PATIENT PERSPECTIVES IN PHARMACEUTICAL POLICY

Information and influence in the diffusion of new medicines

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PATIENT PERSPECTIVES IN PHARMACEUTICAL POLICY
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PATIËNTENPERSPECTIEF IN FARMACEUTISCH BELEID
Informatie en invloed op het gebruik van nieuwe geneesmiddelen
(met een samenvatting in het Nederlands)

A PERSPECTIVA DO DOENTE NA POLÍTICA FARMACÊUTICA
Informação e influência na divulgação de novos medicamentos
(com um resumo em Português)

Proefschrift

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CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

Medicines are powerful agents and the most common intervention provided in health care services. They can treat acute illnesses and chronic conditions, relieve symptoms, and prevent future ill health. Patients are being progressively recognised as active managers of their own health care (1) but that was not always the case. Their role has evolved over time and today patients can be more vocal, informed and eager to participate in processes which affect them. This also applies to the pharmaceutical policy arena – and to debates around the research and development of new medicines, their access and use.

Over time, patients moved from a passive stance as end-users of medication to have an increasing role as decision-makers (2) who share responsibility with their healthcare professionals to weigh the potential therapeutic benefits of an intervention against its possible harms and to jointly decide whether to use a medicine (3). Such a transition has implied acknowledgement by the healthcare community of the expertise that patients have on their own experiences with disease and medication use (4).

Drivers for patient and citizen involvement in health research and policy have also been identified. These include political ideals anchored in the democratic principles of legitimacy, transparency and accountability and the right of the public to be involved in decision-making processes. For instance, arguments for transparency and trust whereby health authorities see their accountability increase when they promote dialogue and collaboration with patients and citizens. Health-related motivations are also an important factor, such as that of driving research and development towards unmet medical needs of patients; or the opportunity of obtaining the unique patient contribution in health and treatment discussions (4).

A by-product of patient empowerment, as described above, was an increased awareness of the need to consolidate structures of representation with the establishment of local, national and international patient group organisations. While the latter can have different aims according to their level – from grass-root patient care to high-level public advocacy – their relevance and contribution to society remain a common denominator and they hold a powerful role in health care (5) (6). The ACT UP siege of the Food and Drug Administration Headquarters in October 1988 was a major demonstration of this role in the history of patient activism (7). It contributed to the recognition of the legitimacy of patient demands and was fuelled by a demonstrated knowledge of the FDA drug approval process and a carefully designed professional media campaign conveying a clear message to the public: "access to healthcare must be everyone's right"(8). The campaign yielded fruits and one year later ACT UP's plea for parallel trials became true and allowed HIV patients that would otherwise be excluded from clinical trials to gain access to experimental drugs (9). At the same time, the biggest HIV epidemic in the world was unfolding in sub-Saharan Africa. Ten years later, similar efforts by civil society and patient activists from the Treatment Access Campaign in South Africa were instrumental in raising public awareness and pressuring national government to increase access to HIV drugs for the overall population (10).

Stakeholder dialogue has been a priority for the European Medicines Agency since its creation in 1995 and patients and other civil society representatives have been no exception. The first formal interaction took place in 2000 when patient representatives became full members of a scientific committee - the Committee for Orphan Medicinal Products (11). Later in 2003, the Working Group with Patients' and Consumer Organisations was established as a Forum for exchange aiming to improve communication and collaboration between the agency and patients and citizen groups (12). The EMA abides to a specific framework for interaction with patient and consumers and their organisations which is regularly updated and expanded (13). The engagement is wide, covering review of product information, guidance on transparency and dissemination of information, advice to the EMA's Scientific Committees on product-related matters (14), participation in public hearings, membership of the Pharmacovigilance Risk Assessment Committee and oversight of the agency activities with dedicated representatives on the EMA management board (13).

In addition to activism by patients affected by specific conditions and diseases, there has been a recognition more generally of the rights of users of health care services, who are represented in policy arenas by national and regional consumer groups. Consumer groups have played an active role in unveiling the harms of medicine use by contributing to the first *ad hoc* spontaneous reporting of adverse drug reactions by medicine users in 2003 in Denmark (15). Even though direct patient reporting was subsequently implemented in some European member states, only in 2012 did the European Union adopt specific legislation enshrining the right for patients to directly report an adverse drug reaction to health authorities (16). The implementation of these legal provisions has resulted in an expansion of spontaneous patient reporting across European countries yet, inevitably, those with a longer experience of patient reporting have more developed structures to raise awareness about, collect, monitor and analyse this type of pharmacovigilance data (17-19).

There have also been developments in what concerns patient and public involvement in health and social research, most notably with specific initiatives in the US and the UK by the Patient-Centered Outcomes Research Institute (20) and the INVOLVE Programme of the National Institute for Health Research (21) respectively. The rationale is to involve patients and the public in research that they directly or indirectly fund, to identify research priorities, engage in the design, conduct and uptake of research, as to increase its value and reduce waste (22, 23). Some peer-reviewed journals and research collaborations have even opted to implement criteria for patient and public involvement as a prerequisite for publication (24, 25).

In addition to advocacy to represent patient interests in decision-making, patient support and advocacy groups also provide information on health and treatment options. Other factors increasing patient and consumers' access to information, albeit of variable quality, include the growth of the media in general and the amount of attention given to health and health-related matters; the emergence of the internet; and the increasing involvement of the pharmaceutical industry in conveying information to patients and consumers by all possible means (26, 27).

New information routes that bypass the traditional healthcare professional-patient relationship are being used by patients who are actively searching out information online,

interacting with companies and being the passive recipients of advertising. However, the quality and veracity of the information being retrieved raises concerns, due to its unregulated nature. The global reach of the internet makes it difficult to control or frame the communication between consumers and drug companies (27). Furthermore, whilst the media communicates prolifically about health and new treatments the information provided does little to support informed decision-making in the way that health policy would recommend (28). The danger of misinformation exists and it can potentially impact on health and treatment decisions.

As highlighted above, patients and consumers can play varied roles in the diffusion of new medicines, such as representing their peers in dedicated platforms hosted by health authorities, providing input on their preferences and their experiences in medicines' use, advocating for reimbursement of new therapies, or being the target of awareness campaigns and pharmaceutical advertising. Throughout a drug's life cycle - from the stages of discovery of the active compound to the clinical research, regulatory review and post-marketing surveillance of the pharmaceutical product- there are many instances for public engagement. These diverse moments in patient involvement also represent unique opportunities for research. The variety of topics depicted in the studies included in this thesis reflects the many dimensions of public involvement in pharmaceutical policy and are complementary and synergistic in their scope.

