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Pharmaceutical algorithms set in a real time clinical decision support targeting high-alert medications applied to pharmaceutical analysis

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Keywords: Artificial intelligence; Pharmaceutical algorithms; Drug-related problems; Clinical decision support system; Patient safety

Abstract

Background

Pharmaceutical analysis of the prescription has to prop up the quality of patients' medication management in a context of medication's risk acculturation. But this activity remains highly variable. Medication-related clinical decision support may succeed in reducing adverse drug events and healthcare costs.

Purpose

This study aims to present AVICENNE as a real time medication-related clinical decision support (rt-CDS) applied to pharmaceutical analysis and its ability to detect Drug related problems (DRP) consecutively resolved by pharmacists.

Basic procedures

A Medication-related rt-CDS is created by integrating the software PharmaClass® (Keenturtle), 5 health data streams on the patient and Pharmaceutical algorithms (PA). PA are created by modeling the pharmaceutical experiment about DRP and the thread of their criticality. They are partially encoded as computerized rules in PharmaClass® allowing alerts' issue.

An observational prospective study is conducted during 9-months among 1000 beds in 2 health facilities. The first step is to identify alerts as DRP; their resolution follows with clear guidelines worked out for the pharmaceutical analysis. A basis on predictive positive values (PPV) of the PA is being built today helping to know the performance of DRP detection and resolution.

Main findings

71 PA are encoded as rules into PharmaClass®: 40 targeted serious adverse drug events. 1508 alerts are analyzed by pharmacists. Among them 921 DRPs were characterized and 540 pharmaceutical interventions transmitted of which 219 were accepted by prescribers. Three PPV are defined depending on software, pharmacist and patient.

Principal conclusion

Clinical pharmacy societies should host, share and update a national corpus of PA and exploit its educational interest.

1 Introduction

The global burden of iatrogenic medication-related harm is an increasingly recognized public health problem. The World Health Organization has contributed to the acculturation both of the institutions and the health professionals. The third global patient safety challenge aims to reduce medication-related harm by 50% within 5 years [1]. Attention is focused on 3 aspects of drug safety that increases the risk of Drug-related problems (DRPs) occurrence: high risk situations, polypharmacy and transition of care. Drug iatrogenia cost is estimated at 42 billion dollars a year for the whole world. In France a range of 13 000 to 30 000 deaths is attributable each year to medication [2, 3]. National institutional programmes based on local initiatives have to sublimate the current dynamic for the common good, especially in e-health [4].

Adverse drug events (ADEs) are “injuries due to medication management rather than the underlying condition of the patient” associated with increased morbidity and mortality, prolonged hospitalizations, and higher costs of care [5, 6]. Nearly half of all adverse drug events are considered preventable [3, 7]. Therefore, the prevention, detection, resolution, and recovery of actual or potential DRPs through Pharmaceutical interventions (PIs) are considered key to reduce ADEs [7].

DRPs are events or circumstances involving drug therapy that actually or potentially interferes with desired health outcomes [8]. The occurrence of DRP can affect all drugs, high-alert medications are not more frequently involved in the onset of adverse drug events but the consequences are more severe or even catastrophic [9]. The French society of clinical pharmacy published a classification of 10 types of DRP and 7 types of PI [10].

Pharmaceutical analysis is a safety barrier for patient and healthcare professionals. It's a regulatory obligation in many countries but remains a challenge [11]. The European association of hospital pharmacists statements integrates pharmaceutical analysis into the pharmaceutical practice by mentioning that « all prescriptions should be reviewed and validated as soon as possible by a hospital pharmacist. Whenever the clinical situation allows, this review should take place prior to the

supply and administration of medicines” [12]. The lack of reproducibility between pharmacists mainly relates to DRP detection. PIs for DRP resolution are usually more consistent [13, 14].

The exploitation of a medication-related Clinical decision support (CDS) is associated with reduced morbidity rates, improved prescribing practices, facilitation of preventative care services, improved patient monitoring, reduced ADE rates and healthcare costs [15, 16]. A CDS is a “software that is designed to be a direct aid to clinical decision-making in which the characteristics of an individual patient are matched to a computerized clinical knowledge base, and patient-specific assessments or recommendations are then presented to the clinician and/or the patient for a decision” [17]. Basic CDS functionalities are frequently proposed by computerized patient order entry software publishers. Advanced functionalities often use only 2 data sources: medication and patient's medical biology results [18, 19]. Associating an advanced CDS with a computerized patient order entry is often limited by the lack of health information systems (HIS) interoperability. This is why initiatives other than AVICENNE are now confined to single health facilities. Corny J *et al* assessed the ability of a machine learning system to detect DRP in the same way as the pharmacist. System performance has been good, knowing that CDS is only capable of replicating past pharmaceutical practice. This CDS should have difficulty finding a rare problem due to the onboard technology [20]. Check-medication appropriateness (CMA) demonstrates its added value to support medication surveillance applied to 4 pharmacotherapeutic categories in synergy with already integrated basic clinical decision support and bedside clinical pharmacy. CMA system uses the same symbolic artificial intelligence technology as AVICENNE and raises the question of the representation and sharing of knowledge in the form of pharmaceutical algorithms (PA) [21]. Rommers MK *et al* report that the most relevant alerts come from clinical rules applied to a combination of pharmacy and laboratory data [22]. To avoid over alerting health professionals and to maintain a good efficiency the alerts have to be analyzed by a pharmacist [23, 24].

Several factors have led our teams to converge towards a system able to systematize the DRP detection: the regulatory obligation, the workload, the economic constraints and the regulatory context that promotes clinical pharmacy activities and e-health [25]. The investment of an Information technology team, the digital and clinical acculturation of pharmacists and the proposal of PharmaClass® by Keenturtle allowed the birth of the AVICENNE project. Financial support by the Grand East Health regional agency was essential. To deal with these challenges we made the choice to perform pharmaceutical analysis by integrating various health data in real time for a personalized medicine. This sets the basis of the big data in clinical pharmacy.

