chantel (Pierre Benite), N. Charhon (Vienne), B. Charpiat (Lyon), M. Chaumont (Le Chesnay), K. Civiletti (Martigues), B. Clerc (Besancon), M. Cleve (Vienne), R. Colomb (Saint-Etienne), C. Combe (Saint-Etienne), O. Conort (Paris), R. Contreras (Besancon), S. Crepin (Limoges), M. Creusat-Aube (Illkirch-Graffenstaden), A. Cuoq (Lyon), C. Decourcelle (Lomme), T. Delanoy (Vienne), C. Derharoutunian (Vienne), A. Deronze (Lyon); M. Desseignet (Lyon), S. Diallo (Le Chesnay), L. Dietrich (Strasbourg), A. Dory (Strasbourg), J. Dos-Reis (Paris), N. Duarte (Draveil), M.O. Duzanski (Strasbourg), L. Escofier (Mayenne), F. Fabre (Clermont-Ferrand), S.

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4 Galtier (Vienne); I. Garreau (Epernay), C. Gerard (Francheville), R. Gervais (Saint Denis), O. Gloulou
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6 Grosse (Grasse), C. Guenaire (Rennes), F. Guerin (Aix les Bains), A. Guillermet (Lyon), S. Hannou
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16 Nivoix (Strasbourg), A. Orly (Paris), E. Orng (Lyon), A. Oufella (Aulnay Sous Bois), I. Paillole
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24 (Strasbourg), J. Scholler (Strasbourg), R. Selmi (Saint Denis), C. Stamm (Pierre Benite), C. Tanguy
25 (Brest), D. Tessier (Saint Denis), H. Thery (Rang-du-Fliers), N. Thiriat (Paris), C. Turci (Saint-Genis-
26 Laval), N. Vantard (Lyon), N. Vauvarin (Joigny), S. Vernardet (Annonay), D. Viard (Besancon), C.
27 Vignand (Lyon), C. Villa (Vienne), P. Vonna (Epernay), S. Wacker (Strasbourg), N. Wereszczynski
28 (Grasse), and L. Zerhouni (Paris).

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45 We thank Kévin Mastrorillo, technical consultant of the Act-IP© observatory, for his contribution to the
46 data extraction and data management.

47 48 49 **Funding statement**

50 This research received no specific grant from any funding agency in the public, commercial, or not-for-
51 profit sectors.

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54 This study was supported by The French Society of Clinical Pharmacy, a nonprofit and independent
55 foundation for clinical pharmacy research and development.

56 57 58 **Statement on conflicts of interest**

59 The authors declare that they have no conflicts of interest.
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3 **Patient consent for publication**

4 Not required
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7 **Ethical approval**

8 Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne,
9 Clermont-Ferrand, IRB 5891).
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13 **Data availability**

14 Deidentified participant data are available upon reasonable request to Act-IP© Administrator (email
15 address: actip@sfdc.eu).
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Summary table

Table 1. Characteristics of Act-IP© observatory PISREs and PIs between 2014 to 2018.

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Summary Figures

Figure 1. Flowchart, PISRE selection in Act-IP© observatory (extraction on 11th February 2019)

Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018

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Table 1. Characteristics of all Act-IP© observatory PISREs and PIs between 2014 to 2018.

Characteristics	PISRE	PI total	ratio	
	(N = 27,058)	(N = 331,678)	%	p-value
Drug related problem				
Supratherapeutic dosage	7,436	72,912	10.2	
Non-conformity with guidelines/hospital formulary	6,069	86,072	7.1	
Improper administration	4,838	49,184	9.8	
Subtherapeutic dosage	4,646	29,105	16.0	
Untreated indication	2,366	30,138	7.9	
Drug without indication	1,302	27,690	4.7	
Drug interaction	161	18,267	0.9	
Drug monitoring	111	10,303	1.1	
Adverse drug reaction	65	5,854	1.1	
Failure to receive drug	64	2,153	3.0	
Type of intervention				
Dose adjustment	7,447	89,390	8.3	
Drug switch	6,649	85,033	7.8	
Drug discontinuation	5,220	62,715	8.3	
Optimization of administration	4,123	32,558	12.7	
Addition of new drug	3,228	34,198	9.4	
Change of administration route	213	6,978	3.1	
Drug monitoring	178	20,806	0.9	
Prescriber Acceptance				
Interventions accepted	21,356	227,223	9.4	< 0.001*

Interventions not accepted	3,068	51,957	5.9	
Not assessable	2,634	52,498	5.0	
Prescriber's status				
Senior	15,152	180,863	8.4	< 0.001
Resident	11,765	150,136	7.8	
Midwife**	141	679	20.8	
Pharmacist's status				
Senior	21,271	231,519	9.2	< 0.001
Resident	4,640	86,728	5.4	
Not assessable**	1,147	13,431	8.5	
CPOE system status				
Not certified	21,385	226,878	9.4	< 0.001
Certified	5,549	101,516	5.5	
Not assessable**	124	3,284	3.8	
Total	27,058	331,678	8.2	

PI: pharmacist's intervention, PISRE: pharmacist's intervention identified as due to a system-related error, ratio = PISRE / PI Total, CPOE: computerized prescriber order entry

**Not accepted and not assessable interventions have been regrouped for chi-square test; **excluded from the chi-square analysis*

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Main Document
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 – Title
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6 – lines 35-37
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6 – lines 40-42
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6 – lines 46-50
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Pages 6 – lines 46-50
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5 – lines 20-23 Page 6 – lines 41-42 Page 6-7 – lines 50 - 65
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6 – lines 46 – 52 Page 7 – lines 53- 65
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Figure 1 Page 7 – lines 73-74
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7 – lines 61-71
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 7 – lines 66 - 71
		(b) Describe any methods used to examine subgroups and interactions	Page 7 – lines 66 - 71
		(c) Explain how missing data were addressed	Figure 1
		(d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	Figure 1