OUTLOOK: INFORMATION AND INFLUENCE IN THE DIFFUSION OF NEW MEDICINES

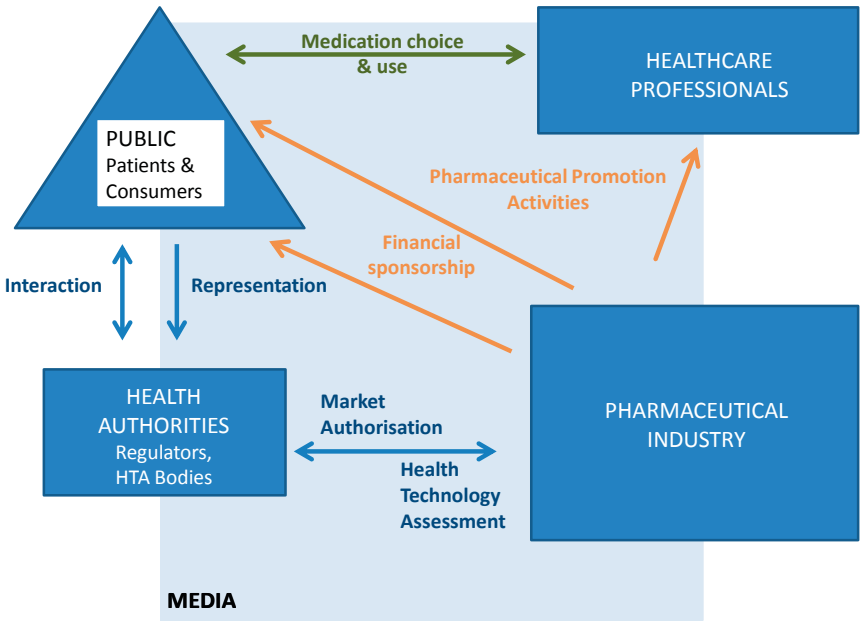

FIGURE 1. A model for interactions among pharmaceutical policy stakeholders where public interests play a key role.

The diffusion of innovation theory is "*the process by which an innovation is communicated through certain channels over time among the members of a social system*" (29, 30). This theory of change explains how and why innovations (new ideas or new technologies) spread and has been used to study the adoption of new technologies by health practitioners (31) mostly through a bilateral interaction between manufacturers and prescribers. In **Figure 1** we mapped pharmaceutical policy debates and the diffusion of new medicines, expanding the traditional producer-prescriber model by including other actors, thus setting the scene for the studies included in this thesis. In our model, four key stakeholders can be identified: the public which is the focus of this thesis and represented by patients and consumers, health authorities (drug regulators and health technology assessment bodies, among others), healthcare professionals and the pharmaceutical industry. Actors differ in their levels of power and influence and are thus represented in Figure 1 by different sizes. Several factors can influence the extent and speed of adoption and diffusion of new medicines (29) and political, historical, cultural and socio-economic determinants also play a role. When seeking market entry and coverage, the pharmaceutical industry communicates with health authorities by providing dossier information and clinical data reports that will inform market authorisation and later reimbursement decisions. At the evaluation stage, patients can also be invited to share their views with health authorities about their condition or a new pharmaceutical product.

One of the strategies used by pharmaceutical companies to exert influence on other stakeholders is pharmaceutical promotion. Both informal and formal communication channels are used to disseminate information of promotional nature to healthcare professionals and to the public through a range of strategies. The information provided is likely to drive the choice of one product over another, ultimately guiding medication selection and use. In parallel, pharmaceutical companies also provide corporate sponsorship to patient groups. Many of these groups have representatives in working relations with health authorities and access to a privileged platform for sharing opinions and interacting with regulators and policy-makers.

The media - here represented by a light blue square in the background - plays a very important role and can generate two distinct effects on the adoption of innovations (32). One primary effect is the dissemination of information directly to potential adopters (healthcare professionals and the public), thereby acting as a major channel of communication in the diffusion process. The secondary effect involves the interaction of the media with actors who actively select information and transmit it across interpersonal or organizational networks, in this case representatives within patient groups, or key opinion leaders within medical or pharmaceutical professional societies. These two effects are complementary and can occur in parallel.

THESIS OBJECTIVE

The studies contained in this thesis cover a wide range of issues and methodologies, yet they all have patient and consumer interests at their core, and highlight current gaps in pharmaceutical regulation, or in the implementation thereof, that affect the overall public. We consider that

medicines are social goods instrumental to public health and therefore equate public needs to those of patients and consumers. When looking at the pharmaceutical policy arena one can identify many activites and interactions taking place. These can be grouped into three thematic areas - access to medicines, rational use of medicines and good governance - and within these, specific case-studies which are very relevant to patients and consumers can be explored. Be it in the regulatory evaluation prior to market approval, throughout reimbursement assessment, or during promotion activities once a drug is already on the market, these key moments pose challenges from a patient and consumer viewpoint. This thesis presents an analysis of these challenging issues from a public perspective and therefore encompasses three main objectives:

- Analysing pre- and post-market drug procedures to ascertain whether drugs receiving market authorisation are responding to public health needs and whether data on patients' quality of life is being taken into consideration during health technology assessments;
- Scoping strategies used by the pharmaceutical industry to influence healthcare professionals and the public through promotional activities, as well the financial sponsorship of patient groups;
- Investigating public disease awareness campaigns on health and treatment conducted by pharmaceutical companies. This type of unbranded advertising generally involves a condition-oriented broadcast or printed campaign which discusses a set of symptoms or a disease while encouraging consumers to seek further treatment by visiting their doctor. These marketing activities represent an important gap in regulatory oversight and are frequently unmonitored.

OUTLINE OF THE THESIS

This thesis includes seven case studies divided into three chapters which address different aspects of patient and public engagement in pharmaceutical policy. The choice of the cases has been framed by the three key thematic areas mentioned above, also considering their focus, broadness of scope and learning potential.

Chapter 2 of this thesis describes two studies which focus on drug assessment**.** In **Chapter 2.1** patient and societal needs are placed at the core of medicines' evaluation as the therapeutic innovation of medicines entering the Brazilian market between 2004 and 2016 is assessed. Both the added therapeutic value of new medicines as well as their alignment with national public health needs are investigated. In **Chapter 2.2** health technology assessment procedures across Europe are the focus. Health-related quality of life is an important outcome to determine the relative effectiveness of new anti-cancer drugs and is of critical importance to patients. Yet, little is known about how quality-of-life data are considered during reimbursement decisions in Europe. The aim of the study included in **Chapter 2.2** is to investigate the extent of use and relevance of quality-of-life data in reimbursement recommendations for oncology drugs across several European jurisdictions.

Later, in **Chapter 3** we gain insight into the strategies fostered by the pharmaceutical industry to influence healthcare professionals and the public. **Chapter 3.1** reviews aspects related to

medicines information and examines how the promotion of pharmaceuticals – either to healthcare professionals or to the public – directly affects the prescribing and use of medicines. In **Chapter 3.2**, a study provides baseline data on the levels of corporate sponsorship among the patient and consumer groups eligible to work with the European Medicines Agency and studies the trends in financial disclosure and transparency between 2007 and 2011. The existence of financial relationships between the industry and these groups which are interacting with regulators raises questions about potential conflicts of interest of their representatives and the co-opting of patient voices.

The studies included in **Chapter 4** focus on the promotion of prescription-only medicines to the public through unbranded advertising. There is little evidence analyzing disease awareness campaigns and their effects remain largely unknown. In **Chapter 4.1** we present a protocol to assess the effects of unbranded advertising of prescription medicines, on consumers' attitudes, knowledge, behaviour, health services use, health outcomes and costs. In **Chapters 4.2** and **4.3** we measure the frequency of disease awareness campaigns in the media in two European countries: the Netherlands and Latvia, respectively. We have also developed an instrument to assess compliance of such campaigns with current international and European guidelines. That instrument has been subsequently applied in **Chapters 4.2** and **4.3**.

Finally, **Chapter 5** comprises the general discussion where the key results of this thesis are presented and put into perspective. In addition, implications for methodology and pointers for future research are further described. Lastly, cross-cutting themes and their implications for policy and practice are explored, and a final conclusion is included.