2 OBJECTIVE

This study aims to present AVICENNE as a real time Medication-related CDS (rt-CDS) applied to pharmaceutical analysis and its ability to report DRP to be consecutively resolved by pharmacists.

3 MATERIALS AND METHODS

3.1 Structuring pharmaceutical analysis digitalization by Pharmaceutical algorithms

The PA are built in order to improve DRP detection and resolution. It consists of 5 elements: pharmacotherapeutic rule which defines a specific DRP, corresponding encoded rule, DRP itself in the light of its cause/consequences, DRP resolution strategy, and potential PI transmitted to prescribers.

The pharmacotherapeutic rule is a finite and unambiguous series of appreciation' elements linked by operators (logical, mathematical, duration). An element of appreciation is a variable defined by its nature and its value either quantitative or qualitative. It sets from different fields and data-collection programs as identity and patient flow, medication data, laboratory results examination, medical history, physiological constants. The second step is mediated by a finite sequence of automated rules which computerized the pharmacotherapeutic rule applied on a finite dataset to issue alerts.

The DRP resolution strategies are the second arm of the PAs which are not yet digitalized in PharmaClass®. It is a synthetic guideline structuring the pharmaceutical analysis of an alert with anamnesis, evidence-based analysis, DRP identification and closed by PI built for DRP resolution.

The CDS system rests on 3 pillars: computerized clinical knowledge base represented by PA, software and patient characteristics. The triple dynamic junction between these pillars gives rise to the AVICENNE Medication-related rt-CDS. With the help of the pharmacist it allows digitalization of pharmaceutical analysis process (figure 1). The role of pharmacist and Medication-related rt-CDS are well defined which facilitates their integration into clinical workflow following the Subjective, Objective, Assessment, Plan method [26, 27].

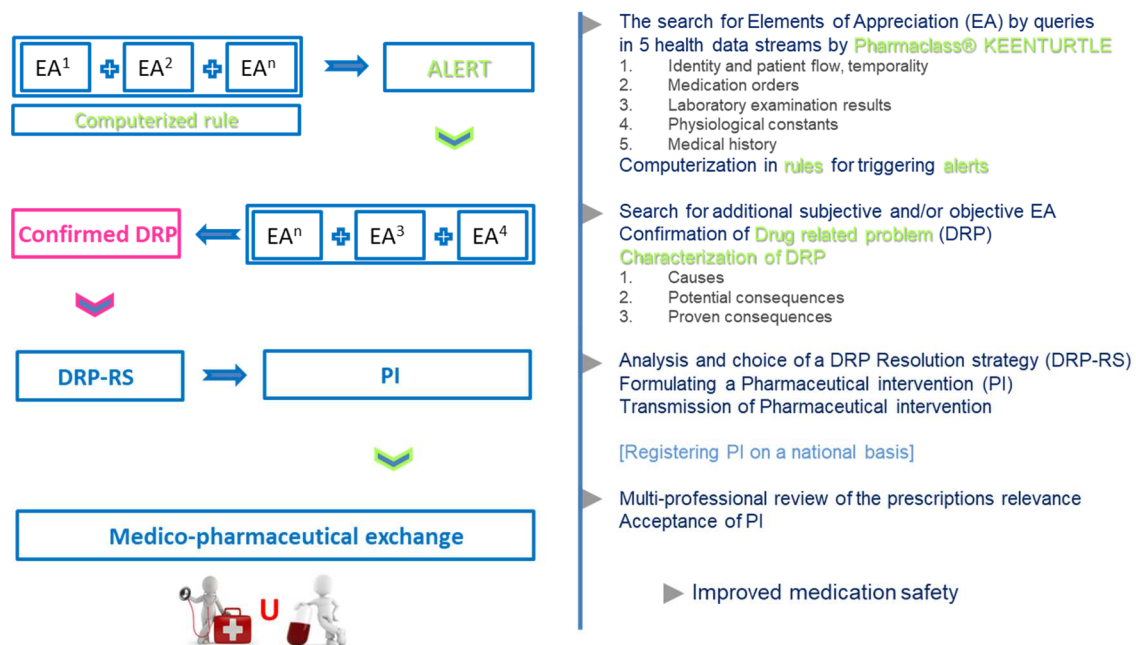


Figure 1. Process of pharmaceutical analysis using pharmaceutical algorithms

The corpus as a structured set of pharmaceutical algorithms is built in a way to better share information among health professionals and manage their actualization. The following characterizations are gathered in the Excel® (Microsoft - USA) file, each algorithm representing 1 line with: denomination, elements of appreciation, pharmacotherapeutic rule, corresponding encoded rule, positive predictive values, dates of creation and validation, creative institution, discipline, bibliographic references, DRP resolution strategy, reference and version number.

3.2 Description of the Medication-related clinical decision support

The AVICENNE rt-CDS is presented according to the Clinical Decision Support Systems Taxonomy to describe its technical, workflow and contextual features [28].

3.2.1 Technical characteristics

It was decided to use PharmaClass® (Keenturtle - F) because it was the only commercially available software meeting the set of specifications in 2017. Health data are lacking of semantic interoperability which PharmaClass® aims at overcoming by integrating the data extracted from the different health and care record software's. This regardless of the type of computerized patient order entry and health data formats provided. Its strength is to ensure the conversion of computerized patient order entry data expressed in proprietary codes into international languages. ICD-10 is used for medical history, ATC/CIP-7/UCD-13 for medication data, LOINC for laboratory examination results and SNOMED-CT for physiological constants.

PharmaClass® is a web application running with a Boolean rule-based reasoning engine. The rules include variables (from health data streams), operators (Boolean, mathematical and duration) and values (biological cut-off, age, presence or absence of any variable, etc). It is installed on the servers of one hospital, the data from the other hospitals are transported via an Internet Protocol Security tunnel. The confidentiality of these sensitive data is respected in accordance with the European general data protection regulation [29]. A partnership and a confidentiality agreement are signed between the health facilities and Keenturtle. A declaration of conformity with the National commission for informatics and liberties is made.