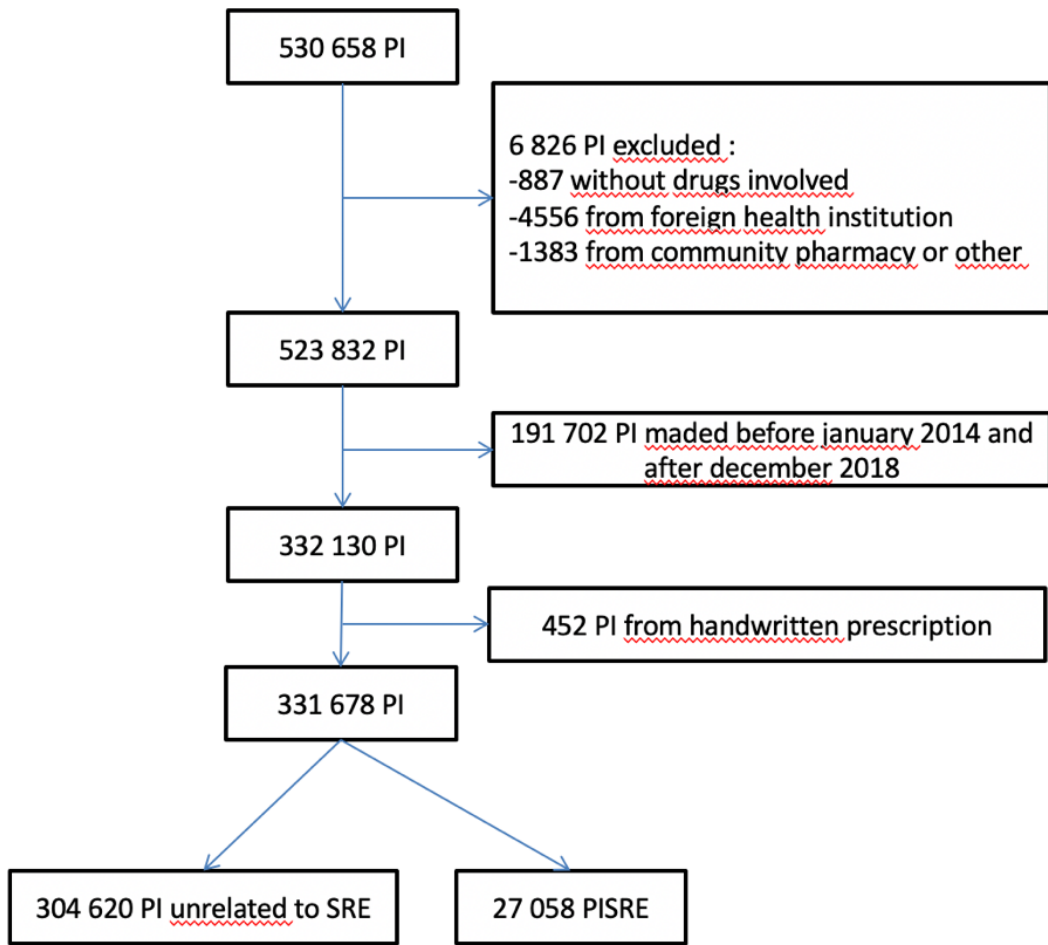
		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Figure 2
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	Page 7 - 8 – line 75 - 88
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1 Page 7 - 8 – line 73 - 83
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 8_9 – lines 95-108
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 11 - 12 – lines 164- 192
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11 – lines 103-163
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11 - 12 – lines 170- 196
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14 – lines 270-275

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

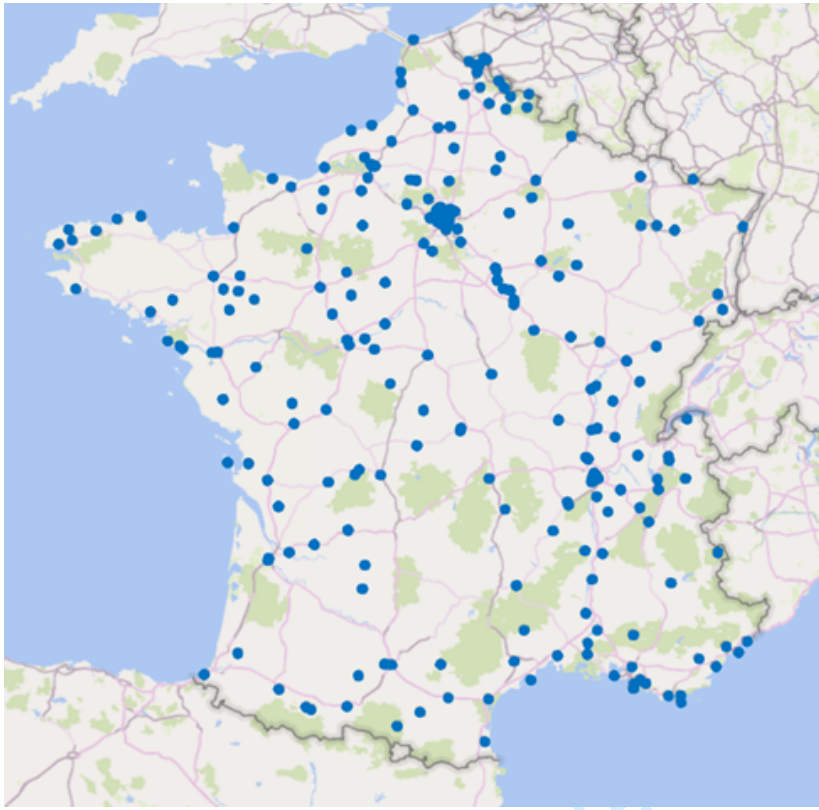
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Figure 1. Flowchart, pharmacist interventions system-related errors (PISRE) selection in Act-IP© observatory (extraction on 11th February 2019)



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Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018



Appendix 1. The Pharmacist intervention form

PHARMACIST INTERVENTION FORM

📅 DATE: / /	📁 INTERVENTION N°:	🏠 CENTER N°:
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PATIENT:

Last name:

First name:

Age: years / Weight: Kg

Sex: M F**Hospital ward:**

- Psychiatry
 Acute care
 Long term care
 Rehabilitation ward

1- DRUG RELATED PROBLEM (1 choice):

- 1 Non conformity to guidelines or contra-indication
2 Untreated indication
3 Subtherapeutic dosage
4 Supratherapeutic dosage
5 Drug without indication
6 Drug interaction
 To be taken into account
 Use with caution
 Combination to be avoided
 Combination contra-indicated
 Documented but not in VIDAL®
7 Adverse drug reaction
8 Improper administration
9 Failure to receive drug
10 Drug monitoring

2- INTERVENTION (1 choice):

- 1 Addition of a new drug
2 Drug discontinuation
3 Drug switch
4 Change of administration route
5 Drug monitoring
6 Administration modalities optimisation
7 Dose adjustment

DRUG NAME (INN):**3- DRUG CLASSIFICATION (ATC):**

- A Alimentary tract & metabolism
 B Blood & blood forming organs
 C Cardiovascular system
 D Dermatological
 G Genito urinary system & sex hormones
 H Systemic hormonal preparations
 J Anti-infective for systemic use
 L Anti-neoplastic & immunomodulating agents
 M Musculo-skeletal system
 N Nervous system
 P Antiparasitic products
 R Respiratory system
 S Sensory organs
 V Various

4- INTERVENTION FOLLOW-UP:

- Accepted
 Non accepted
 Non assessable

DETAILS ⇒If necessary, give details on any aspects of the detected DRP and describe the intervention, precisely
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Context**Problem****Intervention**

Appendix 2. Examples of PISRE and drug by drug-related problems (N = 27,822)