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CHAPTER 2

PLACING PATIENTS' AND SOCIETAL NEEDS AT THE CORE OF DRUG ASSESSMENT

CHAPTER 2.1

ADDED THERAPEUTIC VALUE OF NEW DRUGS APPROVED IN BRAZIL FROM 2004 TO 2016

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Hubert G. Leufkens, Janeth de Oliveira Silva Naves

Submitted

ABSTRACT

Objective

2.1

To assess the level of therapeutic innovation of new medicines approved in Brazil over 13 years and whether they met public health needs.

Methods

Comparative descriptive analysis of therapeutic value assessments performed by the Brazilian Chamber for Medicines' Market Regulation (CMED) and the French drug bulletin Prescrire for new medicines receiving marketing authorization in Brazil, between January 1st 2004 and December 31st 2016. Assessment data were extracted from relevant websites. The extent to which new medicines met public health needs was examined by: checking inclusions into government-funded drug lists and/or clinical guidelines; comparing ATC codes and drug indications with the list of conditions contributing the most to the national disease burden; and assessing whether new medicines aimed to treat neglected diseases.

Findings

253 new drugs were approved. Antineoplastics, immunossupressants, antidiabetics and antivirals were the most frequent therapeutic classes. Thirty-three (14.0%) out of 236 drugs assessed by CMED and sixteen (8.2%) out of 195 assessed by Prescrire were considered innovative. Thirty-six drugs (14.2%) were selected for coverage by the Brazilian Public Health System, seven from these were therapeutically innovative, and none aimed to treat neglected diseases. About 1/3 of approved drugs aimed to treat conditions among the top contributors to Brazil's disease burden.

Conclusion

Few therapeutically innovative drugs entered the Brazilian market from which only a small proportion were approved to be covered by the Brazilian Unified Health System. Our findings suggest a divergence between public health needs, R&D and drug licensing procedures.

INTRODUCTION

There is no consensual definition of what constitutes pharmaceutical innovation (1). In fact, neither the attributes of an innovative product nor the criteria to be considered when assessing its innovation have been clearly established (2). Nonetheless, the belief that new medicines bring therapeutic innovations and better health outcomes is largely shared by contemporary society (3-5), even if that is not confirmed in clinical practice (6). Over time however, it has become acceptable to consider that a new compound must exhibit a clinically relevant advantage over the existing established therapy to be considered an innovation (7, 8); such as better population indicators for morbidity, mortality and quality of life. This notion of therapeutic advance can be useful to recognize and reward medicines' manufacturers which develop products with a high therapeutic value, and therefore incentivize and sustain innovation (2, 9) that meets patients' needs (10, 11).

Álvarez (2) lists the advantages of innovative drugs when compared to available therapeutic options: greater efficacy/effectiveness and safety; improved quality of life and patient satisfaction; reduction in treatment costs; better therapeutic outcomes in patient subgroups; or enabling treatment of otherwise unmet medical needs. The decision to introduce the new drug into clinical practice must consider these aspects as well as users' and providers' interests (2, 12). Several methods have been proposed to probe and define the added therapeutic value of new medicines (7, 13-17). Generally therapeutic advance is identified when a drug's superiority is demonstrated in methodologically robust studies, using active comparators and hard clinically relevant outcomes (16, 18).

Added therapeutic value assessors generally agree that therapeutic advance is rare, despite the alleged increase in research and development costs (16). A recent report by Public Citizen in the US revealed that despite very high profits of more than 100 billion USD per year, the 20-largest pharmaceutical corporations only reported spending half that amount on R&D for new medicines (19). Researchers have called on governments to define policies to align R&D and real health needs (10, 11).

The assessment of added therapeutic value can guide clinical decisions by healthcare professionals thus benefiting patients (2, 15); and drives more effective and efficient decisions in health systems. This is particularly important in poorer settings where drug selection enables the allocation of resources - and therefore access - to those medicines which benefit the population the most (20).

Difficulties in accessing health services and medicines remain a global social problem of great concern (20). Brazil is no exception, even though it was the 8th largest pharmaceutical market in the world during 2016, with sales volumes amounting to approximately 28 billion dollars (21).

A policy was established in Brazil in 2004 to improve access to medicines through price-control measures (22), based on incentive mechanisms to increase the sector's offer and competitiveness. This was the first Brazilian policy enshrining systematic health technology

assessment (HTA) as a component of price-setting procedures, and to be applied to all new drugs approved by the Brazilian health authority - Agência Nacional de Vigilância Sanitária (ANVISA). The maximum price to be borne depends on a drug's added therapeutic value (22, 23).

Bonfim (24) reviewed new pharmaceutical products registered in Brazil between 1999 and 2004 concluding that many new medicines approved were me-too drugs driven by market demands. Another descriptive study analysed new medicines entering the Brazilian market between 2000 and 2004 and reported that only one third were innovative products and none was indicated to treat infectious diseases prevalent in developing countries (25).

Bearing in mind the need to improve access to and the rational use of medicines, our study aimed to assess the added therapeutic value of all new medicines registered in Brazil since the implementation of the HTA assessment policy and to investigate their alignment with national public health needs.

METHODS

Study Design

We conducted a comparative descriptive analysis of therapeutic value assessments for new medicines receiving marketing authorization in Brazil, from January 1st 2004 to December 31st 2016, and examined their alignment with local therapeutic needs.

Data Collection

New medicines approved by ANVISA - from January 1st 2004 to December 31st 2016 - were identified under the codes 175, 1458, 10464 or 1528, which represented respectively: entry for a new medicine, electronic entry for a new medicine, entry for a new biological product. Even though vaccines are biological products, they were excluded from our study as they are identified as non-innovative by the Brazilian criteria (22,26).

The following general data were collected for each medicine: name and country of origin of manufacturer; composition; anatomical therapeutic chemical classification – ATC (5th level) (27); date of first authorization in Brazil; and approved indications.

Assessing the added therapeutic value of new medicines

The CMED is an interministerial Brazilian body responsible for setting the prices of new medicines. It evaluates and classifies products into one of six categories divided into two groups: new molecules (categories I and II) and new formulations (categories III, IV, V and VI). A new medicine is considered innovative (Category I) when it contains a molecule (active ingredient) under national patent and offers a proven treatment gain when compared to available treatment options for that same indication. That treatment gain is translated into greater efficacy, or similar efficacy with significant reduction of adverse effects, or similar efficacy with a significant reduction in the overall treatment costs. A medicine is classified as Category II i.e. as non-

innovative if it has a new molecule (active ingredient) without patent in Brazil or if it does not does not bring along any treatment gain (22,26).

The independent drug bulletin Prescrire evaluates new drugs or new indications approved in France, according to their efficacy, safety and convenience. The Prescrire bulletin and its English edition Prescrire International are fully financed by subscriptions and do not accept advertising or external sponsorship (28). Prescrire classifies new drugs or new indications into added therapeutic value categories as follows (28):

- Bravo: the product represents a major therapeutic advance in an area where previously no treatment was available;
- A real advance: the product is an important therapeutic innovation but has certain limitations;
- Offers an advantage: the product has some value but does not fundamentally change the present therapeutic practice;
- Possibly helpful: the product has minimal additional value, and should not change prescribing habits except in rare circumstances;
- Nothing new: the product may be a new substance but is superfluous because it does not add to the clinical possibilities offered by previous products available;
- Not acceptable: product without evident benefit but with potential or real disadvantages; and
- Judgement reserved: the editors postpone their rating until better data and a more thorough evaluation of the drug are available.