3.2.2 Health data streams applicable by PharmaClass®

Five structured health data streams coming from health facilities are integrated by the rt-CDS of which the formats are detailed in the table 1. Data from in- patients are extracted every 60 minutes. The drug booklet is crushed weekly to keep up to date, the medical history is implemented monthly.

Table 1. Information system and format of data extracted from Health data streams of the two hospitals

Health data streams	University hospital		Main hospital	
	Source	Format	Source	Format
Identity and patient flow	M-GAM® (<i>Maincare - USA</i>)	IHE PAM	Hexagone Web® (<i>Agfa - USA</i>)	<i>Ad hoc .csv</i>
Medication data	DxCare® (<i>Dedalus - F</i>) Pharma® (<i>Computer engineering - F</i>)	PN 13	ImagePharma® (<i>Inlog - F</i>)	<i>Ad hoc .csv</i>

Laboratory examination results	DxCare® (Dedalus - F)	HL7/HPRIM 2.5	Cora DPS® (Maincare - USA)	HPRIM 2.1
Physiological constants	DxCare® (Dedalus - F) ^a	CDA-R2-L3	Cora DPS® (Maincare - USA)	Ad hoc .csv
Medical history	WEB100T (Dedalus - F)	Ad hoc .csv	Cora PMSI® (Maincare - USA)	Ad hoc .csv

^a Physiological constants are not made available by DxCare® (Dedalus - F)

3.3 Production of pharmaceutical algorithms

In the AVICENNE project the field of clinical pharmacy was favored while medico-economics and pharmaco-epidemiology fields were less investigated. PA were carried out according to a "knowledge base framework" by modelling the pharmaceutical experiment which includes the thread of DRP' criticality [27]. The incorporated evidence-based clinical knowledge derived from Summary of health product characteristics (Thériaque® (CNHIM - F)) and national guidelines, randomized trials, Clinical practice guidelines: NICE and HAS guidelines, Cochrane reviews, National thesaurus of drug interactions (ANSM - F), ... [30, 31]. These last recommendations are incorporated if their level of evidence is A or B.

In the corpus PA are grouped into 2 categories according to their subjectively defined criticality: high, targeting serious adverse drug events or moderate. PA targeted the 10 types of DRP and are regrouped according to the type of risk situation [10]. PA are manually encoded in PharmaClass® by a pharmacist assisted by the Keenturtle publishers.

PA are validated by consensus between 5 clinical pharmacists from the 2 hospitals during face-to-face meetings. When necessary, discussions supported by good practice recommendations have taken place before validation with clinical experts in each discipline (cardiology, rheumatology, geriatrics, infectiology). The objective is not limited to the reproduction of the existing practice regarding to medication management but if possible to its improvement by clinical pharmacy expertise. For example, non-supplemented iron deficiency can be detected more systematically, the salt intake by effervescent acetaminophen tracked throughout the hospital and the administration of an anticoagulant contraindicated in cases of severe renal failure detected as soon as the clinical biology result becomes available. PA are submitted to institutional validation by each drug

committee of the two health facilities. A simulation about the applicability of each encoded PA with dedicated fictive patients is done before putting the algorithms into production to ensure the absence of false negatives.

3.4 Pharmaceutical analysis of the alert

The alerts are analyzed by the 5 pharmacists involved in PA validation in their everyday practice. Alert analysis is provided for the entire hospital within the centralized clinical pharmacy service. At this step, the physicians are not concerned because of the risk to be exposed to over alerting and alert fatigue [32 - 34]. A flow chart structures this process and the filling of the basis of pharmaceutical analyzes.

An alert mentions several information laid down in the framework of the corpus. An example is presented in figure 2 for the PA named “Overdosing of metformin in case of renal insufficiency”, whose reference 29_GHT7_IR refers to the unique number of the PA in the field of Renal insufficiency in our group of hospitals. The date and time of the alert is presented (figure 2), the involved elements of appreciation with their value for this patient, the identity of the in-patient and care service where he is hosted, and status of the alert (consulted or not by a pharmacist).

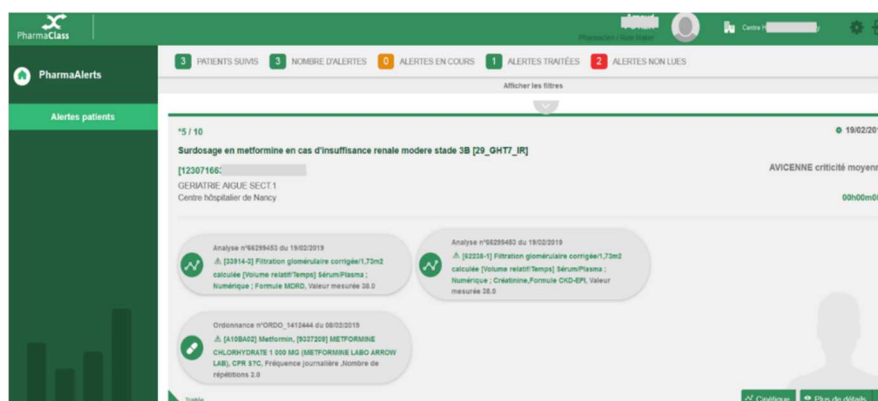


Figure 2. Overview of an alert given by PharmaClass® (Keenturtle - F)

The DRP resolution strategy “How to correct or mitigate the medication risk?” is independent of PharmaClass® and retrieved from external sources. Pharmacists evaluate the DRP relevance by

incorporating other elements of appreciation which can be found as implicit one, uncodable or unqueriable in the patient's file. To qualify the alert as a DRP, they have to select the right strategy among those which are listed in the guidelines of DRP resolution strategies. Applied to the alert presented in figure 2 the pharmacist has to search if the patient has received iodinated contrast product, suffer from Covid-19 or severe cardiac insufficiency, is really receiving Metformin 2 g per day and he must take into changes in renal function. If a DRP already exist, he has to transmit a PI to inform the prescriber of the overdosing of Metformin and propose to and suggest reducing the dosage and suggest reducing the dosage and following the evolution of renal function. Furthermore, the whole prescription is reviewed to eventually detect DRP not sought by PA.

