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Abstract

Objective: When a new drug is marketed, physicians must decide whether they will consider it for their future practice. However, information about new drugs can be biased or hard to find. In this work, our objective was to study whether visual analytics could be used for comparing drug properties such as contraindications and adverse effects, and whether this visual comparison can help physicians to forge their own well-founded opinions about a new drug.

Materials and Methods: First, an ontology for comparative drug information was designed, based on the expectations expressed during focus groups comprised of physicians. Second, a prototype of a visual drug comparator website was developed. It implements several visualization methods: rainbow boxes (a new technique for overlapping set visualization), dynamic tables, bar charts and icons. Third, the website was evaluated by 22 GPs for four new drugs. We recorded the general satisfaction, the physician's decision whether to consider the new drug for future prescription, both before and after consulting the website, and their arguments to justify their choice.

Results: The prototype website permits the visual comparison of up to 10 drugs, including efficacy, contraindications, interactions, adverse effects, prices, dosage regimens,... All physicians found that the website allowed them to forge a well-founded opinion on the four new drugs. The physicians changed their decision about using a new drug in their future practice in 29 cases (out of 88) after consulting the website.

Discussion and conclusion: Visual analytics is a promising approach for presenting drug information and for comparing drugs. The visual comparison of drug properties allows physicians to forge their opinions on drugs. Since drug properties are available in reference texts, reviewed by public health agencies, it could contribute to the independent of drug information.

Keywords: Visual analytics, Information visualization, Drug information, New drugs

1. Introduction

Pharmaceutical innovation sometimes leads to a major improvement of the treatment of a disease, despite the fact that many new drugs bring only slight improvements. The prescription of new drugs is also associated with a higher risk of serious adverse drug events and a higher number of hospitalizations [1, 2]. Moreover, new drugs are generally more expensive than those already in use [3, 4]. Consequently, it is important to adopt new drugs carefully by considering the most recent and independent information available. However, the adoption of new drugs by physicians is often not associated with their clinical interest [5]. It has been shown that non-clinical parameters, such as sex and age of the physicians, are associated with the early utilization of new drugs [6].

New drug prescriptions by GPs are sometimes influenced by patients or specialists, but not systematically [7]. GPs typically have in their mind a "shortlist" of the drugs they usually consider for prescription in a given indication, and, when prescribing, they choose a drug from their "shortlist" depending on the patient profile. Thus, when a new drug comes onto the market, GPs need information about the new drug's pros and cons relative to older drugs for the same indication, in order to decide whether they should consider the new drug for addition in their "shortlist".

Today, finding independent information on new drugs is difficult. Most of the available information either comes from the pharmaceutical companies (*via* their representatives) or from expert opinions in medical journals. But experts usually propose "predigested" opinions that suffer from several drawbacks: (a) these opinions are not always available as soon as a new drug is brought to market, (b) experts and opinion leaders are not exempt from conflicts of interest [8, 9], (c) they may also disagree among themselves, and (d) their opinions are not tailored to the patient base of the physician.

Another approach to providing impartial information on new drugs is the systematic comparison of the properties of drugs, including their efficacy, cost, contraindications and adverse effects, based on the descriptions in the Summaries of Product Characteristics (SPCs) and evaluation reports. However, these documents are very long, making the comparison of the drug SPCs a very long, complex, and tedious task. It is almost im-

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possible for a physician to perform this task manually, and even more so to do it systematically.

In many other medical domains, visual analytics and information visualization [10] have permitted an easy access to voluminous data and complex knowledge. Recent examples include the visualization of infectious disease epidemiology [11] and the representation of spatiotemporal scenarios in homecare monitoring [12]. Visualization is also commonly used in bioinformatics to help interpret protein interaction, gene expression and metabolic profile data [13]. Distributed cognition has shown how the Human cognition can be "amplified" by visual and interactive representations in order to achieve complex cognitive tasks [14]. Thus, we hypothesized that visual analytics could help with the comparison of drug properties between a new drug and existent ones, and make this task possible for a physician in a reasonable time. In a previous work [15], we designed *rainbow boxes*, a new visualization technique that can be used for facilitating and speeding up the comparison of the numerous properties (contraindications and adverse effects) of a small set of 2-10 drugs, and we evaluated this technique against tables. Results showed that rainbow boxes lead to a significantly shorter response time.

In this work, we designed and evaluated a comparative drug ontology and a prototype of a visual drug comparator website, using rainbow boxes in combination with other visualization techniques. Our objective was to study (1) whether visual analytics could be used for enabling the comparison of the properties of a new drug with the properties of already existing similar drugs, and (2) whether this visual comparison can help physicians to forge their own well-founded opinions about new drugs, without the intervention of an expert opinion.

The rest of the paper is organized as follows. Section 2 describes the methods used (1) to design a comparative drug ontology, (2) to select the visualization techniques and to design the website, and (3) to evaluate it with 22 physicians on four new drugs under controlled conditions. Section 3 presents the resulting ontology, the drug comparator website prototype, and the evaluation results. Section 4 discusses the limits of our work and compares it with the literature. Finally, section 5 concludes.

2. Materials and Methods

2.1. Ontology design

First, we determined the main categories of information required by GPs for assessing new drugs, considering the results of previous studies carried out in our medical informatics research laboratory [16], and also two focus groups that included 17 general practitioners (GPs). GPs were recruited *via* SFTG (*Société de Formation Thérapeutique du Généraliste*), a French association responsible for the ongoing training of doctors throughout their career. GPs were paid for their participation, in order to compensate for the time they spent on the evaluation and for reimbursing train tickets for those coming from distant cities.

Each session lasted 3 hours and a half. The objective of the focus groups was to determine the needs and the expectations of GPs concerning information about new drugs. The first part of the focus group session (about 1 hour and a half) consisted of a general discussion about pharmaceutical innovation. The second part (about 2 hours) included personal work on a set of documents corresponding to three of the four following new drugs[1]: Alvesco® (ciclesonide, a new corticoid for asthma), Cialis® (tadalafil, a new indication for benign prostatic hypertrophy), Pylera® (bismuth + metronidazole + tetracyclin, a new therapy for H pylori eradication), Jext® (adrenalin, a new galenic form with a pen). Several types of documents were proposed to physicians: promotional documents from companies, patient leaflets, SPCs, evaluation documents from health insurance providers, tables (including prices and adverse effects, manually designed by HB). GPs were encouraged highlighting excerpts of the documents given to them and these documents were collected and analyzed. In addition, the sessions were recorded.