New medicines were dichotomously classified, as to their added therapeutic value, when compared to available therapies for the same indication, into "therapeutic innovation" or "no therapeutic innovation". To do so, we used the assessments provided by CMED and Prescrire. In a Canadian analysis, Lexchin combined the Prescrire criteria into two broad categories, which we have also applied (29). Lexchin's categorization considers as therapeutic innovation all the medicines rated within the first three Prescrire's categories (bravo, real advance, offers an advantage) and as "no therapeutic innovation" those belonging to the remaining categories (possibly useful, nothing new and not acceptable). Medicines which Prescrire judged to have insufficient evidence to rate for therapeutic advantage are included under the category judgment reserved (29).

Adoption of drugs into national listings of the Brazilian Unified Health System (SUS)

In Brazil, the governmental health technology assessment decisions are the responsibility of the National Committee for Adoption of Technologies of the Unified Health System (CONITEC/MS) created in 2011 (30). CONITEC's reviews are based on scientific evidence, taking into consideration aspects such as efficacy, accuracy, effectiveness and safety, as well as the comparative economic evaluation of the benefits and costs of new technologies versus

existing ones. CONITEC data were retrieved from its public website to assess whether new medicines authorized by ANVISA had been adopted or excluded from national coverage lists as well as from clinical guidelines.

Alignment with national health needs

All new drugs approved during our study period were classified by ATC code and their approved indications were compared with the conditions contributing the most to the Brazilian disease burden, as measured in Disability-adjusted life years (DALYs) (31). A conservative approach was adopted when attributing indications to the various conditions, i.e. only allocating approved indications and ATC code into specific conditions which matched that indication.

Data Analysis

Descriptive statistics are reported with all variables presented as absolute numbers and proportions. The kappa index (32) was calculated to determine the level of agreement between CMED and the grouped Prescrire therapeutic value ratings in our study sample. We used Epi InfoTM version 7.1.4.0 and IBM SPSS Statistics version 24 for data analysis.

RESULTS

From January 1st 2004 to 31st December 2016, 268 new pharmaceutical products were approved by ANVISA. From these, 253 were considered for analysis, after excluding 15 vaccines (Figure 1). Antineoplastics (L01: n = 44; 17.4%), immunosuppressants (L04: n = 18; 7.1%), systemic antivirals (J05: n = 17; 6.7%) and antidiabetics (A10: n = 16; 6.3%) were the most frequent therapeutic classes.

The therapeutic value of 248 of these medicines was evaluated by at least one of the two institutions, and 183 by both (Figure 1). Within the drugs assessed by Prescrire, 16 out of 195 (8.2%) were considered therapeutic innovations, as per the grouped Prescrire criteria. Thirty three out of 236 drugs assessed by CMED were rated as therapeutic innovations (Table 1). Figures 4 and 5 outline the ratings by CMED and Prescrire over time, respectively. There is a slight increase in therapeutic innovation ratings by CMED over time, which is not observed in the Prescrire ratings.

Five drugs - laronidase, nivolumab, pasireotide, sofosbuvir and sunitinib - were considered by both evaluators to be therapeutic innovations. As shown in Table 2, the therapeutic classes with the most innovative drugs were: antineoplastic agents (n=19); systemic antivirals (n=7) and immunosupressants (n=3). Eleven (n=11, 4.3%) drugs were considered innovative by Prescrire but not by the CMED, whereas another 24 (9,5%) drugs were considered innovative by the CMED and non-innovative by Prescrire. Overall, the level of agreement between CMED and Prescrire was weak [kappa = 0.123 (CI 95%: 0.014 to 0.260; p = 0.077)].

Forty-four (17.4%) from the 253 drugs in our sample were rated as therapeutic innovations by at least one of the criteria. From these, seven were adopted into the Unified Health System

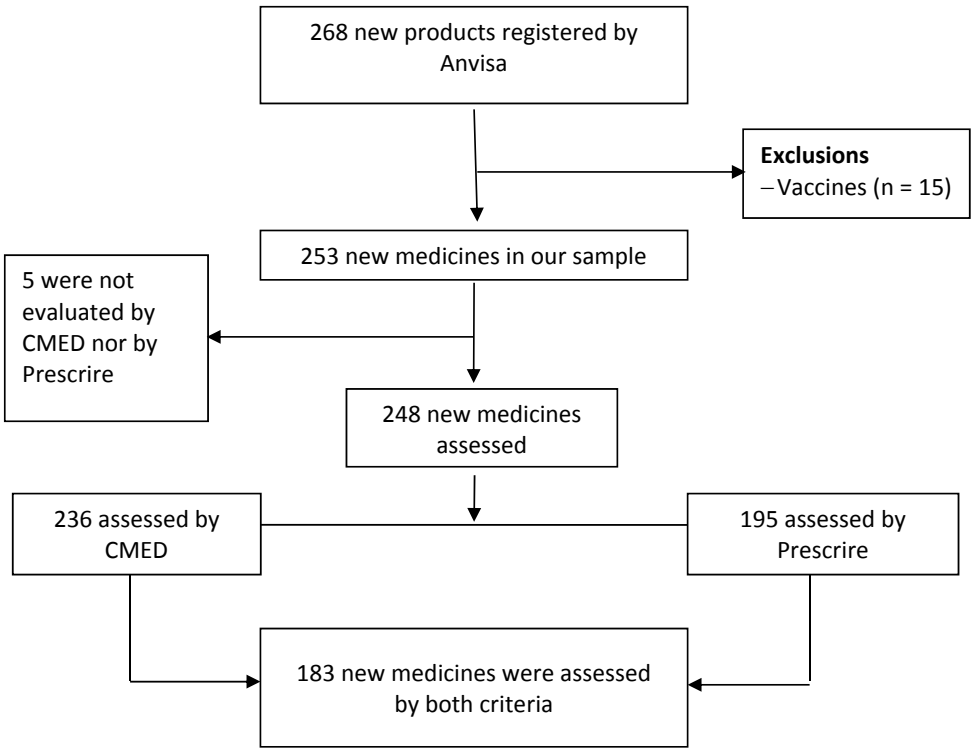

FIGURE 1. New Medicines authorized in Brazil from January 2004 to December 2016

TABLE 1. Rating of the added therapeutic value of newly registered medicines in Brazil, as per three criteria from January 2004 to December 2016

Criteria					
n=236		**n=195**			
CMED Categories	**n (%)**	**Grouped Prescrire Categories**	**n (%)**	**Prescrire Categories**	**n (%)**
Therapeutic Innovation	33 (14.0)	Therapeutic Innovation	16 (8.2)	Bravo	0 (0)
				Real advance	2 (1.0)
				Offers an advantage	14 (7.2)
No therapeutic innovation	203 (86.0)	No therapeutic innovation	162 (83.1)	Possibly helpful	31 (15.9)
				Nothing new	91 (46.7)
				Not acceptable	40 (20.5)
		Judgment reserved	17 (8.7)	Judgment reserved	17 (8.7)