3.5 Evaluation and data analysis

3.5.1 Study design

An observational prospective study has been ongoing since January 2019 during a 9-month experimentation period. A project coordinator pharmacist (0.5 full-time for pharmaceutical analysis and the other half for project management) collected data during 125 days. Data collection is only carried out off workdays because of a limitation in the human resources. Two health facilities are involved: a 1550-beds university hospital and a 450-beds main hospital. Respectively, up to 1000 beds and 95 beds of these 2 hospitals were concerned by the experimentation. Currently 70% of these identified beds in the university hospital take advantage of an organization in which new orders are daily, partially or fully analyzed by a pharmacist. In the main hospital the percentage is greater (97%) with a more entrenched clinical pharmacy practice; both of the new orders and the orders in progress with modification are daily analyzed. No control group or baseline evaluation of pharmaceutical intervention process is specifically available.

The number of 52 867 patients were included with no age limit. They were hospitalized in internal medicine, surgery and long-term care departments. Each hospitalized patient was eligible for inclusion. No exclusion criteria were defined. Patients would not provide informed consent as

AVICENNE was implemented as standard of care. The declaration to the ethics committee is not necessary.

3.5.2 Basis of pharmaceutical analysis

Data from the pharmaceutical analysis of alerts were collected in an Excel® (Microsoft - USA) database. The data includes the patient characteristics, analyzed alert and type of PA, false positive alerts due to Pharmaclass®, DRP detected by Pharmaclass®, DRP detected and resolved by a pharmacist or a physician before the alert from Pharmaclass®, transmitted PI and way of transmission (oral or electronical), acceptance of PI by the prescriber. The acceptance of PI was evaluated from 1 to 7 days after transmission by the number of changed prescriptions in medications involved in a DRP. Reasons of non-acceptance were not investigated.

3.5.3 Basis of indicators

Data collected were used to characterize the inputs that supply the rt-CDS, the outputs corresponding to its production, the outcomes tied to its impact on the patient medication management. The rt-CDS performance in terms of Predictive positive value (PPV) is represented by the:

- Primary outcome as the probability of a potential DRP detection after pharmaceutical analysis of the alert. It represents Pharmaclass® PPV *i.e* the ratio of potential DRP (Number of DRP without technical false positives) to analyzed alerts.
- Secondary outcomes concern the probability of PI transmission after proven DRP identification. It represents Pharmacist PPV *i.e* the ratio of PI to potential DRP, and secondly the probability of PI implementation by modifying patient care. It represents Patient PPV *i.e* the ratio accepted PI to PI transmitted.

This evaluation was only performed with descriptive analyses.

4 RESULTS

4.1 Implementation of the Medication related rt-CDS

PharmaClass® has been integrated in 6 months on the two facilities including all health data streams excepted physiological constants in the university hospital. About 350 000 data points are continuously analyzed.

Seventy one validated PA were encoded into PharmaClass®. The denomination of all PA implemented during the study period is presented in Appendix 1. They were implementing 300 medications representing 50 classes ATC4 among the existing 93. They also operated 35 medical biology exams, 8 medical histories and 4 physiological constants. PA targeted 8 of the 10 types of DRP excepted the Unreceived drug and the Monitoring problem. Different themes are covered by the algorithms such as problems antithrombotics, digoxin and lithium concerning never events, biology monitoring, geriatrics, infectiology or renal failure.

4.2 Results from the exploitation of pharmaceutical algorithms

During this 9-months experimentation period, 52 867 patients were admitted (48 938 in university hospital; 3 929 in main hospital). Respectively the mean age of patients admitted was 50 years and 70 years while it was 70 and 78 years for those who have an analyzed alert. The 1508 analyzed alerts represent 1166 patients (figure 3) during the 125-days data collection period. After excluding technical false positives 1068 DRP are characterized; some of them (147) have already benefited from a health professional intervention.

An in-depth analysis of 921 proven DRP allowed the transmission of 540 PI and the acceptance of 219 PI (41%) with modification of the patient's prescription. The fate of the IP is unknown for 101 cases (19%) and 220 PIs (41%) have not been accepted.