Second, we designed a comparative drug ontology focused on new drugs. We chose to use ontologies because of their ability to deal with subsumption and their semantic reasoning functionalities. This ontology allows the comparison between drugs: it includes the properties of the new drug, its list of comparators (*i.e.* older drugs with the same indication and still available on the market), as well as the properties of the comparators. ICD10 (International Classification of Disease, release 10) was used for coding contraindications and MedDRA 18 (Medical Dictionary for Regulatory Activities) for adverse effects. The recorded focus group sessions were listened to when designing the conceptual model of the ontology, in order to verify that the main concepts mentioned in the discussions of the focus groups were present in the model.

The obtained model was tested and instantiated manually on 15 new drugs by the authors (JBL, CD, AL, HB and MF instantiated 3 drugs each). Each set of three drugs included one drug with a new active principle, one with a new galenic form or administration route, one with a new dose. The model was slightly refined by adding the missing items found during the manual instantiation. In particular, we added information related to marketing date, and we distinguished general drug information from information valid only for a given indication of the drug.

Finally, the ontology was edited using Protégé and formalized using OWL 2 (Ontology Web Language). Semantic reasoning methods were used for facilitating the comparison of drug properties, since these properties are often expressed at different levels of granularity, with subsumption and partition relations between levels. For example, a drug d_1 can be contraindicated with hemorrhagic disorders while another drug d_2 can be contraindicated with *constitutive* or *acquired* hemorrhagic disorders. For an expert, it is obvious that both contraindications are equivalent, because constitutive and acquired actually defines a *partition* of hemorrhagic disorders (*i.e.* an hemorrhagic disorder is necessarily either constitutive or acquired). But they can be coded differently (*e.g.* in drug

[1]These drugs were considered as new or recent in France, for the given indication and galenic form, at the time of the focus group study (November 2013).

(1) $Acquired \sqsubseteq Origin$
$Constitutive \sqsubseteq Origin$
$Acquired \sqcap Constitutive \sqsubseteq \bot$
$Origin \sqsubseteq (Acquired \sqcup Constitutive)$

(2) $Disorder \sqsubseteq ClinicalCondition$
$Disorder \sqsubseteq (\exists hasForOrigin.Origin) \sqcap (\forall hasForOrigin.Origin)$
$HemorrhagicDisorder \sqsubseteq Disorder$
$AcquiredHD \equiv HemorrhagicDisorder \sqcap \exists hasForOrigin.Acquired$
$ConstiHD \equiv HemorrhagicDisorder \sqcap \exists hasForOrigin.Constitutive$

(3) $(ContraIndication \sqcap (\exists hasForClinicalCondition.AcquiredHD) \sqcap (\forall hasForClinicalCondition.AcquiredHD))(ciA)$
$(ContraIndication \sqcap (\exists hasForClinicalCondition.ConstiHD) \sqcap (\forall hasForClinicalCondition.ConstiHD))(ciC)$
$AcquiredHD \sqsubseteq hasForClinicalCondition^{-}.\{ciA\}$
$ConstiHD \sqsubseteq hasForClinicalCondition^{-}.\{ciC\}$
$(Drug \sqcap (\forall hasForContraIndication.\{ciA, ciC\}))(d_2)$
$hasForContraIndication(d_2, ciA)$
$hasForContraIndication(d_2, ciC)$

(4) $ContraIndicatedWith\_d_2 \equiv ClinicalCondition \sqcap (\exists hasForDisorder^{-}.(\exists hasForContraIndication^{-}.\{d_2\}))$

(R) $HemorrhagicDisorder \sqsubseteq ContraIndicatedWith\_d_2$

Figure 1: Example of semantic reasoning on contraindications, in formal notation. Drug d_2 is contraindicated with both acquired hemorrhagic disorder (*AcquiredHD*) and constitutive hemorrhagic disorder (*ConstiHD*). Steps 1-4 formally described the contraindications, and step R shows the inference produced by an automatic reasoner.

	Drug #1	Drug #2	Drug #3	Drug #4	Drug #5
Fungal ear infection	X	√	√	√	√
Viral ear infection	X		√	√	√
Viral infection of external auditory canal	X	X	√	√	√
Tympanic membrane perforation	√	X	X	X	√
Pseudomonas otitis	√	√	√	X	√

Figure 2: Example of a table presenting 5 contraindications on 5 drugs. Red cross indicates contraindications and green checks the absence of contraindications (proved using the ontology).

database) and thus they are considered as different by a computer program.

Figure 1 shows how a semantic reasoning can be set up to solve this problem in five steps. Step 1 defines two classes, *Acquired* and *Constitutive*, which are a partition of the *Origin* class. Step 2 defines the two disorders, *AcquiredHD* (Acquired Hemorrhagic Disorder) and *ConstiHD* (Constitutive Hemorrhagic Disorder), with their associated origin (*Acquired* and *Constitutive*, respectively). Step 3 defines two instances of the *ContraIndication* class, *ciA* and *ciC* ; *ciA* is related to *AcquiredHD* using the *hasForClinicalCondition* relation, and *ciC* to *ConstiHD*. Then, drug d_2 is related to *ciA* and *ciC* using the *hasForContraIndication* relation. Step 4 defines $ContraIndicatedWith\_d_2$, the class of all clinical conditions contraindicated with drug d_2. Finally (step R), a reasoner can automatically infer that drug d_2 is contraindicated with hemorrhagic disorders (and not only acquired and constitutive hemorrhagic disorders, as initially stated).

2.2. *Development of visualization techniques and design of a drug comparator website*

In terms of visualization, the most difficult problem when comparing drugs is the presentation of the numerous drug properties related to safety: contraindications, interactions, and adverse effects. Two different approaches were followed for the selection and the development of visualization techniques.

In a first time, we considered the tables commonly used by physicians and experts. These tables usually have drugs in columns and properties in rows. They are easy to understand but often difficult to read due to the high number of properties. We tried to improve these tables as much as possible, by (1) adding symbols and icons, (2) highlighting rows corresponding to properties for which the new drug differs from the comparators, and (3) making table interactive, for dynamically filtering the table content. This first approach led to a first tool, *dynamic table*. Figure 2 shows an example of a table with symbols, on a small dataset (more complex examples will be presented in the results section). In the figure, the subsumption relation between "viral ear infection" and "viral ear infection of external auditory canal" is shown on the left using indentations, and it is responsible for the missing symbol at the intersection of drug #2 and "viral ear infection" (since the drug is contraindicated with some forms of viral ear infection, but not all, we cannot put either a green symbol or a red one). Absences of contraindications are only shown when they can be proved (using the ontology), and only for the drugs for which all contraindications are shown (so as the user can control the absence himself).