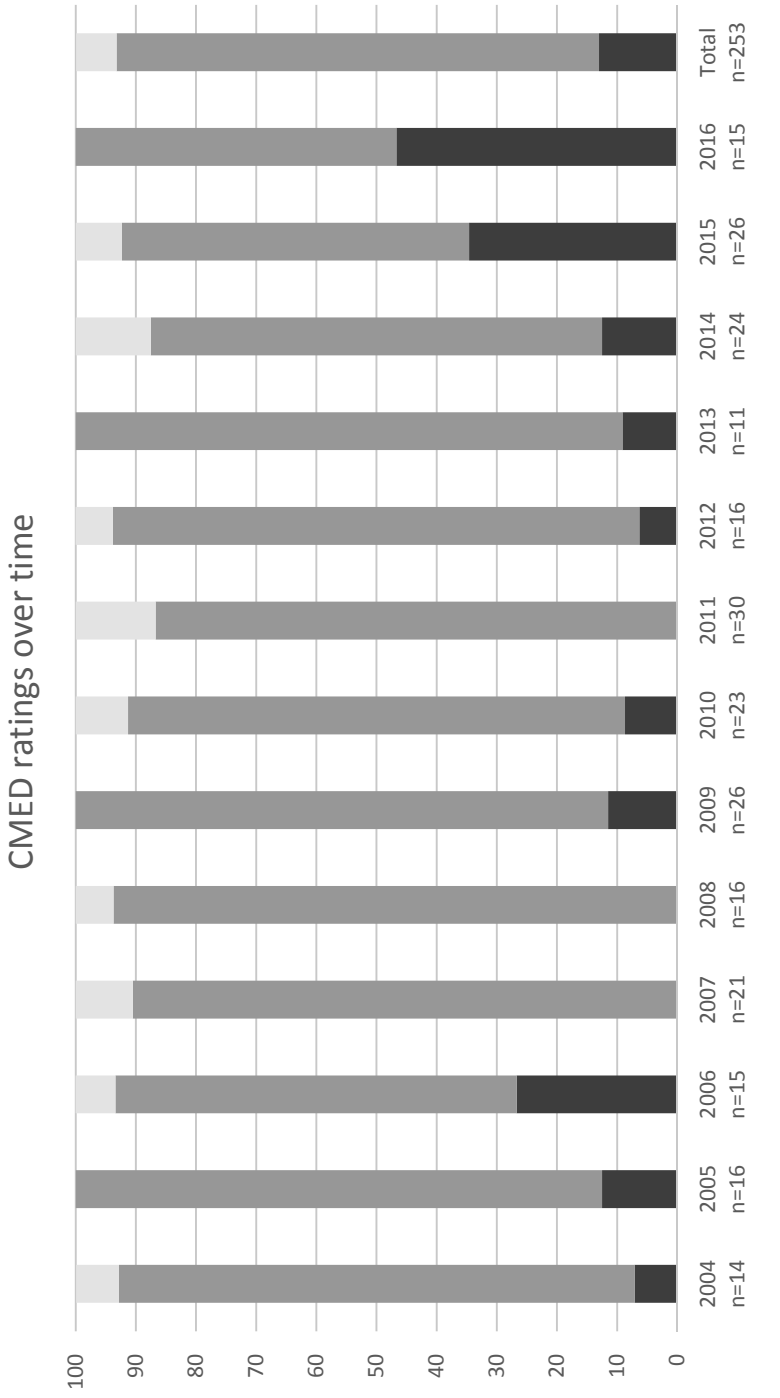

FIGURE 2. CMED ratings over time (percentage): Newly registered medicines in Brazil from January 2004 to December 2016

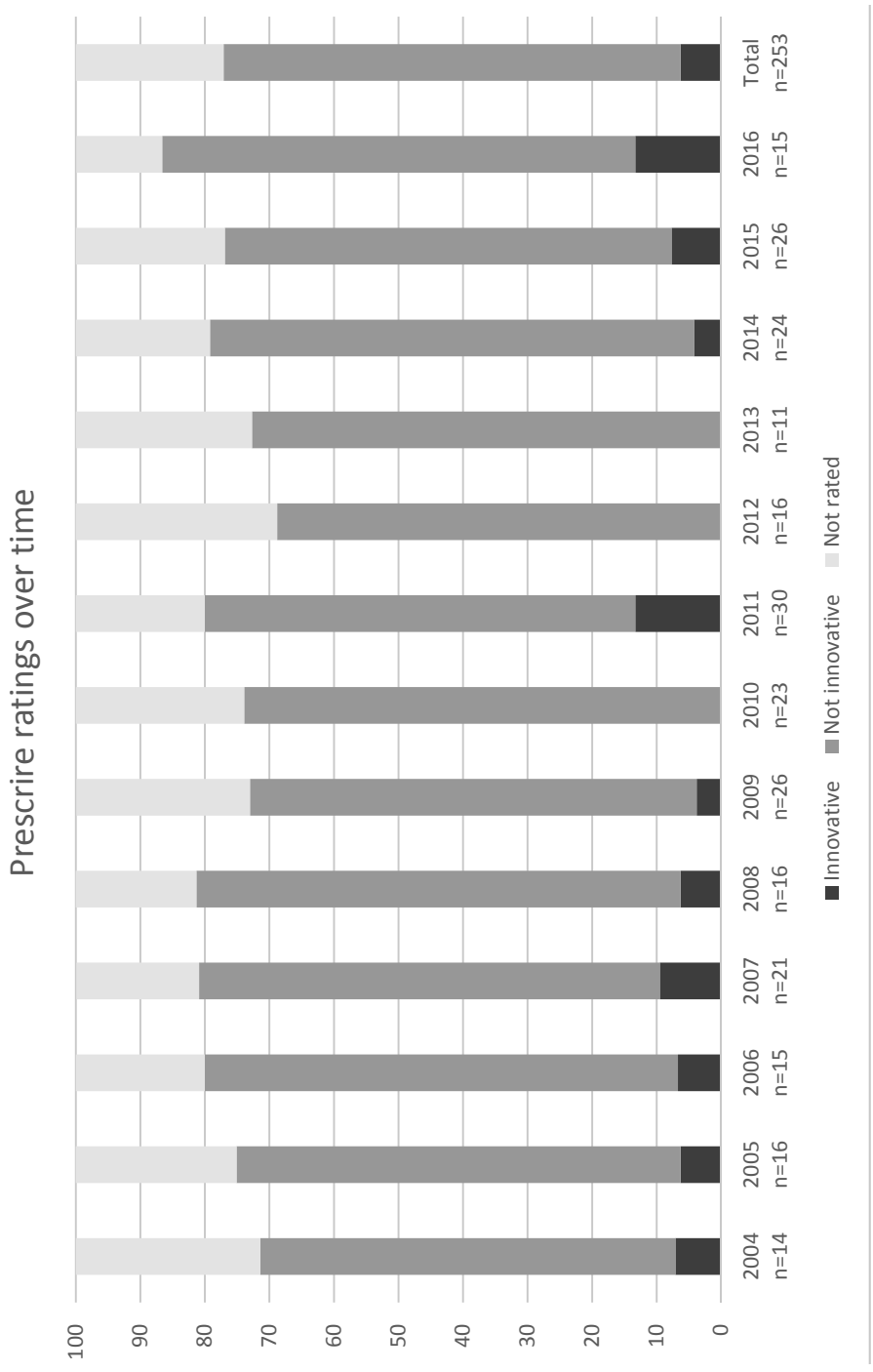

FIGURE 3. Grouped Prescrire ratings over time (percentage): Newly registered medicines in Brazil from January 2004 to December 2016

TABLE 2. Distribution of therapeutic innovations by ATC class: newly registered medicines in Brazil from 2004 to 2016 that were considered therapeutic innovations by either CMED or Prescrire and their distribution by ATC class (n = 44)