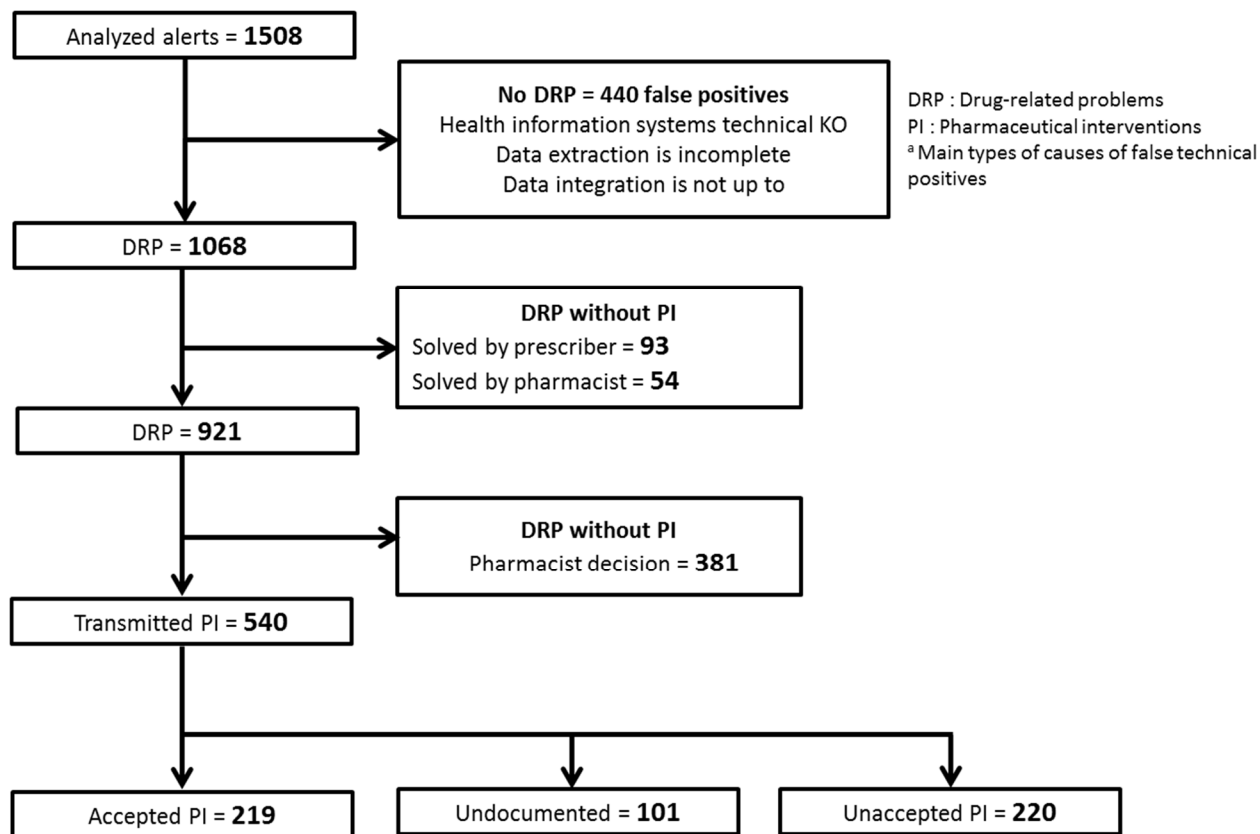


Figure 3. Flowchart of analyzed alerts by pharmacists

There are 3 main causes behind technical false positives. First, when data extraction is incomplete (complex posology, “if needed” prescription), then data integration is not up to date (Patient is out, Drug is stopped, Drug prescription is unique, New version of element is not taken into account, poor management of turning off alerts). The reasons of non-intervention after pharmacist’s analysis are presented for each PA concerned in Appendix 1.

Table 2 presents the rt-CDS performance in terms of PPV associated to the outcomes of:

- Software: 70.8% (1068 DRP/1508 alerts analyzed alerts)

It depends on the input queryability of the hospital information system, on the capacity of PharmaClass® to request the right data and to improve the software in order to issue more relevant alerts, and third on the coding quality by pharmacists including the management of the most recent data,

- Pharmacist: 50.6% (540 PI transmitted/1068 DRP)

It underlines the professional expertise with more particularly the relevant use of clinical knowledge base in the PA building, the quality in the pharmaceutical practice organization and the responsiveness of healthcare professionals

- Physician: 40.6% of analyzed alerts led to modifications in the orders (219 PI accepted /540 PI transmitted)

It underlines the clinical relevance of the PI, the confidence between physicians and pharmacists and the performance of the way in which the exchange is shared.

Table 2. Results of pharmaceutical analysis of alerts: overall, by hospital and according to the

	Analyzed alerts	Technical False positive	Pharmaclass PPV %	Solved DRP		Non relevant DRP according to pharmacist	Pharmaceutical interventions	Terms of transmission		Pharmacist PPV %	Acceptation		Patient PPV %
				By prescriber	By pharmacist			Electronic note	Phone call		Electronic note	Phone call	
General results	1508	440	70.8	93	54	297	540	460	80	50.6	152	67	40.6
High criticality	712	255	64.2	38	28	136	231	177	54	50.5	67	47	49.4
Moderate criticality	796	185	76.8	55	26	161	306	283	26	50.6	85	20	34.0
University hospital	1299	349	73.3	66	46	270	491	418	73	51.6	130	60	38.7
Secondary care hospital	209	91	56.5	27	8	27	49	42	7	41.5	22	7	59.2

criticality of the algorithms

The overall acceptance rate of transmitted PI is better in the facility with advanced clinical pharmacy practices than in the university hospital; Physician PPV are respectively 59.2% (IC 95%=[45.4-73.0]) versus 38.7% (IC 95%=[34.3-43.0]). The acceptance rate is also higher when PI is transmitted during oral exchange 83.8% (IC 95%=[80.7-86.9]) versus electronic note exchange 33.0% (IC 95%=[27.0-37.0]). Nevertheless, only 14.8% of PI are transmitted by phone call. It is similar with the high PA

49.4% (IC 95%=[43.0-55.8]) versus moderate PA 34.0% (IC 95%=[28.7-39.3]) (Table 2). High criticality alerts include antithrombotic medicines, contra indications or untreated severe hypokalemia for example; these situations are explained in the appendix 1.

The 5 PAs that issued the highest number of alerts are presented (table 3) as well as the 5 PAs whose PI were mostly accepted (table 4).

Table 3. The PI acceptance rate of 5 algorithms with the highest number of alerts

Denomination	DRP ^a type	Analyzed alerts	Technical False positive	Pharmaclass PPV ^b (%)	Unrelevant DRP according to pharmacist	Solved DRP	Pharmaceutical interventions	Pharmaceutical interventions type	pharmacist PPV (%)	Accepted PI	Patient PPV (%)
Anticoagulant Inappropriate route of administration Hemorrhage	Inappropriate route of administration	59	3	95.0	4	3	44	Optimising medication administration	78.6	21	47.7
No potassium prescription Untreated indication Moderate hypokalemia	Untreated indication	60	15	75.0	1	21	22	Adding	48.9	17	77.3
Heparinotherapy and obesity Drug underdosing Thromboembolic event	Drug underdosing	65	19	70.8	12	3	27	Dose adaptation	58.7	4	14.8
Anticoagulant and antiarrhythmic drug underdosing Inefficiency	Drug underdosing	66	5	92.4	4	7	47	Dose adaptation	77.0	23	49.0
Direct factor Xa inhibitors and heparin Contraindication Hemorrhage	Contraindication	11 1	62	44.1	13	9	24	Stop	49.9	21	87.5