Drug-related problem	Number of drugs involved – n (%)	Most frequent drug (international nonproprietary names) (n)	Examples
Supratherapeutic dosage	7,571 (27.2)	Paracetamol (1,043), tramadol (223), pantoprazole (212), enoxaparin (204)	“Duplicate prescription: 1 in predefined protocol and 1 outside predefined protocol = 8 g of paracetamol per day”
Non-conformity to guidelines/contraindication	6,212 (22.3)	Alfuzosin (515), dutasteride (493), silodosin (469), paracetamol (460), tamsulosin (373)	“prescription of dutasteride, which is not in the hospital drug formulary, with a risk of treatment omission”
Improper administration	4,972 (17.9)	Paracetamol (277), levothyroxine (130), pregabalin (130), methylprednisolone (124)	“selection of IV terbutaline for administration by aerosol”
Subtherapeutic dosage	4,738 (17.0)	Enoxaparin (965), heparin (450), tinzaparin (186), paracetamol (140), macrogol (105),	“Enoxaparin 4000 UI/0.4 ml prescription: 1 IU instead of 1 syringe”
Untreated indication	2,441 (8.8)	acetylsalicylic acid (82), pregabalin (80), paracetamol (74), tinzaparin (69), bisoprolol (69), enoxaparin (68),	“prescription of pregabalin not renewed (hospital stay longer than the duration of the prescription)”

1 2 3 4 5 6 7 8 9 10 11 12 13 14	Drug without indication	1,340 (4.8)	Pantoprazole (66), amoxicillin and beta-lactamase inhibitor (44), cholecalciferol (40), ceftriaxone (34), enoxaparin (30)	“duplicate prescription of pantoprazole per os and IV by two prescribers”
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	Drug interaction	262 (0.9)	Amiodarone (27), fluindione (9), levothyroxine (9)	“cordarone and escitalopram combination contra-indicated: risk of “torsade de pointes” not modified during drug interaction alert with Clinical Decision Support System (CDSS)”
30 31 32 33 34 35 36	Drug monitoring	124 (0.4)	Fluindione (25), polystyrene sulfonate (8), paracetamol (4)	
37 38 39 40 41 42 43 44	Adverse drug reaction	70 (0.3)	Polystyrene sulfonate (11), furosemide (6), atorvastatin (4), tramadol (3), macrogol (3)	“increased risk of adverse reactions by the combination of atorvastatin and fenofibrate”
45 46 47 48 49 50 51 52 53	Failure to receive drug	92 (0.3)	Esomeprazole (3), cholecalciferol (3), acetylsalicylic acid (3), furosemide (3)	“Prescription of furosemide not appearing on the nursing plan”

BMJ Open

Characteristics of Pharmacist's interventions triggered by prescribing errors related to computerized physician order entry in French hospitals: a cross-sectional observational study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-045778.R2
Article Type:	Original research
Date Submitted by the Author:	09-Aug-2021
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Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Health informatics, Health services research, Pharmacology and therapeutics
Keywords:	Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

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3 **Characteristics of Pharmacist’s interventions triggered by prescribing errors related to**
4 **computerized physician order entry in French hospitals: a cross-sectional observational study**
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14 Pharmaceutiques – Act-IP©” of the French Society for Clinical Pharmacy (see composition and
15 members in acknowledgments)
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33 **Keywords:** drug related problem, prescribing error, pharmacist intervention, computerized physician
34 order entry (CPOE)
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39 Abstract: 305/300 words

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41 Main text: 3125/4000 words
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Abstract

Objectives

Computerized physician order entry (CPOE) systems facilitate the review of medication orders by pharmacists. Reports have emerged that show conception flaws or the misuse of CPOE systems generate prescribing errors. We aimed to characterize pharmacist interventions (PIs) triggered by prescribing errors identified as system-related errors (SREs) in French hospitals.

Design

This was a cross-sectional observational study based on PIs prospectively documented in the Act-IP© observatory database from January 2014 to December 2018.

Setting

PISREs from 319 French computerized healthcare facilities were analyzed.

Participants

Among the 319 French hospitals, 232 (72.7%) performed SRE interventions, involving 652 (51%) pharmacists.

Results

Among the 331,678 PIs recorded, 27,058 were qualified as due to SREs (8.2%). The main drug-related problems associated with PISREs were suprathereapeutic (27.5%) and subtherapeutic dosage (17.2%), non-conformity with guidelines/contraindications (22.4%), and improper administration (17.9%). The PI prescriber acceptance rate was 78.9% for SREs versus 67.6% for other types of errors. The PISRE ratio was estimated relative to the total number of PIs. Concerning the certification status of CPOE systems, the PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p -value<0.001). The PISRE ratio for senior pharmacists was 9.2% and that for pharmacy residents 5.4% (p -value<0.001). Concerning prescriptions made by graduate prescribers and those made by residents, the PISRE ratio was 8.4 % and 7.8%, respectively (p -value<0.001).

Conclusion

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3 Computer-related prescribing errors are common. The PI acceptance rate by prescribers was higher than
4 that observed for PIs that were not CPOE related. This suggests that physicians consider the potential
5 clinical consequences of SREs for patients to be more frequently serious than interventions unrelated to
6 CPOE. CPOE medication review requires continual pharmacist diligence to catch these errors. The
7 significantly lower PISRE ratio for certified software should prompt patient safety agencies to undertake
8 studies to identify the safest software and discard software that is potentially dangerous.
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For peer review only

Article Summary

Strengths and limitations of this study

- This study provides an overview of prescribing issues related to the use of CPOE systems at the national level.
- Beyond this large register of prescribing problems related to CPOE use, this is the first study to evaluate pharmacist interventions in daily practice for such a large sample of interventions, pharmacists, and hospitals.
- This study focuses on declarative data based on interventions performed by hospital pharmacists.
- These pharmacist interventions highlight prescription problems, but they are not exhaustive.

1. Introduction

Every day, numerous hospitalized patients are subject to drug-related problems (DRPs), resulting in suboptimal therapy, suffering, and decreased quality of life, as well as high healthcare costs for society [1, 2]. Computerized physician order entry (CPOE) systems, along with clinical decision support systems, improve the safety, quality, and value of patient care [3]. According to a meta-analysis, CPOE systems have reduced hospital medication errors by approximately 12.5% IC95% [10.6-14.4%] [4]. However, CPOE systems also have the potential to introduce or contribute to errors. Indeed, new mechanisms that lead to prescription errors have been identified with CPOE: wrong patient selection, failure to report drug allergies, incorrect entry or wrong selection of medication, dose, route, or time of administration, and confusing free-text comments [5-10].

In France, as in other countries, various incentives and requirements have been put in place to encourage computerized drug prescribing, such as France's "Digital Hospital" program [11]. Since the 2000s, prescribing errors associated with the use of CPOE have been slowly coming to light as healthcare has become increasingly computerized [9]. Compared to handwritten prescriptions, the analysis of electronic prescriptions requires a particular effort on the part of pharmacists and other health professionals to detect errors [9]. System-related errors (SREs) are defined as those in which the electronic prescribing system functionality or design contributed to the error, with little possibility that another cause, such as lack of knowledge, produced the error. For example, an order for an inappropriate drug located on a drop-down menu next to a likely drug selection is a system-related error [12].