ATC Class (Code)	Therapeutic Innovation (n)	Percentage within ATC Class (%)
Antineoplastic Agents (L01)	19	43%
Antivirals for Systemic Use (J05)	7	41%
Immunosuppressants (L04)	3	17%
Ophtalmologicals (S01)	2	20%
All other Therapeutic Products (V03)	2	50%
Other Hematological Agents (B06)	2	100%
Agents acting on the Renin-Angiotensin System (C09)	1	50%
Antibacterials for Systemic Use (J01)	1	20%
Antihypertensives (C02)	1	25%
Antithrombotic Agents (B01)	1	9%
Endocrine Therapy (L02)	1	33%
Lipid Modifying Agents (C10)	1	20%
Other Alimentary Tract and Metabolism Products (A16)	1	10%
Other Nervous System Drugs (N07)	1	25%
Pituitary and Hypothalamic Hormones and Analogues (H01)	1	50%

coverage listings, which means that they are to be made freely available to Brazilian patients (Table 3 and Supplementary Table 1). None of these drugs was included into the Basic Pharmaceutical Care Package nor aimed to treat a neglected disease. Of the 29 drugs adopted by the Unified Health System which were rated as 'no therapeutic innovation', 8 were only assessed by one of the criteria (Supplementary Table 2).

Table 4 shows the distribution of indications approved in relation to the burden of disease. Sixty-three (30.9%) of the 204 non-therapeutically innovative drugs and nine (20.4%) out of the 44 therapeutically innovative drugs aimed to treat a condition within the top 15 contributors to the national disease burden.

DISCUSSION

This study has shown that relatively few new medicines approved in Brazil from 2004 to 2016 were considered therapeutic innovations and were adopted into national drug listings. Most (82%) were non-innovative medicines. Despite their low added therapeutic value ratings, more than 11% of these non-innovative drugs were included in government-funded drug listings. One-third of all new drugs approved during the study period aimed to treat one of the fifteen conditions contributing the most to the Brazilian disease burden.

These are worrying findings from a public health perspective. First, they suggest that over the last thirteen years many medicines approved in Brazil had low utility levels (4). Second,

TABLE 3. Adoption of new medicines approved in Brazil from January 2004 to December 2016 into coverage listings (Unified Health System)

	Adopted in UHS listing[1]	
Therapeutic Innovation [2]	**Yes n=36 (14.2%)**	**No n=217 (85.8%)**
Yes	7	37
(n = 44; 17.4%)	(2.8%)	(14.6%)
No	29	175
(n = 204; 80.6%)	(11.4%)	(69.2%)
Not assessed	0	5
(n = 5; 2%)	(0%)	(2%)

[1] National formulary editions between 2004 and 2016 were consulted as well as recommendations from the reimbursement committee that were published up to 6 months after the last drug approval within our study period.

[2] Based on the CMED and/or Grouped Prescrire criteria. Yes = therapeutic innovation; No = no therapeutic innovation. Five new medicines were not assessed by CMED nor Prescrire.

they indicate a poor allocation of resources by allowing public money to be spent on new, often expensive, non-innovative drugs. Although this is not different from more industrialized settings (33) it is problematic for Brazil where limited resources are available to ensure public coverage (34). Finally, most new drugs entering the market target specific niches and chronic conditions rather than other indications of greater relevance to public health, such as neglected diseases. Taken together, these findings are contrary to the principles of rational medicine use (35).

Our results match those of previous studies where no more than 10% of newly approved drugs were considered therapeutic innovations (4,6,14,24,29).

One could presume that the partial overlap between approved indications and the national disease burden confirms that the available therapeutic arsenal is sufficient to treat the conditions contributing the most to DALYs. Yet, this mismatch showcases a focus on new drug approvals for specific indications, such as oncology. This might be explained by the fact that market pressures do not necessarily mirror public health needs, especially for health conditions that mainly occur in low to medium income countries. Notwithstanding the importance medicines hold in society as a treatment modality and their contribution to health care costs, medicines' production is the domain of a few large multinational companies, which opt to focus on specific market niches and chronic conditions (36). Four out of the five medicines considered therapeutically innovative by both CMED and the grouped Prescrire criteria have orphan drug product denomination either in the EU or in the USA. Within our sample antineoplastics, immunosupressants, systemic antivirals and antidiabetics were the most frequent therapeutic classes. Silva et al. (37) reported that diabetes type 2, breast cancer and bronchial or lung cancer were among the conditions more frequently studied in clinical trials in Brazil. While research in neglected diseases is a high

TABLE 4. Drugs approved by ANVISA from January 2004 to December 2016 distributed by the 15 conditions contributing the most to the Brazilian disease burden (31) and categorized as to their therapeutic innovation rating

Disease Burden (top 15 main contributors to DALY)	DALY Rate[1] men/women	Average	Number of drugs approved per condition[2] (n)	No Therapeutic Innovation (n)	Therapeutic innovation (n)	Not rated (n)
Depression	7.1/25.1	16.1	4	4	0	0
Ischaemic heart disease	15.4/11.3	13.3	9	8	1	0
Diabetes	9.4/9.0	9.2	20	18	1	1
Stroke	9.7/8.4	9.0	4	3	1	0
Chronic obstructive pulmonary disease	7.5/6.2	6.8	6	6	0	0
Alcohol abuse and dependence	10.1/2.1	6.1	2	2	0	0
Lower respiratory tract infections	6.1/4.8	5.4	5	4	1	0
Bipolar disorder	5.3/5.6	5.4	1	1	0	0
Alzheimer and other dementia	2.9/5.3	4.1	0	0	0	0
Asthma	3.2/4.3	3.7	2	2	0	0
HIV/AIDS	3.4 (m)	3.4	9	6	3	0
Breast Cancer	3.3 (w)	3.3	4	2	2	0
Osteoarthritis	2.8 (m)	2.8	3	3	0	0
Hypertensive heart disease	2.8/2.4	2.6	4	3	1	0
Epilepsy	1.9 (m)	1.9	5	5	0	0
Total approved for the 15 main DALYs contributors			73[2]	63	9	1
Drugs approved for other indications			180	141	35	4
TOTAL			253*	204	44	5

[1]DALY rates/1000 inhabitants; [2] Five drugs covered two indications from the top 15 main contributors to DALYs .

priority for Brazil, it does not yield returns on investment for the pharmaceutical industry (37). Nevertheless, there are two ongoing initiatives by multinational companies within neglected diseases in collaboration with the Institute of Drug Technology Farmanguinhos: a product development for a praziquantel pediatric formulation to treat schistosomiasis (now at phase 2); and a cooperative Research and Development Agreement to develop a dengue virus vaccine (at preclinical stage) (38).

Our study has shown that only 36 (14.3%) of the new medicines registered during these 13 years were listed for public coverage under the Brazilian Unified Health System, and that 21 out of the 36 medicines included in these listings were considered non-innovative by both CMED and Prescrire. Such a low number of therapeutic innovations stresses the importance of strengthening pharmacy and therapeutics committees (39-41). While they have been established in many health facilities in Brazil their roles are somewhat limited due to financial and human resources constraints (41). Many new technologies receive poor health technology assessments. About 40% of all HTA recommendations around the world are negative and so are those of CONITEC (42). There have been suggestions to improve ANVISA procedures, with a focus on added therapeutic value and systematic disclosure of assessment' results. These measures would benefit medicine users, health professionals and managers (43).