In a second time, we considered more sophisticated visualization techniques. The visualization of the numerous contraindications or adverse effects of several drugs is an *overlapping set visualization* problem [17]. The drugs can be considered as elements and their properties as sets made of these elements (*e.g.* the set of drugs contraindicated with renal failure

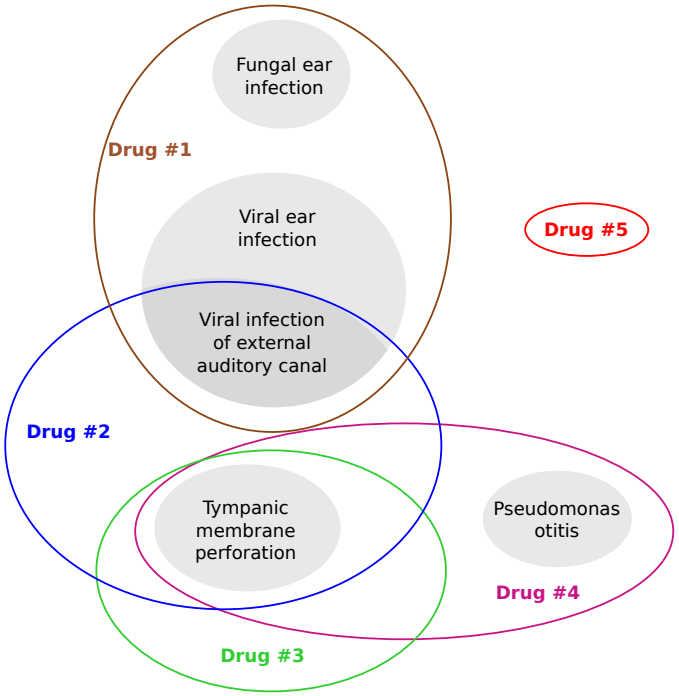

Figure 3: Example of a Venn diagram presenting 5 contraindications on 5 drugs.

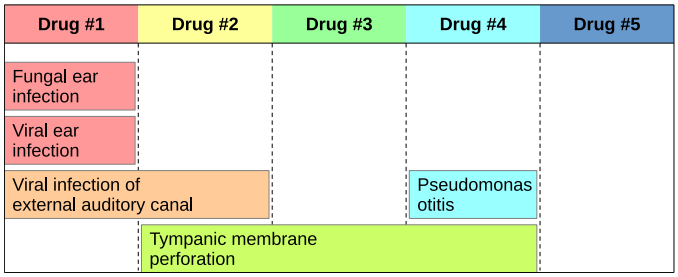

Figure 4: Example of rainbow boxes presenting 5 contraindications on 5 drugs.

or the set of drugs sharing the vomiting adverse effect). These sets are potentially overlapping, *i.e.* a drug can belong to more than one set and a set can include several drugs. As overlapping sets visualization is a "symmetric" problem, it is also possible to consider the properties as the elements and the drug as the sets (*e.g.* the set of all properties of a given drug).

We tried several overlapping set visualization approaches, including the well-known Venn diagram. For Venn diagram, we considered the drugs as the sets, because properties are typically more numerous than drugs and Venn diagram works better with fewer sets that elements. However, we encountered two problems: first, we found the readability of the diagrams rather low (see example Figure 3 on a small dataset), and second, the automatic generation of Venn diagrams is still a matter of research, especially when the number of sets is above 4 (which occurred frequently in our application). Figure 3 was produced manually, but more complex datasets would be difficult to deal with. Consequently, we did not include Venn diagrams in our prototype.

Then, we developed *rainbow boxes*, a new visualization technique for facilitating and speeding up the comparison of the properties of a small set of 2-10 drugs [15]. This time, we considered the drugs as elements, and their properties as the sets. The technique presents the drugs in columns, and orders them by local similarity using a specific heuristic algorithm. Properties are displayed in rectangular boxes covering one or more columns (see example Figure 4). A box might have holes in it, if the associated columns are not consecutive. Contrary to tables, rainbow boxes can place two contraindications on the same horizontal row (as long as no drug has both contraindications), and therefore, they are more compact. The generation of rainbow boxes was implemented as a Python 3 module. It produces HTML pages with CSS and JavaScript. The module can be downloaded [2] as Free Software (licensed under GNU LGPL v3), and it includes several usage examples.

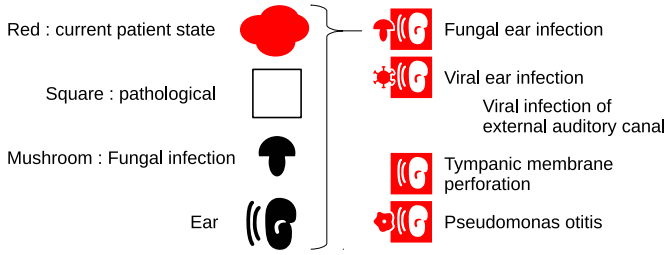

Figure 5: Example of icons for the 5 contraindications. The first one is decomposed.

Additional simpler techniques were also used. Bar charts were used for presenting clinical study results. Icons were used to illustrate the list of contraindications and facilitate the search for a given type of contraindications (*e.g.* cardiac or renal). We used icons from the VCM (Visualization of Concept in Medicine) language [18, 19] developed previously in our lab. In particular, VCM icons can represent the main disorders and patient conditions (*e.g.* pregnancy), using a compositional language (see Figure 5).

Finally, we implemented a drug comparator website using the ontology and the visualization techniques. The website was generated by Python scripts, producing HTML pages with CSS and JavaScript. The ontology was accessed using the Owl-Ready ontology-oriented programming tool [20] and medical terminologies were managed with PyMedTermino [21].

2.3. Evaluation methods

Four new drugs were included in the website prototype: Antarene codeine® (ibuprofen+codeine, for moderate-to-severe pain), Ciloxan® (ciprofloxacine, for ear infections), Vitaros® (alprostadil, for erectile dysfunction) and Pylera® (bismuth+metronidazole+tetracycline, for *H. pylori* stomach infections). Drug information for these four new drugs and their comparators was extracted and coded by a pharmacist specialized in drug knowledge (HB), for a total of 26 drugs. Evaluators were GPs recruited through the SFTG association and were paid as previously described in section 2.1. All GPs but one

[2] http://bitbucket.org/jibalamy/rainbowbox (consulted 18/4/2017)

were different from those involved in the focus groups. The evaluation study did not require an IRB approval, because no patients were involved, and data was collected anonymously during the evaluation.