A pharmacist intervention (PI) due to a SRE is defined as any PI resulting from the identification of a prescribing error by a pharmacist that would probably not have occurred in the context of a handwritten prescription and of which at least one cause is related to the use of a computer (software system configuration issue, software functionality issue, or software misuse) [13-16].

Most studies concerning PIs triggered by system-related prescribing errors were conducted within a single hospital [17-19]. As a result, it is not possible to assess the extent of prescribing errors related to electronic systems or draw conclusions about subsequent PIs at a national level.

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3 In 2003, the French Society of Clinical Pharmacy (SFPC) developed and validated a tool for classifying
4 and documenting clinical PIs [20]. This tool allows the reporting of DRPs and PIs performed during the
5 daily review of medication orders [21]. In 2006, a website, Act-IP©, was created with the objectives to
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7 (a) create a documentation system that is freely accessible to any pharmacist, through the French Society
8 of Clinical Pharmacy Web site (<http://www.actip.sfpc.eu/actip/index/ficheip/>) and (b) pool the data
9 recorded by all pharmacists to conduct epidemiological studies concerning DRPs detected by
10 pharmacists [22]. The data recording is on a voluntary basis. The pooling of PIs constitutes an
11 observatory of clinical pharmacy practices, called the “Act-IP© Observatory”.

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21 The aim of this study was to characterize PIs triggered due to SREs in French hospitals between 2014
22 and 2018. Our secondary objective was to determine the physician acceptance rate and its frequency
23 according to the certification status (certified versus non-certified) of the CPOE systems.

28 **2. Methods**

30 *2.1. Study design*

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32 This was a cross-sectional observational study using PIs prospectively documented in the Act-IP©
33 observatory over a five-year period from January 1, 2014 to December 31, 2018. The main outcome was
34 a PI due to a SRE (PISRE) reported by French hospital pharmacists on the Act-IP© observatory. Ethical
35 approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne, Clermont-
36 Ferrand, IRB 5891).

43 *2.2. Data sources*

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45 The data comes from PIs registered in the Act-IP© Observatory from January 2014 to December 2018.
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47 Based on the SFPC criteria, using the report form developed and validated for routine documentation of
48 the PIs, Act-IP© users completed the online report form notifying the date, type of DRP, PI, type of
49 drug involved (according to the ATC (Anatomical Therapeutic Chemical) classification), acceptance of
50 the intervention by the prescriber, and free-text details of the context. Ten categories were determined
51 for DRPs and seven for PIs (Appendix 1). A PI was considered to be “accepted” if the physician took it
52 into account and modified the prescription as suggested by the pharmacist or “refused” if the prescription
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3 remained unchanged, including cases of expressed refusal by the prescriber. If acceptance of the
4 intervention was impossible to ascertain (i.e. discharged patients or those transferred to another ward
5 before acceptance), the PI was noted as “not assessable”. The pharmacist’s academic background,
6 hospital characteristics, and software used were documented online by the pharmacist when he/she
7 registered onto the Act-IP© website. To be registered onto the Act-IP© website, pharmacists had prior
8 to accept terms and conditions and allowed the use of their data for analysis. Since July 2013,
9 pharmacists have been able to indicate whether the DRP was “related to the electronic system” or not
10 for each registered PI. For the purpose of this study, PISREs were DRPs rated by each pharmacist as
11 “related to the electronic system” in the Act-IP© website.
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23 The reliability of the classification of the type of drug therapy problem and intervention according to
24 the SFPC classification was determined in a previous study by assessing the degree of agreement
25 between 12 pharmacists using the kappa concordance coefficient (kappa=0.76 for drug problems and
26 kappa=0.89 for drug interventions) [20]. Database quality controls were performed by an independent
27 pharmacist to ensure that data coding and entry errors were minimal [22].
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34 French law made the certification of CPOE systems mandatory on December 29, 2011. However, two
35 decrees abolished this obligation in 2017. Certification is now based on the sole initiative of the software
36 developer. Forty-eight hospital CPOE software packages are currently certified by the agency for patient
37 safety [Haute Autorité de Santé (HAS)] [23]. For our analysis, PISREs were classified according to the
38 HAS status of the CPOE system (certified versus not certified).
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45 *2.3. Analysis*

46 The PISRE ratio was estimated relative to the total number of PIs. Proportions were compared using the
47 chi-square test. PISREs coded as “refused” or “not assessable” were combined and compared to the
48 accepted PISREs. Probability values < 0.001 were considered to be statistically significant. Statistical
49 analyses were performed using Stata 13 (Stata Corporation, College Station, Texas, USA). Several
50 qualitative examples are given to illustrate PISREs.
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58 *2.4. Study participants and public involvement*

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3 This research was done without study participant involvement. Patients and/or the public were not
4 involved in the design, or conduct, or dissemination plans of this research.
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8 **4. Results**

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10 From January 2014 to December 2018, 331,678 PIs were entered into the Act-IP© observatory. Among
11 them, 27,058 (8.2%) were indicated to be system-related prescribing errors (Figure 1).
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15 Over the study period, 1,219 pharmacists from 319 hospitals recorded PIs in the Act-IP© observatory
16 database. The geographical location of the hospitals involved is shown in Figure 2. Among them, 232
17 (72.7%), involving 652 (51%) pharmacists, performed SRE interventions. Among the 319 hospitals, 87
18 (27.3%) did not qualify any PIs as being due to a SRE. PIs come from 82 software involving 19 certified
19 systems.
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25 The characteristics of the PISREs are summarized in Table 1. The most commonly identified type of
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The characteristics of the PISREs are summarized in Table 1. The most commonly identified type of
DRP was “supratherapeutic dosage”, followed by “non-conformity with guidelines/contraindications”
and “improper administration”. Among the 27,058 PISREs, 78.9% (n = 21,356) were accepted. The
PISRE ratio was 9.4% for non-certified systems versus 5.5% for certified systems (p-value < 0.001).
Appendix 2 presents examples of drug-related problems classified as being triggered by prescribing
errors due to the CPOE system. For example: Prescription errors can be the same whether they are
handwritten prescriptions or computer-assisted prescriptions. Indeed, the combination of amiodarone
and escitalopram can appear on handwritten prescription because of prescriber’s lack of knowledge.
With CPOE, Clinical Decision Support System (CDSS) tool can alert on drug-drug interaction.
However, high frequency of alerts and dozens of daily interruptions for clinicians are responsible of
"alert fatigue" and practitioners override alerts [24]. We can also find duplicate orders, meaning the
same drug is prescribed twice. With predefined order set, it is common to have 8 grams of paracetamol
per day prescribed. Duplication errors are partially explained by the fact that many screens are required
to view patient medications, making intrinsically difficult to spot duplicates [25].