^a DRP: Drug-related problem ^b PPV: Predictive positive value

Table 4. The PI acceptance rate of 5 algorithms with the highest proportion of PI

Denomination	DRP ^a type	Analyzed alerts	Technical False positive	Pharmaclass PPV ^b (%)	Unrelevant DRP according to pharmacist	Solved DRP	Pharmaceutical interventions	Pharmaceutical interventions type	Pharmacist PPV (%)	Accepted PI	Patient PPV (%)
Absence vitamins parenteral nutrition	Untreated indication	48	34	29.2	0	2	12	Adding	85.7	6	50.0

Untreated indication Deficiency											
Calcium inhibitor Drug non indicated Side effects	Non indicated drug	15	1	93.3	0	1	12	Stop	85.7	6	50.0
No potassium prescription Untreated indication Moderate hyperkalemia	Untreated indication	37	9	75.7	11	8	7	Adding	25.0	4	57.1
Metformin and severe renal failure Contra indication Lactic acidosis	Contraindication	11	2	81.8	1	1	6	Stop	6 6 7	4	60.0
No iron and chronic renal failure Untreated indication Chronic anemia	Untreated indication	15	4	73.3	3	3	5	Adding	45.5	3	60.0

^a DRP: Drug-related problem ^b PPV: Predictive positive value

5 DISCUSSION

5.1 Main results

AVICENNE offers in the field of Clinical Pharmacy an advanced Medication-related rt-CDS.

The alerts analyzed by Pharmacist are 1508 and 540 PI have been transmitted to prescribers resulting in 219 changes in medication management by the prescriber. In these experimentation period only 14.8% of the PIs were transmitted orally, which can explain why overall only 40.6% of them were accepted. This rate is rather low. The results obtained differ significantly between the 2 hospitals. Those with established clinical pharmacy activities benefit from fewer alerts, DRP detected already resolved and a better acceptance rate of PI. However, its obsolete HIS generated more technical false positive.

Among the strengths of AVICENNE, the modeling of clinical reasoning by PA to detect a DRP that it is possible to solve by a unambiguous PI, easy to implement and having a significant impact on patient care is a key point. A wide range of medical domains are addressed by PA. They combine hundreds of situations defined from heterogeneous patient data. The management of temporality is included in the PAs; the extinction of alerts must be managed by PharmaClass®.

Targeted DRPs are those whose detection is difficult in real life by health professionals. Rare DRPs are targeted with a low alerting threshold while more frequent DRPs are targeted in very specific ways.

The goal is to have an appropriate prescription for each patient; the liberty of judgment of the pharmacist and the doctor must be preserved to create a relationship of trust. Future results will have to say whether when the prescription had the most potential for harm, the physician accepts more PI [32].

5.2 About the method

The strength of AVICENNE is to exploit 5 health data streams on 2 different hospitals. PharmaClass(r) has the advantage of not being a home-grown system [33]. PA are validated only by 5 clinical pharmacists and are being validated by physicians. Furthermore, PA formalized so far represents only a small part of all the DRPs sought by the pharmacist during his pharmaceutical analysis [18]. On the other hand, they detect in a systematic way the DRPs, whether or not they have already been identified by the pharmacist. All the alerts issued have not been analyzed because of understaffing. The alerts processed first are those that seem subjectively the most relevant, this implies a selection bias. False negatives are not documented which explains that NPV, sensibility and specificity could not be determined.

The study is an observational prospective study with no control group or baseline evaluation of pharmaceutical intervention process. AVICENNE is implemented as standard of care in addition to the regularly performed pharmaceutical analysis. This practice does not benefit from a documented standard and is heterogeneous around French hospitals including those of the AVICENNE project [14]. The AVICENNE evaluation presents some of the characteristics of pragmatic trials [34].

5.3 Limits highlighted by this experiment

A peculiarity of the development of AVICENNE as a clinical pharmacy tool is the absence of a standard for the practice of pharmaceutical analysis. It is sometimes difficult to represent all clinical situations using the available patient data; the absence of false negatives guaranteed by a low alerting threshold is then the objective pursued. The temporality of the elements of appreciation must be framed in the pharmacotherapeutic rule. It allows to limit the duration of emission of an

alert. This leads to significantly fewer alerts. The analysis of alerts by the pharmacist rather than by the physician, the algorithm design and the iterative implementation are likely to alleviate alert fatigue [23 – 24, 32 - 34].

Overall, the number of alerts to be analyzed conditions the occurrence of fatigue alert, mainly if a large number of false technical positives are present among these. The reality of practices is sometimes irrelevant, making the detection of certain DRP more difficult and generating demotivating alerts for the pharmacist; for example the systematic assay of aPTT biases the detection of an underdosing of heparin.

Reasons for non-compliance with the pharmacist's advice were not investigated.

The performance of the rt-CDS is based on the evolution of the three pillars. Guidelines must be explicit *i.e.* define completely and precisely some elements of appreciation. It is still a challenge [36].

PAs must be made up in part at least of elements of appreciation encodable *i.e.* what can be transcribed unequivocally in source code. Encoding must use international standards like LOINC and SNOMED-CT to increase interoperability [38]. Software publishers have to make data queryable from health data streams by HIS convergence, which is far from the case today. Cimino JJ suggest therefore to “add information to the record that explains the “why” of a patient's care” and “that we modify electronic health records to support explicit representation of this information using formal structure and controlled vocabularies” [39].

5.4 Perspectives

Number and specificity of encoded PA is improving to enhance the rt-CDS performances. The scope of pharmacotherapy, however, is very broad. The PA will have to be updated according to the guidelines evolution. The development of PA should be patient-oriented and experience-centered rather than regulatory drug information centered. It highlighted the clinical pharmacist role instead his substitution.