Evaluation session lasted about 3 hours (including a meal). During the evaluation, the website was briefly presented to the GPs (20 minutes). Before consulting the website, the GPs completed a first questionnaire asking whether they were familiar with each of the four new drugs (yes/no), whether they were ready to prescribe them (yes/no), and why (four possible reasons: efficacy, contraindications and interactions, adverse effects, cost; GPs could select zero, one or several items and an "other" box was also provided, with an open field). GPs consulted the comparative website (45 minutes). They then completed a second questionnaire, containing the same questions as the first one, and a third questionnaire with nine questions about their views on the website.

The primary endpoint was the percentage of GPs who felt that they had forged a well-founded opinion about the four new drugs using the website (a yes/no question in the third questionnaire). The secondary endpoint was the percentage of GPs who changed their minds concerning the prescription of each of the new drugs (this criterion evaluated the ability of the website to modify the physician's prescribing decisions, and corresponded to the difference between the responses of the first and the second questionnaire). Finally, a general discussion was conducted with the GPs.

Statistical analysis was conducted using R software version 3.2.3.

3. Results

3.1. Comparative drug ontology

The ontology belongs to the $\mathcal{SHOIQ}(D)$ family of description logics. The general part of the ontology (*i.e.* excluding drug-specific classes and individuals) contains 240 classes, 167 properties, 154 individuals and 2071 axioms. 20 partitions were considered and described in a similar way than the origin partition detailed in section 2, involving chronicity (acute / chronicle), severity (severe / moderate / mild), control (controlled by treatment / non controlled), causality (primitive / secondary), *etc*. The ontology is currently not publicly available, for two reasons: first, all the ontology is in French, and second, the ontology includes some significant parts of medical terminologies (ICD10 and MedDRA), that we cannot redistribute publicly without permission from the institutions that manage these terminologies.

The ontology contains information related to the type of innovation of the new drug, the efficacy, the security (contraindications, interactions, adverse effects, and excipients with known effects), and the cost. Table 1 shows the drug properties included in the ontology, for the new drug and for comparators. This ontology has three noticeable particularities. First, some properties are defined at the drug level and some other at the indication level. This distinction is meaningful for drugs with several indications. For example, the composition of a drug is independent from the indication it is prescribed for. On the contrary, the dose regimen depends on the indication, *e.g.* for aspirin, the dose regimen is not the same for treating pain or when prescribed for prevention of thromboembolic events.

Second, some properties were considered only for new drugs. Examples include the type of novelty and ASMR (*Amélioration du Service Médical Rendu*, improvement of actual benefit), a score given by French national health services. Since ASMR is relative, we considered that ASMR attributed at different dates

	Per-drug	Per-indication	New drug	Comparators
Type of novelty	X		X	-
List of comparators		X	X	-
Therapeutic class	X		X	X
Indications	X		X	X
Terrain				
Dose regimen		X	X	X
Costs (treatment and dose)		X	X	X
Repayment rate		X	X	X
Action delay and duration		X	X	X
Actual benefit (SMR)		X	X	X
Improvement of actual benefit (ASMR)		X	X	-
Driving	X		X	X
Clinical study results		X	X	-
Contraindications				
- absolute	X		X	X
- relative	X		X	X
Interactions			X	X
- contraindicated	X		X	X
- unadvised	X		X	X
- caution for use			-	-
- take into account			-	-
Adverse effects :				
- serious	X		X	X
- frequent or very frequent	X		X	X
- others (not serious, not frequent)			-	-
Excipients with known effect	X		X	X
International nonproprietary name	X		X	X
Composition	X		X	X
Galenic form	X		X	X
Route	X		X	X
Companies	X		X	X
Marketing date	X		X	X
Links to SPCs	X		X	X

Table 1: The drug properties included in the ontology. For each property, the table indicates whether it is defined for a drug (per-drug) or for a drug in a given indication (per-indication), whether the property is present for the new drug and whether it is present for comparators. The horizontal lines delimit the 8 sections in the interface. SMR (*Service Medical Rendu*, clinical benefit) and ASMR (*Amélioration du Service Medical Rendu*, improvement of the clinical benefit) are two scores attributed by the French national health services, evaluating the usefulness of the drug (absolutely for the SMR, relative to the already existing drugs for the ASMR).

VITAROS 300 micrograms, cream

alprostadil (Prostaglandin E1)
New administration route for an already existent molecule

Synthesis

Indications
Treatment of men ≥ 18 years of age with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

Efficacy
SMR : low
ASMR : no therapeutic progress (V)
2 clinical studies

Comparators
Prostaglandin E1
Edex (alprostadil)
Caverject (alprostadil)
Muse (alprostadil)
Phosphodiesterase type 5 inhibitors
Viagra (sildenafil)
Cialis (tadalafil)
Levitra (vardenafil)
Spedra (avanafil)

Contraindications
Hypersensibility to prostagland...
Syncope
Orthostatic Hypotension
Pathology contraindicating sex...
Sexual intercourse without a c...
Female
Balanitis
Predisposition to priapism
Male uretritis
Anatomic malformation of penis
Child below 18

Interactions
(none)

Adverse effects
(serious)
Priapism
Erection prolonged
(frequent)
Rash
Urethral pain
Penile pain
Penile erythema
Penile oedema
Penile burning sensation
Penis disorder
Genital pruritus male
Non-specific vaginitis
Balanitis
Genital pain male
Genital erythema
Genital discomfort
Vulvovaginal burning sensation

Excipients with known effect
(none)

Figure 6: Section #1 (synthesis) for Vitaros® (alprostadil).

Terrain, posology, cost, efficacy and driving

		Prostaglandin E1			Phosphodiesterase type 5 inhibitors			
	Vitaros	Edex	Caverject	Muse	Viagra	Cialis	Levitra	Spedra
Terrain	Adult Man, + 18 years	Adult Man, + 15 years	Adult Man, + 15 years	Adult Man, + 15 years	Adult Man, + 18 years	Adult Man, + 18 years	Adult Man, + 18 years	Adult Man, + 18 years
Posology	1 unidose 1 time per day 2 to 3 times per week.	5 to 20 µg 1 time per day 1 to 2 time per week.	5 to 20 µg 1 time per day 1 to 2 time per week.	1 stick 1 to 2 time per day. Maximum 7 sticks per week.	1 tablet 1 time per day.	2.5 mg and 5 mg: 1 tablet 1 time per day. 10 and 20 mg: 1 tablet 1 time per day 1 to 2 time per week.	1 tablet 1 time per day.	1 tablet 1 time per day.
Dose cost	10.05 €	11.47 €	10.79 €	16.50 - 18.90 - 23.60 €	6.35 (Ge) to 12.62 € (VIAGRA)	8.95 €	10.54 €	6.33 €
Repayment rate	0%	0%	0%	0%	0%	0%	0%	0%
Action delay	5 to 30 mn	5 to 10 mn	5 to 10 mn	5 to 10 mn	60 mn	30 mn	25-60 mn	30 mn
Action duration	1 to 2 h	30 to 60 mn	30 to 60 mn	30 to 60 mn	4 h	17 h	4 h	6 à 17 h
Actual benefit (French SMR)	low	medium	medium	-	high	high	high	-
Improvement of actual benefit (French ASMR)	no therapeutic progress (V)							
Driving	level 1	level 1	level 1	level 1	level 1	level 1	level 1	level 1

Figure 7: The comparative table in section #2 for Vitaros® (alprostadil). Economic data (prices, repayment rates, *etc*) correspond to those in France.

were not comparable, and thus we did not include ASMR for comparators. Clinical study results were also limited to studies including the new drug.