We found very weak agreement between CMED and Prescrire's evaluations of therapeutic innovativeness. This can be partly attributed to differences in the organisations, as well as their rationale and criteria. For instance, the CMED considers patent protection as a prerequisite for therapeutic innovation, whereas that is not the case for Prescrire. Nonetheless, both criteria examine the available scientific evidence on a drug's efficacy, safety and effectiveness. In Canada, Lexchin compared drug assessments by the Patented Medicine Prices Review Board (PMPRB) and Prescrire (29). His results mirror ours. In addition, notwithstanding Prescrire's scientific standards, one could argue that its reviews are led by healthcare professionals living in another, social, health and economic context than Brazil, and that therefore, their ratings might not be transferable to other settings. Likewise, the political context in Brazil and changes in the government and at ANVISA might also have affected the CMED ratings. Moreover, assessing a drug's therapeutic innovativeness in comparison with existing treatment options depends partly on other available treatments and can therefore vary by setting and over time. Nonetheless, the clarity and validity of the criteria adopted, their evidence-based approach and extensive peer-review are all factors that minimize that likelihood.

Some caution is warranted when interpreting these assessments as there is no benchmark for the evaluation of the therapeutic value of new medicines. Much of the data used is available at the time of approval and is limited, as new evidence is likely to arise at a later stage once the medicine has been marketed and used by a larger patient population (4).

The CMED's under-patent requirement as a prerequisite for therapeutic innovation is highly questionable. Although the existence of a patent presumes demonstrated progress over previous knowledge (16), patents are frequently granted based on technical aspects which are unrelated to a drug's efficacy or its therapeutic benefits, and consequently play a limited role when ascertaining the quality of pharmaceutical innovation (16, 44).

The data in this study were collected in parallel and cross-referenced from different sources, most of which publicly available, thus contributing to the reliability of our findings. Additional studies would be needed to explore the divergence between therapeutic value assessment criteria and to promote greater harmonization and reproducibility.

This discussion on drug innovation cannot be separated from an analysis of the R&D trends both nationally and globally, as these reflect the interests and priorities of public and private research funders. Some authors have advocated that to foster future innovation the current criteria for drug approval should be changed to introduce clear demonstration of added therapeutic value as a requirement to obtain a marketing authorization (4,45,46). Sandroni defends a dual role for the State: to stimulate and redirect R&D towards therapeutically innovative medicines treating unmet medical needs, and to reward value based on results (47). While industry stakeholders in Brazil agree that innovation should bring therapeutic gains and real benefits for patients, they have called for early price-setting discussions, before investments are made in R&D, claiming that this would prompt national innovation (47). Ultimately, clinical research priorities should be based on local epidemiological data, with value placed on studies that examine important health aspects and respond to current and future gaps in services, thus protecting systems from becoming reliant on a few multinational pharmaceutical companies that dominate the sector (48). Undoubtedly, this approach would benefit Brazil, a major emerging economy that still faces many public health challenges while striving to provide universal health coverage.

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TABLE S1. New medicines registered in Brazil which were considered therapeutic innovations by either CMED or the grouped Prescrire criteria and their date of inclusion into national reimbursement listings (n = 44)

New Medicine	ATC	First approved indication	Therapeutic innovation [1]		Publicly reimbursed (date and component [4])
			CMED [2]	Grouped Prescrire- [3]	
abiraterone	L02BX03	metastatic prostate cancer	N	Y	No
axitinib	L01XE17	advanced renal cell carcinoma	Y	N	No
azacitidine	L01BC07	myelodysplastic syndrome	N	Y	No
azilsartan medoxomil	C09CA09	essential hypertension	Y	NA	No
boceprevir	J05AE12	chronic hepatitis C genotype 1	N	Y	No
c1-inhibitor, plasma derived	B06AC01	hereditary angioedema types I and II	N	Y	No
cabazitaxel	L01CD04	metastatic prostate cancer	Y	N*	No
carfilzomib	L01XX45	multiple myeloma	Y	N	No
cobimetinib	L01XE38	melanoma BRAF V600 mutation positive	Y	N	No
crizotinib	L01XE16	non-small cell lung cancer	Y	N	No
daclatasvir	J05AX14	chronic hepatitis C genotype 1-4	N	Y	06/2015 (SP)
darunavir	J05AE10	HIV-1 infection	N	Y	03/2015 (ST)
enfuvirtide	J05AX07	HIV-1 infection	N	Y	04/2014 (ST)
eribulin	L01XX41	advanced or metastatic breast cancer	Y	N	No
erlotinib	L01XE03	non-small cell lung cancer	Y	N	11/2013 (HOSP [6])
evolocumab	C10AX13	hypercholesterolaemia	Y	N	No
ibrutinib	L01XE27	mantle cell lymphoma	Y	NA	No
icatibant	B06AC02	attacks of hereditary angioedema	Y	N	No
laronidase	A16AB05	mucopolysaccharidosis I	Y	Y	No
lenvatinib	L01XE29	differentiated thyroid carcinoma	Y	N	No
nintedanib	L01XE31	idiopathic pulmonary fibrosis	Y	N	No
nivolumab	L01XC17	advanced melanoma	Y	Y	No
ocriplasmin	S01XA22	vitreomacular traction	Y	N	No
pasireotide	H01CB05	Cushing's disease	Y	Y	No
raltegravir	J05AX08	HIV-1 infection	N	Y	10/2014 (ST)

TABLE S1. (continued)

New Medicine	ATC	First approved indication	Therapeutic innovation [1]		Publicly reimbursed (date and component [4])
			CMED [2]	Grouped Prescrire- [3]	
ranibizumab	S01LA04	neovascular macular degeneration	N	Y	No
rasburicase	V03AF07	acute hyperuricaemia	Y	N	No
regorafenib	L01XE21	gastrointestinal stromal tumours	Y	N	No
riociguat	C02KX05	chronic thromboembolic pulmonary hypertension	Y	N	No
ruxolitinib	L01XE18	myelofibrosis	Y	N	No
siltuximab	L04AC11	multicentric Castleman's disease	Y	N	No
sofosbuvir	J05AX15	chronic hepatitis C genotype 1-3	Y	Y	06/2015 (SP)
sorafenib	L01XE05	advanced renal cell carcinoma	Y	N	No
sugammadex	V03AB35	reversal of neuromuscular blockade	Y	NA	No
sunitinib	L01XE04	gastrointestinal stromal tumor	Y	Y	No
telaprevir	J05AE11	chronic hepatitis C genotype 1	N	Y	No
ticagrelor	B01AC24	thrombotic event prevention	Y	N	No
tigecycline	J01AA12	bacterial infections	Y	N	No
tofacitinib	L04AA29	rheumatoid arthritis	Y	NA	No
trastuzumab emtansine	L01XC14	breast cancer with HER2 overexpression	Y	N	07/2012 (HOSP [6])
ustekinumab	L04AC05	plaque psoriasis, moderate to severe	Y	N	No
vandetanib	L01XE12	medullary thyroid cancer	Y	N	No
varenicline	N07BA03	smoking cessation	Y	N	No
vemurafenib	L01XE15	melanoma BRAF V600E mutation positive	N	Y	No

[1] Added therapeutic value rating: Y = therapeutic innovation; N = no therapeutic innovation; NA = not assessed; N* = assessed yet not rated due to lack of evidence.
[2] CMED data are from 01/01/2004 to 31/12/2016.
[3] Lexchin, 2015 (Ref. 29).
[4] Pharmaceutical Care Components in the Brazilian Unified Health System: SP = specialist; ST = strategic.
[6] Hospital component: HOSP.