57 **5. Discussion**

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3 This study provides an overview of prescription problems related to CPOE systems used in French
4 hospitals. It provides insights into the main situations and medications involved in computer-related
5 prescribing problems detected by pharmacists by providing a broad description of PIs performed during
6 the daily review of routine medication orders. Thus one strength of this study is that it is based on a
7 large number of hospitals scattered throughout France, as no prior study of such extent evaluating PIs
8 in daily practice has been published.
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15 16 17 *5.1. PISRE rate*

18 Our PISRE rate (8.2%) is within the range reported by Korb-Savoldelli et al. [19]. They analyzed peer-
19 reviewed studies (n = 14) that quantitatively reported medication-prescription errors related to CPOE.
20 The prevalence of CPOE system-related medication errors relative to all prescription medication errors
21 ranged from 6.1 to 77.7% (median = 26.1% [IQR:17.6–42,1]) and was less than 6.3% relative to the
22 number of prescriptions reviewed. Ours is the first large-scale descriptive study using an observatory
23 hospital pharmacy practice database to study computer-related prescribing errors.
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32 33 *5.2. DRPs induced by CPOE*

34 The main category of DRPs identified as PISREs were suprathereapeutic (27.5%, 7,436) and
35 subtherapeutic dosage (17.2%, 4,646), non-conformity to guidelines/hospitals' drug formularies (22.4%,
36 6,069) (i.e. medication selection non-compliant with the hospital drug formulary), and improper
37 administration (17.9%, 4,838) (i.e. incorrect or no formulation, wrong timing). According to Korb-
38 Savoldelli et al., all studies reported “wrong dose” and “wrong drug” errors [19], with the “wrong dose”
39 error being that most frequently reported (from 7 to 67.4%, median = 31.5% [IQR:20.5–44.5]). Many of
40 the prescription errors due to CPOE systems can have serious consequences for patients, depending on
41 the clinical circumstances. Although some of are unlikely to occur (e.g. IV ketoprofen 150 ampoules/day
42 instead of 150 mg/d), they nevertheless illustrate flaws in certain CPOE systems [26]. However, our
43 data do not allow the discrimination between software errors, connection problems, and human error.
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55 56 57 *5.3. CPOE systems*

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3 The proportion of PIs triggered by software-related prescription errors was higher for non-certified
4 (9.4%) than certified software (5.5%). In France, certification tests produced by the HAS are intended
5 to technically assess the functionality of the software in various situations, as the CPOE evaluation
6 methodology simulates various clinical scenarios [27]. French regulations do not require CPOE
7 developers to carry out usability studies before the systems are marketed. Nevertheless, despite the
8 limitations of this type of certification criteria, which have already been highlighted [28], our results
9 show that prescribing with CPOE-certified systems results in fewer prescription errors than prescribing
10 with non-certified software. These results are consistent with those of other studies, i.e. all software is
11 not equal and some is safer than others [29-31].

22 23 *5.4. Prescribers*

24 The PISRE ratio was higher for prescriptions made by graduate prescribers (8.4%) than medical
25 residents (7.8%) (p-value < 0.001). This finding is, at first glance, counterintuitive, as one would expect
26 that a prescriber who has been practicing for several years in the same health facility would make fewer
27 CPOE-related prescription errors with the software than a resident who has only been using the software
28 for a few months. Observational studies show that medical residents make most prescriptions and
29 transcribe them to the software prescription instructions of senior prescribers during the medical
30 examination [32]. It is thus possible that, in some hospitals, senior physicians are only occasional users
31 of the prescription software. According to Nerich et al., the occasional use of software (< 1 prescription
32 per day) is a risk factor for prescription error (OR = 3.85, 95% CI [2.08-7.14]) [33]. Tolley described
33 how a junior doctor remarked that there was no one he could ask for help with using the ePrescribing
34 system, as he was “the most experienced person on this floor with regards to the ePrescribing system”.
35 She also described how one consultant admitted she had not “learnt how to prescribe properly” because
36 she did not “use the system often enough and regularly enough to know the quirks and tweaks”. This
37 consultant relied on her junior staff to prescribe on the system [34].

54 55 *5.5. Act-IP© Pharmacist’ users*

56 The PISRE ratio for senior pharmacists (9.2%) was higher than that of pharmacy residents (5.4%). This
57 is consistent with the results of a study performed in a UK teaching hospital showing that the likelihood
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3 of senior pharmacists identifying errors was greater than that of junior pharmacists [35] and in
4 accordance with our expectations. A study concerning French pharmacy students showed that they trust
5 the contribution of computerization to healthcare without critical analysis. This results in overconfidence
6 in the computer tool, perceived to be reliable, and makes users less willing to search for the errors
7 produced by this tool [36]. They are therefore not aware that the review of computerized prescription
8 orders requires additional effort to identify prescription errors. This is the consequence of the lack of
9 teaching/training about this subject in French pharmacy schools. This situation contrasts strikingly with
10 the content of the curricula taught in the United Kingdom and USA, for example [37,38].
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20 21 *5.6. Prescriber Acceptance rate*

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23 The rate of acceptance of PISREs by prescribers was 78.9% versus 67.6% for other PIs. This suggests
24 that prescribers recognize the relevance of such interventions due to the potential clinical consequences
25 of such prescription errors. This rate varies from 65.9 to 92% in studies of drug errors induced by
26 computerized prescription [10, 14], suggesting that physicians consider the potential clinical
27 consequences of SRE to patients to be more frequently serious than interventions unrelated to CPOE. In
28 light of our findings, a CPOE-related prescription error is a factor that favors acceptance of the
29 PI. These points warrant further studies.
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38 39 *5.7. Limits*