Third, the list of interactions and adverse effects can be very long. As demanded by GPs during focus groups, we limited drug interactions to the first two levels (contraindicated and unadvised), and adverse effects to serious and/or frequent effects (including very frequent). On the contrary, all contraindications were included.

We created a separate ontology for each new drug; each of these ontologies imports the general part of the ontology (whose metrics were given at the beginning of the section) and describes the new drug and its comparators. Semantic reasoning was performed using the HermiT reasoner (computation time: 20-35 seconds, on a recent computer, depending on the ontology).

3.2. Presentation of the drug comparator website

The website presents each new drug on a single webpage containing eight sections: (1) the title, the type of innovation, a synthesis with the new drug properties (non-comparative information), and the list of comparable drugs (see example in Figure 6), (2) a comparative table, with patients (terrain), dosing (posology), costs, efficacy, and driving information (Figure 7), (3) bar charts showing the main results of clinical trials involving the new drug, (4) a comparison of the contraindications of the new drug and those of the comparators, (5) a comparison of drug interactions, (6) a comparison of adverse effects, (7) a comparison of excipients with known effects, and (8) a comparative table, with active principles, dosage, administration, and links to official documents.

For the comparison of the clinical properties related to security, the website proposes the two previously mentioned tools: *dynamic tables* and *rainbow boxes*, with buttons for switching between them. For contraindications (Figure 8), the dynamic table shows drugs in columns, contraindications in rows, and it uses three symbols: a red cross for absolute contraindication, an orange triangle for relative contraindication, and a green mark for otherwise. The table is dynamic because visible properties are adapted to one of the following usages: (a) the contraindications of the new drug, (b) a 1 *vs* 1 comparison of the contraindications of the new drug and a comparator selected by the user (in this mode the rows that differ between the two drugs are highlighted), (c) every contraindications for all drugs, and (d) the noticeable absence of contraindications of the new drug, *i.e.* the situations in which the majority of the comparators are contraindicated, but the new drug is not.

In rainbow boxes, the drugs are shown in columns, and ordered as follows: (a) the new drug is the left-most one, (b) drugs of the same pharmacotherapeutic class are grouped together, and (c) drugs sharing contraindications are placed next to each other. A contraindication is displayed as a rectangular box that covers all the columns of the drugs having that contraindication. The box may have holes in it (see example of "History of cerebrovascular events" on Figure 8), although the column ordering heuristic algorithm avoids this as much as possible. Boxes are ordered vertically by size, with larger boxes at the bottom. Each drug receives an arbitrary color of the spectrum (hence "rainbow"), and the color of a box is the mean of the colors of the drugs it covers. Hashes indicate relative contraindications. The boxes were also enriched with VCM icons [18].

Rainbow boxes provide a global overview of the contraindications of the new drug and its comparators. They display all contraindications of all drugs in a single screen, but also highlight similarities between drugs, *e.g.* in Figure 8, an important *class-effect* can be seen between the first four drugs (prostaglandin E1 class) and the last four (phosphodiesterase type 5 inhibitors). Additionally, it is easy to find which comparator is the closest to the new drug, in terms of contraindications (here, Muse®). Rainbow boxes are also interactive: by clicking on a comparator, the user obtains a 1 *vs* 1 comparison between the new drug and the chosen comparator.

Finally, age-related contraindications are displayed in both tools using colored bars (red, orange, green, same meaning as the previous colored symbols).

For adverse effects, seriousness and frequency are also considered, in addition to their nature. Non-serious, infrequent effects were not included in the ontology, and thus they are not presented. In dynamic tables, serious effects are displayed in red, and the frequency is shown using 1 to 5 squares corresponding to the usual 5-level scale for frequency. In rainbow boxes (Figure 9), the box color is modified to represent seriousness and frequencies.

Rainbow boxes support various tasks at a glance, such as: (a) finding the most problematic adverse effects of a given drug (*e.g.* in Figure 9, the bright red color in the bottom-left box indicates that Vitaros® has an effect that is both frequent *and* serious: prolonged erection), (b) discovering similarities between drugs (*e.g.* many adverse effects of Viagra® are shared with Cialis®), (c) finding the drug with the fewest adverse effects (*e.g.* Spedra® seems to have fewer adverse effects than other drugs).

If the new drug has more than one indication (such as Ciloxan®), the site includes a separate webpage for each indication, with indication-specific comparators. Hypertext links allow navigation between the pages.

The entire webpage for Vitaros® (translated into English) is available[3].

3.3. Evaluation results

We enrolled 22 GPs (12 men, 10 women, mean age 54.6) to evaluate the prototype of the website. The 22 GPs and the 4 drugs correspond to 88 cases (=22 × 4). Before consulting the website, the GPs lacked information about the new drugs in 27 of 88 cases (31%, Figure 10). After consulting the website, only one GP lacked information about one drug (1/88, 1%).