Creation of an ontology can help update and share AVICENNE knowledge currently in rule-encoded PA form. Clinical reasoning ontology will be developed to improve CDS by simulating the decision-

making processes carried out by clinicians from detection to resolution [39]. Making inferences by following the relationships within the ontology to replace the rule-based computational methods for inferencing is being investigated.

The severity of the potential clinical, economical and organizational impacts will be studied using the CLEO scale of the French society of clinical pharmacy [35]. Quintens *et al* transmitted 3205 PI after analysis of 39481 alerts (8.5%) [21]. This rate is higher for AVICENNE. Improving the overall acceptance rate requires a reorganization of clinical pharmacy practices with medico-pharmaceutical exchanges promotion. An 'adverse drug event alerting system' (ADEAS) is in daily use in an holland hospital pharmacy [22]. It is used by hospital pharmacists to select patients at risk of possible adverse drug events. During 5 months 2650 safety alerts were generated resulting in 270 PI whose 204 leading to a safely medication use among patients. A machine learning-based CDS to identify prescriptions with a high risk of medication error. Its purpose is to reproduce the results of previous pharmaceutical analyzes. This technology seems efficient, has advantages but exposes to some limitations: the lack of ability to detect a DRP that occurs rarely, the lack of ability to detect a problem not previously detected by pharmacists, application to evolving practices [20].

We assess here the proof of concept of the efficacy of AVICENNE. It is now necessary to repeat analyses to evaluate variation in quality of data (interrupted time-series to take into account pharmacists or physicians changes, update of computerized patient order entry softwares) [41].

Cooperation with the Department of Medical Information is underway to improve the detection of associated comorbidities that enhance the funding of hospital stays. AVICENNE is a powerful vehicle for evaluating professional practices medico-economics. Clinical pharmacy societies should host and take care of updating a national corpus of PA and exploit its educational interest. The pedagogical role of PAs with conduct to be held should be fully made available for initial and continuing training.

6 Conclusion

AVICENNE Medication related rt-CDS is a health innovation aiming to perform pharmaceutical analysis. Clinical pharmacist uses pharmaceutical algorithms set through a software connected to the patient's medical files. The quality of the pharmaceutical analysis is put to the test by the AVICENNE provided effectiveness. It foreshadows the creation and implementation of more specific pharmaceutical algorithms. To improve the acceptance rate of PI AVICENNE must be coupled with clinical pharmacy practice transformation to improve patient safety.

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- Authors' contributions

Arnaud POTIER wrote the article.

Project strategy and management is assumed by Edith DUFAY, Béatrice DEMORE and Arnaud POTIER.

All authors made substantial contributions to the data acquisition, the data analysis and approved the manuscript.

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- Summary table

Summary table

'What was already known on the topic'

Clinical pharmacy services are associated with reduced mortality rates which highlights the safety barrier offered by pharmacist

Medication-related clinical decision supports are associated with the decrease of adverse drug events, morbidity, healthcare costs and the improvement of prescribing practices

To review and validate all prescriptions as soon as possible by a pharmacist is still a challenge

'What this study added to our knowledge'

AVICENNE structures pharmaceutical algorithms on drug-related problems and improves the real time pharmaceutical analysis because of its digitalization

AVICENNE underlines the necessity to link to the implemented CDS a new organization which reinforce the relationship between physicians and pharmacists

Appendix 1: Pharmaceutical algorithm denomination and associated reasons of non-intervention after pharmacist's analysis

*Pharmaceutical algorithm denomination; ‡ pharmaceutical reason of non-intervention