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41 Our study had several limitations. First, our work is based on declarative data. These interventions are
42 performed by hospital pharmacist and entered on Act-IP © website on a voluntary basis. There for, these
43 PIs highlight prescription problems, but are not exhaustive. Moreover, our team annually analyzes the
44 quantitative and qualitative evolution of the data recorded on the Act-IP © website (unpublished data).
45 We observed that data entry can be irregular or performed with a delay. Indeed, data can be conditioned
46 by pharmacist workload. For example, many pharmacists record prospectively their data on paper on a
47 daily basis and thereafter register them by series on Act-IP©. Data entry can also be total on a given
48 period and can stop during a change of assignment. We consider that these elements have consequences
49 on the quantity of recorded data but not on their quality. However, as illustrated by publications related
50 to other databases on information technology incidents, despite their limitations, studies based on
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3 voluntary reports remain relevant to examine the nature of technology safety problems [39,40].
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5 Moreover, the large sample size probably provides a relatively precise vision of the problem at the
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7 national level. Second, several pharmacists analyzing the same drug prescriptions may not all track
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9 down the same problems. One of major determinant of a PI is the knowledge of the pharmacist who
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11 analyzes the prescription. It is this knowledge that enables him to detect a problem. Thus, a PI that is
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13 considered as necessary and is not performed means that it is not recorded and will be absent from the
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15 database. This happens when a doctor routinely makes a certain type of prescribing error and the
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17 pharmacist fails to detect it [41]. It has been shown that, if several pharmacists analyze the same drug
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19 prescriptions, they don't all track down the same problems. In a study involving 57 hospital pharmacies,
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21 the mean percentage of detected prescribing errors was 59%, with a broad range of 7–88% between
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23 pharmacies [42]. In the absence of specific studies to determine the performance of pharmacists in
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25 detecting prescription errors induced by CPOE-system flaws and misuse, we are reduced to simply
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27 assuming that such variation may be observed. In addition, there are various definitions of PISREs in
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29 the literature [13-16]. This suggests that there is a certain level of subjectivity when a pharmacist
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31 characterizes a PI as being related to a computer-generated prescription. Among hospitals that entered
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33 the PIs on Act-IP©, 87 never qualified a PI as being a SRE. There are two possible explanations for this
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35 observation. The first, and relatively unlikely, is that the software is near perfect and that there was no
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37 misuse by prescribers. For example, the absence of PISREs for these hospitals could result from the
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39 absence of computer-related errors due to the use of high-performance software and/or appropriately
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41 trained prescribers. The second possibility is that pharmacists do not establish a link between certain
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43 prescription errors and misuse of the prescription software and/or its design flaws. Conversely, a high
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45 rate of PISREs for a given hospital may result from software conception flaws and/or misuse of the
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47 software by prescribers and pharmacists who are very aware of the role of CPOE-systems in generating
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49 prescription errors. Regardless of the considered scenario, it is important to remember that differences
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51 in PISRE rates may also be due to the quality of the training provided. Studies have shown that
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53 insufficient training on an ePrescribing system can contribute to errors [43,44]. Tolley illustrated how
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55 pharmacists did not receive any formal training about the system after starting at a hospital trust and
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57 observed that no formal training was offered when pharmacists changed roles. It has been shown that
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3 training plays a role in the users' experience but there is a lack of published research in this area [34].

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5 Thus, further research is warranted to lift the veil on these unknowns.

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8 Our results highlight that prescribing problems related to computer software are common in France.

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10 This is a concern that affects most (if not all) CPOE systems currently being used and therefore all
11 hospitals, to varying degrees. Identifying the most dangerous software appears to be a priority to
12 improve the quality and safety of patient care.
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16 17 **6. Conclusion**

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19 Computer-related prescribing errors are common, with wrong dose being the most frequent type of error.

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21 Such errors concern all drug classes and have potentially serious adverse clinical consequences if they
22 are not intercepted by pharmacists when performing their daily medication review. The message appears
23 to be well received by prescribers who agree to change their prescription more frequently than for PIs
24 not related to CPOE use. CPOE medication review requires additional pharmacist diligence to catch
25 such errors. As the PISRE ratio is significantly lower for certified software, patient safety agencies
26 should undertake studies to identify the safest software so as to discard software that is potentially
27 dangerous.
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Author contributions

Manon Videau and Bruno Charpiat designed the study, performed the statistical analyses, interpreted the results, and wrote the first version of the manuscript. Céline Vermorel contributed to the design of the study, performed the statistical analyses, and revised the manuscript. Jean-Luc Bosson contributed to the design of the study and revised the manuscript. Ornella Conort contributed substantially to the interpretation of the data and contributed to the revision of the manuscript. Pierrick Bedouch designed the study, performed the statistical analyses, interpreted the results, and revised the manuscript.

Acknowledgements

The authors would like to thank the team of THEMAS and VIP working group for assistance in this project. We thank the clinical pharmacists of the SFPC Act-IP© group who participated in the data collection.

Members of the working group “Valorization of Pharmaceutical Interventions/ Valorisation des Interventions Pharmaceutiques – Act-IP©” of the French Society for Clinical Pharmacy: Pierrick Bedouch (Grenoble), Magalie Bourdelin (Villefranche-sur-Saone), Bruno Charpiat (Lyon), Ornella Conort (Paris), Julien Gravoulet (Leyr), Audrey Janoly-Dumenil (Lyon), Michel Juste (Epernay), and Céline Mongaret (Reims).

Clinical pharmacists of the SFPC Act-IP© group who participated in the data collection: S. Abkhtaoui-Couriat (Corbie), B. Allard-Latour (Saint-Genis-Laval), C. Andrieu (Saint-Etienne), X. Armoiry (Lyon), E. Armoiry (Villeurbanne), D. Attivi (Neufchâteau), L. Audibert (Alix), A. Barbet (Amiens), M. Bascoulergue (Aulnay sous bois), C. Basselin (Saint-Genis-Laval), F. Baud (Paris), P. Bedouch (Grenoble), M. Belhout (Amiens), S. Benhaoua (Saint Denis), J. Beny (Alix), S. Berthet (Lyon), J. Berthou (Besancon), D. Bichard (Besancon), A.C. Blandin (Besancon), E. Blondel (Aix les Bains), S. Bonn Loue (Luneville), A. Bonvin (Lyon), F. Bouchand (Garches), P. Bouniot (Francheville), M. Bourdelin (Besancon), C. Bouret (Lyon), L. Bourguignon (Lyon), C. Bourne (Saint-Egrève), M. Bouteille (Lyon), J. Burdin (Lyon), C. Bureau (Alix), C. Bureau (Villeurbanne), M. Burgin (Luneville), M. Buyse (Paris), E. Cabaret (Hyerres), D. Cabelguenne (Pierre Benite), C. Capele (Saint André lez Lille), D. Carli (Vienne), I. Carpentier (Saint-Genis-Laval), E. Chambrey (Rang-du-Fliers), S. Chantel (Pierre Benite), N. Charhon (Vienne), B. Charpiat (Lyon), M. Chaumont (Le Chesnay), K. Civiletti (Martigues), B. Clerc (Besancon), M. Cleve (Vienne), R. Colomb (Saint-Etienne), C. Combe (Saint-Etienne), O. Conort (Paris), R. Contreras (Besancon), S. Crepin (Limoges), M. Creusat-Aube (Illkirch-Graffenstaden), A. Cuoq (Lyon), C. Decourcelle (Lomme), T. Delanoy (Vienne), C. Derharoutunian (Vienne), A. Deronze (Lyon); M. Desseignet (Lyon), S. Diallo (Le Chesnay), L. Dietrich (Strasbourg), A. Dory (Strasbourg), J. Dos-Reis (Paris), N. Duarte (Draveil), M.O. Duzanski (Strasbourg), L. Escofier (Mayenne), F. Fabre (Clermont-Ferrand), S.