After consulting the website, GPs changed their mind about whether to prescribe the new drug in 29 cases (33%, Table 2). In 11 cases, the GPs were ready to prescribe the drug, but changed

[3] http://www.lesfleursdunormal.fr/static/viiip_proto/html/page_medicament_he_60731732_Vitaros_en.html (accessed on 18/4/2017)

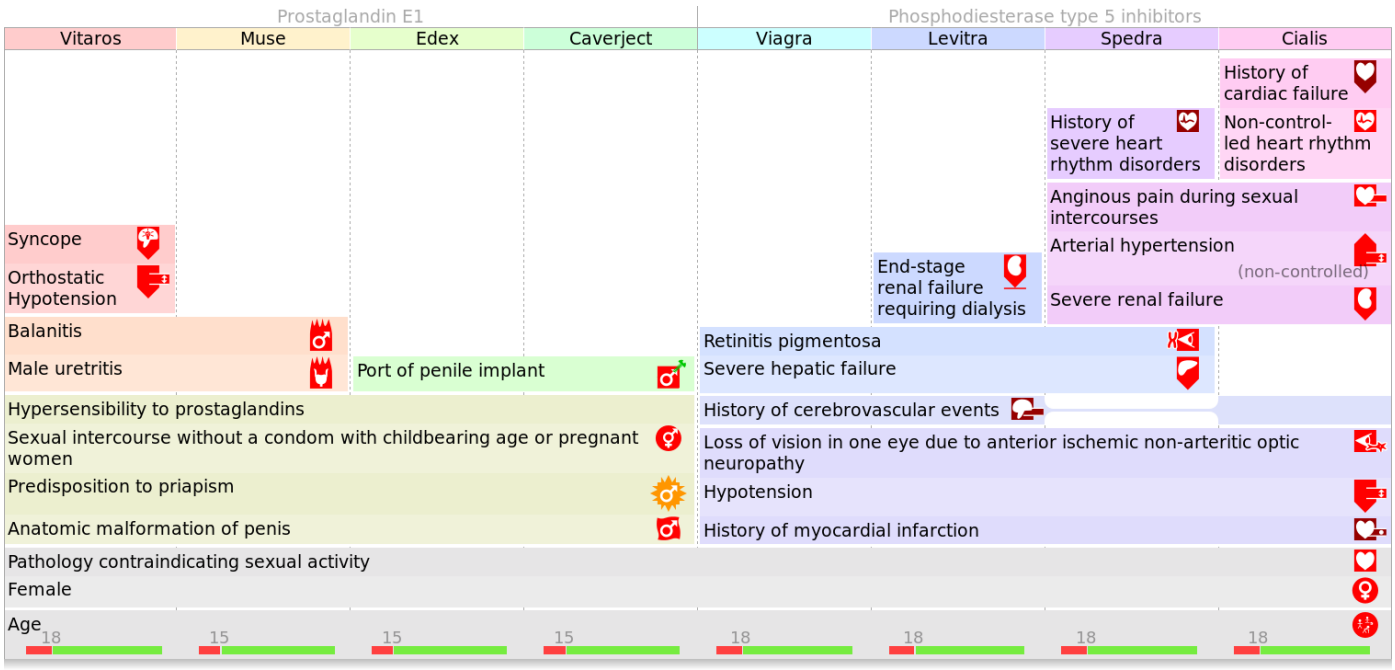

Figure 8: Comparison of contraindications in section #4 for Vitaros®, with the two visual tools: dynamic table (top) and rainbow boxes (bottom). The dynamic table shown here displays a 1 *vs* 1 comparison between Vitaros® and Viagra®, after the user selected this comparator; contraindications absent from these two drugs are hidden (the number of hidden contraindications is mentioned below the table for each drug).

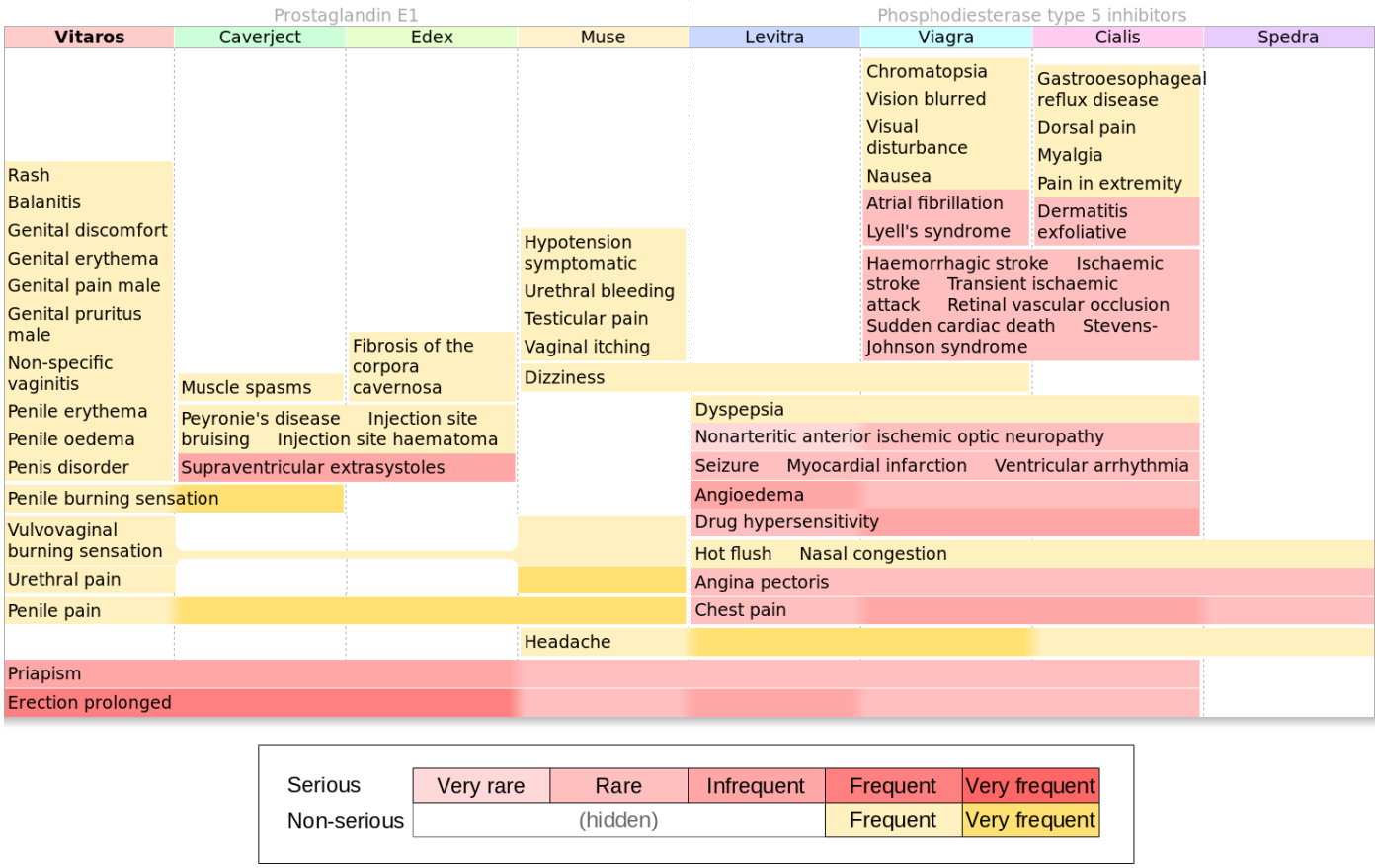

Figure 9: Comparison of adverse effects in section #6 for Vitaros®, using rainbow boxes. The colors indicate the seriousness and frequency of effect.

their minds after consulting the website. In the remaining 18 cases, the GPs were not ready to prescribe the drug, due to lack of information, but changed their minds after consulting the website. The GPs did not change their minds in 40 cases (46%), but provided different arguments for justifying their choices before and after consulting the website. The total number of arguments (for all GPs and all drugs) was 48 before consulting the website and 111 after. In 19 cases (22%), the GP did not change his mind nor his arguments.