No potassium prescription Untreated indication Moderate hypokalemia*

Potassium was added less than an hour ago and the alert has not yet disappeared‡

Potassium Underdosing Moderate hypokaliemia

Potassium supplementation has been added, serum potassium is not yet normalized

No potassium prescription Untreated indication Severe hypokalemia

Potassium was added less than an hour ago and the alert has not yet disappeared

No potassium prescription Untreated indication Moderate hyperkalemia

Potassium was added less than an hour ago and the alert has not yet disappeared

Hyperkalemic drugs Adverse effect Moderate hyperkaliemia

The kalaemia is hemolyzed

Hyperkalemic drugs Adverse effect Severe hyperkaliemia

The dosage of the hyperkalaemic drug that triggered the alert has been reduced

Glucose-containing hypotonic solution Untreated indication hyponatremia

None

Statin and Daptomycin Adverse effect CPK rise

Patient admitted after fall with ground station

Myocardial infarction

Colchicin Overdosing Digestive disorders

Kidney function being improved

Heparinotherapy and obesity Underdosing Thromboembolic event

Medical patient

High hemorrhagic risk

Digoxin Overdosing Cardiotoxicity

None

Digoxin and severe renal failure Contra indication Cardiotoxicity

Digoxin prescribed on demand

Kidney function being improved

Normal digoxinemia

Colchicin and severe renal failure Contra indication Overdosing

Kidney function being improved

Normal glomerular filtration rate adapted to body surface

Metformin and moderate renal failure 3A stage Overdosing Lactic acidosis

Kidney function being improved

Normal glomerular filtration rate adapted to body surface

Metformin and moderate renal failure 3B stage Overdosing Lactic acidosis

Kidney function being improved

Normal glomerular filtration rate adapted to body surface

Metformin and severe renal failure Contra indication Lactic acidosis

Minimum dose of metformin validated by nephrologist

NSAID and risk factors Non indicated drug Worsening kidney failure

None

NSAID and severe renal failure Contra indication Nephropathy

None

No anti-glaucomatous eye drops	Untreated indication	Acute crisis
<i>Patient in consultation with a history of glaucoma without a computerized prescription of medicines</i>		
Unfractionated heparin	Overdosing	Hemorrhage
<i>Unfractionated heparin dose already reduced</i>		
<i>Slight under aPTT without anti-Xa result</i>		
Unfractionated heparin	Underdosing	Thromboembolic event
<i>Unfractionated heparin dose already augmented</i>		
<i>Slight over aPTT without anti-Xa result</i>		
Low molecular weight heparin	Overdosing	Hemorrhage
<i>None</i>		
Apixaban 5 mg and risk factors	Overdosing	Hemorrhage
<i>Normal glomerular filtration rate adapted to body surface</i>		
<i>Age over 80 on the birthday date</i>		
Rivaroxaban 20 mg cpr	Overdosing	Hemorrhage
<i>Decreasing kidney function</i>		
<i>Normal glomerular filtration rate adapted to body surface</i>		
Apixaban 2.5 mg	Underdosing	Thromboembolic event
<i>Decreasing kidney function</i>		
<i>Altered glomerular filtration rate adapted to body surface</i>		
Direct oral anticoagulant and Heparin	Contra indication	Hemorrhage
<i>Antithrombotic stopped within an hour</i>		
<i>The stop of the antithrombotic is not traced on the prescription</i>		
Direct oral anticoagulant and severe renal failure	Contra indication	Hemorrhage
<i>Antithrombotic stopped within an hour</i>		
Direct oral anticoagulant and VKA	Drug interaction	Hemorrhage
<i>Antithrombotic stopped within an hour</i>		
ACEi and sartan	Drug interaction	Renal failure and fluid and electrolyte disturbances
<i>None</i>		
Xabans and Enzymatic inhibitor	Drug interaction	Hemorrhage
<i>Drug association not recommended but not contra indicated</i>		
Methotrexate and absence of folinate	Untreated indication	Toxicity
<i>Folinate not prescribed on the day of methotrexate but later</i>		
Abiraterone and absence of Glucorticoïd	Untreated indication	Relapse
<i>None</i>		
Protein kinase inhibitor and Pump proton inhibitor	Drug interaction	Decreased bioavailability
<i>Pump proton inhibitor cannot be stopped</i>		
Protein kinase inhibitors	Inappropriate administration	Decreased bioavailability
<i>Protein kinase inhibitors is administrated as recommended</i>		
<i>Patient eats very little</i>		
Bradycardic drugs	Adverse effect	Bradycardia
<i>Transient bradycardia</i>		
<i>Entry error by the nurse</i>		
Ticagrelor or Prasugrel and Absence Aspirin	Untreated indication	Thrombosis
<i>Aspirin contra indicated</i>		
<i>Ticagrelor or Prasugrel added within an hour</i>		
Heparin and VKA	Non indicated drug	Hemorrhage
<i>Higher INR target in a patient with an artificial valve</i>		
Calcium channel blocker	Drug non indicated	Side effects
<i>Transient or on-demand prescription of an intravenous calcium channel blocker</i>		

Bisphosphonate Overdosing Hypocalcemia

None

Injectable iron Overdosing Toxicity

Pediatric dosage ok

Transdermic Fentanyl or Scopolamin Overdosing Adverse effects

None

Absence vitamins parenteral nutrition Untreated indication Deficiency

Vitamins prescribed via a complex protocol

Parenteral antibiotic and multiple oral drugs Inappropriate route of administration Undue costs

None

Anticoagulant and antiarrhythmic Underdosing Inefficiency

Interacting drug prescribed on demand

Tamoxifen or Codein and Selective serotonin reuptake inhibitors Drug interaction Inefficiency

None

Antiepileptics Drug interaction Epileptic seizure

Interacting drug prescribed on demand

Lithium Contra indication Renal insuficiency

None

No iron and chronic renal failure Untreated indication Chronic anemia

Limitation of care in this patient

Absence of a venous route

Caspofungin Underdosing Infectious risk

None

Miconazol and Direct oral anticoagulant or hypoglycemic sulfonamides Drug interaction Hemorrhage
Hypoglycemia

None

Anti-parkinsonian drugs Drug interaction Inefficiency

Interacting drug prescribed on demand

Pregabalin Underdosing Inefficiency

Well-balanced usual treatment for the patient

Dosage being reduced

Opioids and absence of laxatives Untreated indication Constipation

Fasting or post-operative patient

Anticoagulant Inappropriate route of administration Hemorrhage

No possibility of changing administration route for preventive anticoagulation

Valproic acid Adverse effects Thrombopenia or Hepatopathy

Other medical cause or drug cause of thrombocytopenia/ hepatic cytolysis

Acetaminophen Overdosing Hepatitis

Slightly overdosed post-operative prescription

Enoxaparin or Calcic heparin prophylaxis and Thin patient Overdosing Hemorrhage

None

Absence of iron and Iron deficiency Untreated indication Anemia

Non-significant iron deficiency

Absence of a venous route

VKA Overdosing Hemorrhage

VKA stopped within an hour

Triple Whammy Drug interaction Renal insuficiency

Post-operative pain treated with NSAIDs for a few days

Diabetes and absence ACEi - Sartan Untreated indication Renal insufficiency

None

Allopurinol and Azathioprin Contra indication Cytopenia

None

Immunosuppressants Adverse effects Cytopenia grade 2 and over

Other medical cause of thrombocytopenia

Idiopathic thrombocytopenic purpura for which immunosuppressants are part of the treatment

Vancomycin Underdosing Infection

None

Myasthenia Contra indication Aggravation

Patient without myasthenia gravis after investigation

Calcic heparin prophylaxis Drug non indicated Hemorrhage

Altered glomerular filtration rate adapted to body surface

Antithrombotics and Thrombocytopenia Contra indication Hemorrhage

None

Insulin or GLP1 Inappropriate administration Hypoglycemia

Expert agreement which recommended splitting Insuline glargine into 2 administrations per day for 2 patients

Anti epileptics Underdosing Epileptic seizure

Carbamazepine once a day for effective long-term treatment of trigeminal neuralgia

Heparin Adverse effect Heparin induced thrombocytopenia

None

Low molecular weight heparin and chronic renal insufficiency Contra indication Hemorrhage

None