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3 Fare (Paris), J. Fillon (Paris), A. Fonteneau (Amiens), A. Fouquet (Vienne); A. Gadot (Lyon), H.
4 Galtier (Vienne); I. Garreau (Epernay), C. Gerard (Francheville), R. Gervais (Saint Denis), O. Gloulou
5 (Saint Denis), I. GraguebChatti (Vienne), A. Grass (Lyon), I. Gremeau (Clermont-Ferrand), P.Y.
6 Grosse (Grasse), C. Guenaire (Rennes), F. Guerin (Aix les Bains), A. Guillermet (Lyon), S. Hannou
7 (Illkirch-Graffenstaden), A. Henry (Lyon), G. Herbin (Bayeaux), N. Herment (Epernay), A.
8 JanolyDumenil (Pierre Benite), C. Jarre (Vienne), L. Jovenaux (Martigues), M. Juste (Epernay), A.S.
9 Kaczmarek (Clermont-Ferrand), W. KiniMatondo (Saint Denis), H. Labrosse (Lyon), C. Laillier
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20 (Créteil), L. Poy (Lyon), E. Prevost (Epernay), E. Prunier (Besancon), F. Ranchon (Lyon), M. Rave
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23 Roubille (Vienne), A. Sambarino (Bourgoin Jallieu), D. Sankhare (Saint Denis), R. Santucci
24 (Strasbourg), J. Scholler (Strasbourg), R. Selmi (Saint Denis), C. Stamm (Pierre Benite), C. Tanguy
25 (Brest), D. Tessier (Saint Denis), H. Thery (Rang-du-Fliers), N. Thiriat (Paris), C. Turci (Saint-Genis-
26 Laval), N. Vantard (Lyon), N. Vauvarin (Joigny), S. Vernardet (Annonay), D. Viard (Besancon), C.
27 Vignand (Lyon), C. Villa (Vienne), P. Vonna (Epernay), S. Wacker (Strasbourg), N. Wereszczynski
28 (Grasse), and L. Zerhouni (Paris).

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45 We thank Kévin Mastrotillo, technical consultant of the Act-IP© observatory, for his contribution to the
46 data extraction and data management.

47 48 49 **Funding statement**

50 This research received no specific grant from any funding agency in the public, commercial, or not-for-
51 profit sectors.

52
53
54 This study was supported by The French Society of Clinical Pharmacy, a nonprofit and independent
55 foundation for clinical pharmacy research and development.

56 57 58 **Statement on conflicts of interest**

59 The authors declare that they have no conflicts of interest.

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3 **Patient consent for publication**

4 Not required
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7 **Ethical approval**

8 Ethical approval for the study was obtained on February 19, 2020 (CECIC Rhône-Alpes-Auvergne,
9 Clermont-Ferrand, IRB 5891).
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13 **Data availability**

14 Deidentified participant data are available upon reasonable request to Act-IP© Administrator (email
15 address: actip@sfdc.eu).
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3 **Summary table**
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5 Table 1. Characteristics of Act-IP© observatory PISREs and PIs between 2014 to 2018.
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3 **Summary Figures**
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5 Figure 1. Flowchart, PISRE selection in Act-IP© observatory (extraction on 11th February 2019)
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8 Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory
9 between 2014 and 2018
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Table 1. Characteristics of all Act-IP© observatory PISREs and PIs between 2014 to 2018.

Characteristics	PISRE	PI total	ratio	
	(N = 27,058)	(N = 331,678)	%	p-value
Drug related problem				
Supratherapeutic dosage	7,436	72,912	10.2	< 0.001
Non-conformity with guidelines/hospital formulary	6,069	86,072	7.1	-
Improper administration	4,838	49,184	9.8	< 0.001
Subtherapeutic dosage	4,646	29,105	16.0	< 0.001
Untreated indication	2,366	30,138	7.9	< 0.001
Drug without indication	1,302	27,690	4.7	< 0.001
Drug interaction	161	18,267	0.9	< 0.001
Drug monitoring	111	10,303	1.1	< 0.001
Adverse drug reaction	65	5,854	1.1	< 0.001
Failure to receive drug	64	2,153	3.0	< 0.001
Type of intervention				
Dose adjustment	7,447	89,390	8.3	-
Drug switch	6,649	85,033	7.8	< 0.001
Drug discontinuation	5,220	62,715	8.3	< 0.001
Optimization of administration	4,123	32,558	12.7	< 0.001
Addition of new drug	3,228	34,198	9.4	< 0.001
Change of administration route	213	6,978	3.1	< 0.001
Drug monitoring	178	20,806	0.9	< 0.001
Prescriber Acceptance				
Interventions accepted	21,356	227,223	9.4	< 0.001*

Interventions not accepted	3,068	51,957	5.9	
Not assessable	2,634	52,498	5.0	
Prescriber's status				
Senior	15,152	180,863	8.4	< 0.001
Resident	11,765	150,136	7.8	
Midwife**	141	679	20.8	
Pharmacist's status				
Senior	21,271	231,519	9.2	< 0.001
Resident	4,640	86,728	5.4	
Not assessable**	1,147	13,431	8.5	
CPOE system status				
Not certified	21,385	226,878	9.4	< 0.001
Certified	5,549	101,516	5.5	
Not assessable**	124	3,284	3.8	
Total	27,058	331,678	8.2	

PI: pharmacist's intervention, PISRE: pharmacist's intervention identified as due to a system-related error, ratio = PISRE / PI Total, CPOE: computerized prescriber order entry

**Not accepted and not assessable interventions have been regrouped for chi-square test; **excluded from the chi-square analysis*

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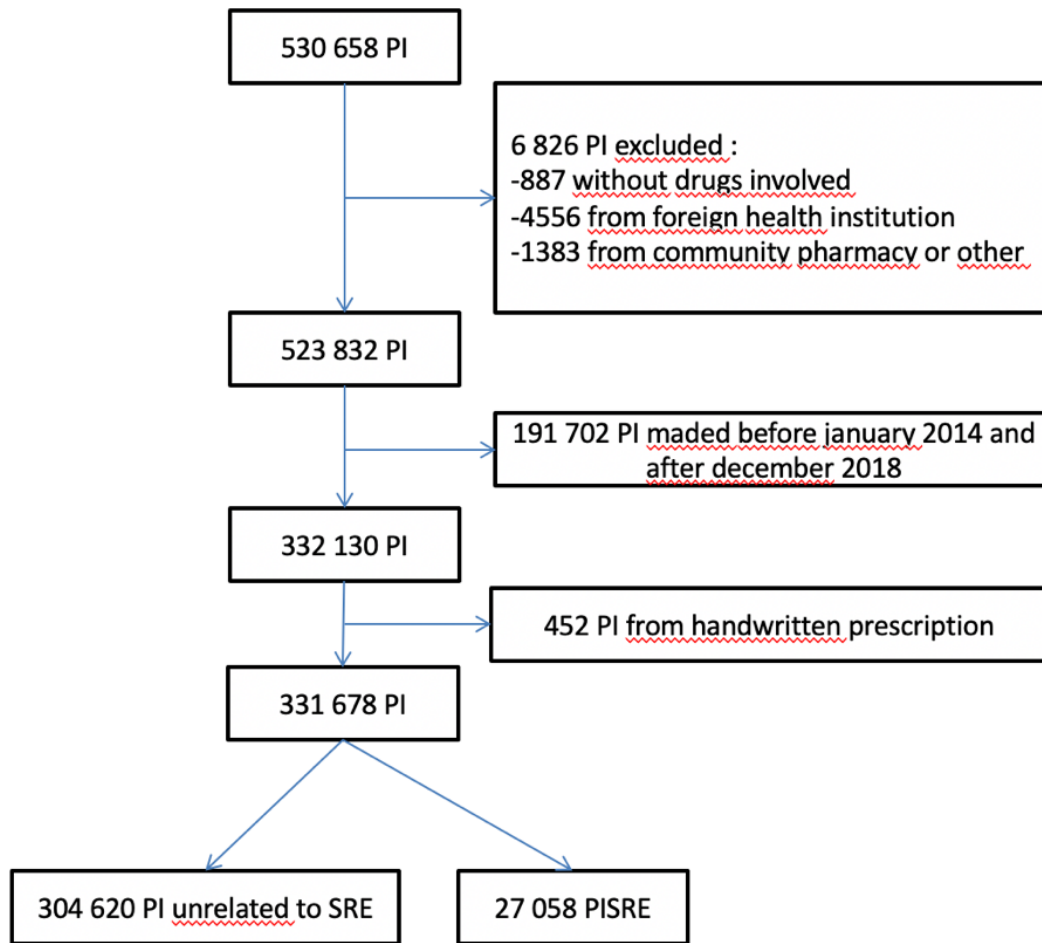
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Figure 1. Flowchart, pharmacist interventions system-related errors (PISRE) selection in Act-IP© observatory (extraction on 11th February 2019)