Table 3 shows the results obtained from the third questionnaire, requesting their opinion of the website. All GPs (22/22, 100%) felt that they had forged a well-founded opinion about the four new drugs using the website, and preferred comparative to non-comparative information (*i.e.* limited to a single drug). Twenty GPs (91%) found the website easy to use once they became familiar with it, and 21 (95%) would recommend it to their colleagues.

During the general discussion, the GPs appreciated the idea of comparative drug information and also the neutral presentation of the information, contrasting with that of pharmaceutical company sales representatives and traditional opinion journals. Here are several quotations from the GPs: *"Better than Doroz"* (a well-known practical guide to drugs in France), *"You created a need"*, *"The website keeps a certain neutrality"*, *"No tool like this exists"*.

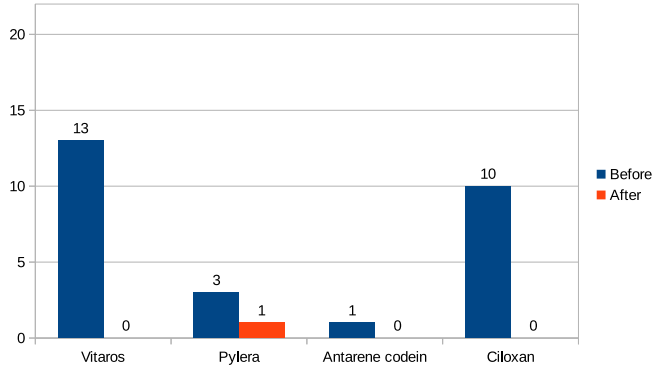

Figure 10: Bar charts showing the number of GPs who indicated that they were lacking information about each of the four new drugs, before and after they consulted the website.

4. Discussion

In this study, we designed an ontology for structuring comparative drug information, allowing the comparison of the properties of a new drug with the properties of older similar drugs. We proposed visual analytics methods for enabling the visual comparison of the properties of a small set of 2-10 drugs, and we implemented a prototype of a visual drug comparator website. 22 GPs evaluated this prototype website for four new drugs.

Before consulting the website		After
The GP **is ready** to prescribe the new drug (35/88, 39.7%)		The GP **changes his mind** and is no longer ready to prescribe the new drug (11/35, 31.4%)
		The GP does not change his mind but justifies his choice using different arguments (15/35, 42.9%)
		The GP does not change his mind nor his arguments (9/35, 25.7%)
The GP is **not** ready to prescribe the new drug (53/88, 60.2%)	The GP does not know about the new drug, or lacks information (39/88, 44.3%)	The GP **changes his mind** and is now ready to prescribe the new drug (18/39, 46.2%)
		The GP does not change his mind (21/39, 53.8%)
	The GP knows about the new drug (14/88, 15.9%)	The GP changes his mind and is now ready to prescribe the new drug (not observed, 0%)
		The GP does not change his mind but justifies his choice using different arguments (8/14, 57.1%)
		The GP does not change his mind nor his arguments (6/14, 42.9%)

Table 2: Evolution of the GPs' decisions to prescribe the new drugs and of the arguments they used for justifying their choices, before and after the consultation of the website (88 cases).

The results of the evaluation showed that GPs were able to forge well-founded opinions about the new drugs by consulting the properties of the new drug and comparing them to those of older drugs, but without an expert opinion. The results also showed a high rate of GPs changing their minds about a given drug after consulting the website, which may indicate that GPs trusted the website. In addition, the website allowed GPs to better argue their choice.

4.1. Comparison to literature

Very few solutions have been proposed in the literature for simultaneously visualizing the properties of several drugs, and all rely on simple tables for displaying drug properties. Wroe *et al.* [22] proposed DOPAMINE, a spreadsheet-like matrix-based tool, but this approach was limited and mostly aimed toward reviewing and reporting on drug properties. Iordatii *et al.* [23] proposed a similar matrix-based approach for comparing the contraindications and the adverse effects of a new drug to a reference drug. Drug Fact Boxes [24] offer some comparative drug information, but target patients rather than physicians and are limited to a subset of the properties of the drugs. More recently, Informulary proposed a drug fact boxes website (http://drugfactsbox.co, accessed on 9/2/2017), but without comparative information other than clinical trial results. Duke *et al.* [25] designed an original system for viewing the adverse effects of several drugs: the effects are "summed" together. This system is useful for analyzing the risk associated with a drug order consisting of several drugs, but is not oriented towards the comparison of similar drugs. Warner *et al.* [26] proposed a graph-based visualization for viewing a set of clinical trials. Each drug treatment is a node and each comparison in a trial is an edge linking the two treatments that are compared. The size and color of nodes and edges are used to indicate the observed difference in efficacy and the strength of the evidence.

Twinlist[4] [27] is a visualization method proposed for medication reconciliation, *i.e.* for reconciliating the list of drugs prescribed to a given patient outside the hospital with the list of drugs prescribed at the hospital, in order to produce a single list during the discharge process. This task requires to compare the two lists of drugs. The task is difficult because some drugs can be different but similar (*e.g.* due to generic drugs). Twinlist presents the two lists in five columns: (a) one column with the drugs identical in both lists, located at the center of the interface, (b) two columns with the drugs specific to one of the list, at the left and the right side of the interface, and (c) two columns with drugs similar (but not identical) in both lists, displayed as pairs (one drug from the first list with one from the other list). Twinlist shares some similarities with rainbow boxes: both visualization techniques can compare two lists/sets and distinguish the common elements with the elements specific to a single list/set. However, Twinlist provides more detail for 1 *vs* 1 comparisons, including "similar but not identical" elements, while rainbow boxes are able to compare more than 2 lists/sets.

On the Internet, there are comparator tools for many commercial products, such as air travel, hotels, or electrical appliances, but there are currently almost none for drugs. Iodine (http://www.iodine.com, accessed on 9/2/2017) is a website that collects drug information from patients, including the efficacy of the drug and the adverse events they encountered. Iodine uses tables to compare similar drugs, but the list of the effects of each drug is displayed in a single row for comparing adverse effects, which is tedious for making comparisons. In addition, the quality of data collected by patients is difficult to assess, and it is vulnerable to Sybil attack [28] (*i.e.* someone could easily create a high number of fake patient profiles, reporting false data in favor of a given drug).

In the literature, several drug ontologies were proposed, focused on various aspect of drugs, such as drug identification [29], indications [30], adverse drug reactions [31] and pharmacogenomic [32]. The ontology we propose here focuses on the comparison of drug properties and the relation between new drugs and similar older drugs.

[4] http://www.cs.umd.edu/hcil/sharp/twinlist (accessed on 18/4/2017)

Questions	% (95% CI)	Yes	No	No reply
This website allowed me to forge a well-founded opinion about the four new drugs	100%	22	0	0
I easily learned to use the website	85% (69-100)	17	3	2
After learning, I found the website easy to use	91% (79-100)	20	2	0
I would use this website frequently if it was systematically updated for each new drug	95% (86-100)	20	1	1
I found that information was missing	52% (31-74)	11	10	1
I prefer comparative information (new drug *vs* comparators) rather than information limited to the new drug	100%	22	0	0
In the website, I found useful:				
...the synthesis	59% (39-80)	13		
...the list of comparators	82% (68-98)	18		
...the clinical trial results for the new drug	45% (25-66)	10		
...the comparison of contraindications	77% (60-95)	17		
...the comparison of interactions	64% (44-84)	14		
...the comparison of adverse effects	95% (87-100)	21		
...the comparison of excipients with known effects	50% (29-71)	11		
...the comparison of dosage regimens	50% (29-71)	11		
...the comparison of treatment costs	82% (68-98)	18		
For comparisons, I found useful:				
...1 *vs* 1 comparisons	67% (44-89)	12	6	4
...global overview	95% (85-100)	19	1	2
I would recommend this website to my colleagues	95% (87-100)	21	1	0

Table 3: Responses obtained to the questions posed to GPs to measure their satisfaction and opinion of the website.

4.2. Limits

The evaluation protocol was not comparative. We initially wanted to consider a comparative protocol, however, we were unable to find a satisfying comparator. Comparing our website with pharmaceutical company sales representatives was difficult without working with companies. Another possibility would have been to compare the website with the textual SPCs. However, this was not possible in the time frame we had for the evaluation: just for Vitaros®, the time for reading the 8 SPCs for the new drug and the 7 similar drugs would have exceeded the time available, according to the experience we had from the focus groups (in which only 3 drugs were studied by each GP). In addition, this would not have been realistic, because GPs do not commonly read SPCs of new drugs.

In the evaluation the nine questions of the third questionnaire (table 3) were not related to the standard SUS (System Usability Scale) test, which is frequently used for evaluating system usability. We did not use SUS because it is a generic test and we wanted to ask more specific and medical questions (*e.g.* about missing information or about the sections considered as useful for the GPs). In addition, we used SUS in former studies, but some GPs had difficulties with it : they found that several questions were very similar, and some of them puzzled the GPs (*e.g.* the question about the need for an assistance was found strange for a website – "who needs a technician for consulting a website?" asked a GP). Possibly SUS needs some adaptation.

The information related to clinical trials in our website was limited to a bar chart with the primary criterion. Physicians suggested enriching the website with more details of the clinical trials, and indirect comparisons between drugs, in a similar spirit as network meta-analyses [33]. Drugs are frequently compared to a placebo in clinical trials; in this case, it would be informative to add the results of placebo studies involving the comparator drugs and perform indirect comparison by "chaining" the new drug-placebo and the placebo-old drug comparisons. However, this raises the question as to what extent the various clinical trials are comparable.

4.3. Perspectives

As stated in the result section, GPs appreciated the neutrality of the presentation of the website. On the contrary, information on new drugs is currently provided mostly by pharmaceutical company sales representatives (from 39% [34] to 42% [35]). These individuals have limited medical knowledge [36] and might deliver biased information because they are not independent of the companies. A review showed that a physician's exposure to information from pharmaceutical companies was associated with higher prescribing frequencies, higher costs, lower prescribing quality, or no effect, but never with a net improvements in prescribing quality [37]. As seen in introduction, medical experts are not exempt from conflicts of interest and the independence of their opinions is sometimes difficult to assess. The visual comparison of drug properties might lead to a more neutral and impartial information on new drugs, compared to explicit expert recommendations such as "this drug should be preferred to other ones", as experts or clinical practice guidelines often do. Despite the absence of explicit recommendations, the prototype permitted physicians making a decision

about whether they should consider a new drug for their future prescriptions.

However, in this study, drug properties were extracted manually by an expert pharmacist (HB). This manual extraction might be a source of partiality, since a different expert might provide different extractions. A more impartial alternative to manual extraction would be automatic extraction of drug knowledge, either from drug databases, or official texts using Natural Language Processing (NLP) [38]. Automatic extraction could help to keep the data up-to-date, since SCPs are frequently modified [39]. However, our first experiments, using both databases available in France and NLP on the adverse effects section of SPCs [40], showed that automatic drug knowledge extraction still remains a challenge.

GPs agreed that the website was appropriate for use in continuing education (our original objective). In addition, some suggested the use of the website during consultation to help them choose a drug for a given patient. They proposed to generalize the drug comparator concept beyond new drugs, to allow the comparison of drugs available in a given indication or therapeutic class. They also proposed to link the website with prescribing software. Finally, they explicitly stated that, during the evaluation, they also learned things about already existing drugs. Thus, they suggested extending our approach to all drugs, rather than limiting it to new drugs. They would like a visual tool for comparing available drugs in a given indication.

Future studies could also consider the potential advantages and limitations of providing comparative drug information to patients, as opposed to health professionals.

5. Conclusion

This work showed that visual analytics is a promising approach for presenting structured comparative drug information (such as indications, summary of clinical trial results, contraindications and adverse effects) and for comparing a small set of 2-10 similar drugs. This visual comparison can provide a snapshot of the efficacy, safety, and cost of a new drug, relatively to existing drugs, and allows physicians forging well-founded opinions on new drugs. This approach can be used as a continuing educational tool for clinicians.

The study also showed that physicians were greatly interested in comparative drug information. Consequently, the proposed approach could be extended to all drugs, for comparing visually the drugs available in a given indication (without necessarily including a new drug). Finally, the proposed approach is based on drug properties, of which the impartiality could be more easily verified than expert opinions. Therefore, it might contribute to a more independent and impartial information on drugs.

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