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Figure 2. Geographical location of French hospitals that entered data into the Act-IP © observatory between 2014 and 2018



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Appendix 1. The Pharmacist intervention form

PHARMACIST INTERVENTION FORM

📅 **DATE:** / / 📁 **INTERVENTION N°:** 🏠 **CENTER N°:**

PATIENT:

Last name:

First name:

Age: years / Weight: Kg

Sex: M F**Hospital ward:**

- Psychiatry
 Acute care
 Long term care
 Rehabilitation ward

1- DRUG RELATED PROBLEM (1 choice):

- 1 Non conformity to guidelines or contra-indication
2 Untreated indication
3 Subtherapeutic dosage
4 Supratherapeutic dosage
5 Drug without indication
6 Drug interaction
 To be taken into account
 Use with caution
 Combination to be avoided
 Combination contra-indicated
 Documented but not in VIDAL®
7 Adverse drug reaction
8 Improper administration
9 Failure to receive drug
10 Drug monitoring

2- INTERVENTION (1 choice):

- 1 Addition of a new drug
2 Drug discontinuation
3 Drug switch
4 Change of administration route
5 Drug monitoring
6 Administration modalities optimisation
7 Dose adjustment

DRUG NAME (INN):**3- DRUG CLASSIFICATION (ATC):**

- A Alimentary tract & metabolism
 B Blood & blood forming organs
 C Cardiovascular system
 D Dermatological
 G Genito urinary system & sex hormones
 H Systemic hormonal preparations
 J Anti-infective for systemic use
 L Anti-neoplastic & immunomodulating agents
 M Musculo-skeletal system
 N Nervous system
 P Antiparasitic products
 R Respiratory system
 S Sensory organs
 V Various

4- INTERVENTION FOLLOW-UP:

- Accepted
 Non accepted
 Non assessable

DETAILS ⇒ If necessary, give details on any aspects of the detected DRP and describe the intervention, precisely

Context**Problem****Intervention**

Appendix 2. Examples of PISRE and drug by drug-related problems (N = 27,822)

Drug-related problem	Number of drugs involved – n (%)	Most frequent drug (international nonproprietary names) (n)	Examples
Supratherapeutic dosage	7,571 (27.2)	Paracetamol (1,043), tramadol (223), pantoprazole (212), enoxaparin (204)	“Duplicate prescription: 1 in predefined protocol and 1 outside predefined protocol = 8 g of paracetamol per day”
Non-conformity to guidelines/contraindication	6,212 (22.3)	Alfuzosin (515), dutasteride (493), silodosin (469), paracetamol (460), tamsulosin (373)	“prescription of dutasteride, which is not in the hospital drug formulary, with a risk of treatment omission”
Improper administration	4,972 (17.9)	Paracetamol (277), levothyroxine (130), pregabalin (130), methylprednisolone (124)	“selection of IV terbutaline for administration by aerosol”
Subtherapeutic dosage	4,738 (17.0)	Enoxaparin (965), heparin (450), tinzaparin (186), paracetamol (140), macrogol (105),	“Enoxaparin 4000 UI/0.4 ml prescription: 1 IU instead of 1 syringe”
Untreated indication	2,441 (8.8)	acetylsalicylic acid (82), pregabalin (80), paracetamol (74), tinzaparin (69), bisoprolol (69), enoxaparin (68),	“prescription of pregabalin not renewed (hospital stay longer than the duration of the prescription)”

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	Drug without indication	1,340 (4.8)	Pantoprazole (66), amoxicillin and beta-lactamase inhibitor (44), cholecalciferol (40), ceftriaxone (34), enoxaparin (30)	“duplicate prescription of pantoprazole per os and IV by two prescribers”
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	Drug interaction	262 (0.9)	Amiodarone (27), fluindione (9), levothyroxine (9)	“cordarone and escitalopram combination contra-indicated: risk of “torsade de pointes” not modified during drug interaction alert with Clinical Decision Support System (CDSS)”
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Drug monitoring	124 (0.4)	Fluindione (25), polystyrene sulfonate (8), paracetamol (4)	
	Adverse drug reaction	70 (0.3)	Polystyrene sulfonate (11), furosemide (6), atorvastatin (4), tramadol (3), macrogol (3)	“increased risk of adverse reactions by the combination of atorvastatin and fenofibrate”
	Failure to receive drug	92 (0.3)	Esomeprazole (3), cholecalciferol (3), acetylsalicylic acid (3), furosemide (3)	“Prescription of furosemide not appearing on the nursing plan”

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Main Document
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 – Title
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6 – lines 35-37
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6 – lines 40-42
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6 – lines 46-50
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Pages 6 – lines 46-50
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5 – lines 20-23 Page 6 – lines 41-42 Page 6-7 – lines 50 - 65
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6 – lines 46 – 52 Page 7 – lines 53- 65
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Figure 1 Page 7 – lines 73-74
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7 – lines 61-71
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 7 – lines 66 - 71
		(b) Describe any methods used to examine subgroups and interactions	Page 7 – lines 66 - 71
		(c) Explain how missing data were addressed	Figure 1
		(d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	Figure 1

		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Figure 2
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	Page 7 - 8 – line 75 - 88
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1 Page 7 - 8 – line 73 - 83
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 8_9 – lines 95-108
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 11 - 12 – lines 164- 192
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11 – lines 103-163
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11 - 12 – lines 170- 196
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14 – lines 270-275

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.