TABLE S2. New medicines registered in Brazil which were considered not to be therapeutic innovations or were not assessed but were added to reimbursement listings (n = 29)

New Medicine	ATC	First approved Indication	Therapeutic Innovation [1]		Publicly reimbursed (date and component [4])
			CMED [2]	Grouped Prescrire- [3]	
abatacept	L04AA24	rheumatoid arthritis	N	N	SP*
ambrisentan	C02KX02	pulmonary arterial hypertension	N	N	11/2013 (SP)
bimatoprost	S01EE03	open-angle glaucoma	NA	N	07/2013 (SP)
certolizumab pegol	L04AB05	Crohn's disease	N	N	01/2017 (SP)
cinacalcet	H05BX01	secondary hyperparathyroidism	N	N	09/2015 (SP)
deferasirox	V03AC03	transfusion-dependent thalassaemia	N	N	07/2013 (SP)
dolutegravir	J05AX12	HIV-1 infection	N	N	10/2015 (ST)
entecavir	J05AF10	chronic hepatitis B	N	N	07/2013 (SP)
etravirine	J05AG04	HIV-1 infection	N	N	03/2017 (ST)
fingolimode	L04AA27	relapsing-remitting multiple sclerosis	NA	N	07/2014 (SP)
fosamprenavir	J05AE07	HIV-1 infection	N	N	12/2016 (ST)
gefitinib	L01XE02	non-small cell lung cancer	N	N	11/2013(HOSP)[5]
golimumab	L04AB06	rheumatoid arthritis	N	N	09/2012 (SP)
iloprost	B01AC11	primary pulmonary hypertension	N	N	07/2013 (SP)
laropiprant + nicotinic acid	C10AD52	combined mixed dyslipidaemia	N	N	SP*
maraviroc	J05AX09	HIV-1 infection	N	N	10/2012 (ST)
miglustat	A16AX06	type-1 Gaucher disease	N	N	07/2013 (SP)
natalizumab	L04AA23	relapsing-remitting multiple sclerosis	N	N	08/2013 (SP)
rifabutin	J04AB04	*Mycobacterium avium* infection prophylaxis	NA	N	2011 (ST)
sapropterin	A16AX07	phenylketonuria	N	N	ST* (human rabies)
simeprevir	J05AE14	chronic hepatitis C	N	N	06/2015 (SP)
taliglucerase alfa	A16AB11	type-1 Gaucher disease	N	NA	09/2014 (SP)
tenofovir disoproxil + emtricitabine	J05AR03	HIV-1 infection	N	NA	ST*
teriflunomide	L04AA31	relapsing-remitting multiple sclerosis	N	N	SP*
tipranavir	J05AE09	HIV-1 infection	N	N	ST*

TABLE S2. (continued)

New Medicine	ATC	First approved Indication	Therapeutic Innovation [1]		Publicly reimbursed (date and component [4])
			CMED [2]	Grouped Prescrire-[3]	
tirofiban	B01AC17	prevention of cardiac ischemia	NA	N	HOSP [5]
tocilizumab	L04AC07	rheumatoid arthritis	N	N	SP*
travoprosta	S01ED51	open-angle glaucoma	NA	N	SP*
velaglucerase alfa	A16AB10	type-1 Gaucher disease	N	NA	SP*

[1] Added therapeutic value rating: N = no therapeutic innovation; NA = not assessed.
[2] CMED data are from 01/01/2004 to 31/12/2016.
[3] Lexchin, 2015 (Ref. 29).
[4] Pharmaceutical Care Components in the Brazilian Unified Health System: SP = specialist; ST = strategic.
[5] HOSP - Hospital component in the Brazilian Unified Health System.
* adoption date is unavailable

CHAPTER 2.2

THE IMPACT OF QUALITY-OF-LIFE DATA IN RELATIVE EFFECTIVENESS ASSESSMENTS OF NEW ANTI-CANCER DRUGS IN EUROPEAN COUNTRIES

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ABSTRACT

Purpose

The aim of this study is to investigate the role of health-related quality of life (QoL) data in relative effectiveness assessments (REAs) of new anti-cancer drugs across European jurisdictions, during health technology assessment procedures.

Methods

Comparative analysis of guidelines and publicly available REAs in six European jurisdictions of anti-cancer drugs approved by EMA between 2011-2013.

Results

Fourteen anti-cancer drugs were included, adding up to 79 REAs. Whilst all guidelines state that QoL is a relevant endpoint to determine the relative effectiveness of new cancer drugs, QoL data were included in only 54% of the 79 reports and their impact on the recommendations was limited.

Conclusions

Whilst national guidelines recognize the relevance of QoL to determine the relative effectiveness of new anti-cancer drugs, this is not well-reflected in current assessments. Developing and implementing into REAs specific evidence requirements for QoL data would improve the use of this patient-centered outcome in future reimbursement and pricing decisions.

INTRODUCTION

As the aim of anti-cancer therapies is to allow patients to live better and/or longer, treatment outcomes showing improvements in patient survival (e.g. overall survival) and/or health-related quality of life (QoL) are central to determine the clinical meaningfulness of a new treatment (1).

Health-related QoL can reflect a patient's day-to-day functioning (2), and is defined as the patient's subjective perception of his or hers physical, psychological, social, somatic functioning and general well-being (3). Health-related QoL is particularly relevant in diseases such as cancer that greatly affect all dimensions of daily life (4), as it can convey (additional) information to assess the overall burden of disease, the effectiveness and side effects of the treatment (5). For example, QoL data can be very informative in advanced disease stages when survival differences are expected to be minimal and treatment-related toxicity is of interest and/or one of the treatments is expected to be more palliative than the others (6). In addition, QoL data can help understand the impact of novel treatment on patient functioning and to identify treatment-related symptoms that need management (7).

Over the years there has been a growing discussion on how to define and measure health-related QoL in cancer (5). A patient's QoL is usually measured through self-completion of validated questionnaires, which can be subdivided into generic- and disease-specific instruments. Most QoL measures are multidimensional, designed to reflect multiple domains of impact. These vary by instrument, but often include physical, psychological, and social components of outcome (5). Examples of commonly used disease-specific questionnaires in cancer research are the "European Organization for the Research and Treatment of Cancer Quality of life Questionnaire" (EORCT-QLQ) and the "Functional Assessment of Cancer Therapy" (FACT). These questionnaires mainly express QoL in terms of tumour-, treatment- and symptom-specific scores by asking patients to answer questions about, for instance, side-effects or discomfort (8, 9). Commonly used generic QoL instruments in cancer research, on the other hand, are the EuroQol (EQ-5D) and its visual analogue subscale (EQ-VAS). The EQ-5D measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression at three levels of response, while the EQ-VAS represents health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) (10).

Whereas disease-specific QoL data may be more sensitive to detect changes in disease-related symptoms and patient functioning, generic instruments are particularly important to ensure coherence when assessing health benefits across different interventions and multiple indications as they encompass all dimensions relevant to patients, not only those on which an effect is expected (11). Therefore, both instruments are often seen as complementary.

Although the value of QoL data is evident, there are considerable challenges with collecting and interpreting such data (3, 12). QoL data collection is time consuming for advanced cancer patients who are hardly able to fulfill the requirements of intensive patient participation. Consequently, data are often incomplete or lacking, making it difficult to identify meaningful effects of treatments on QoL. In addition, the interpretation of health-related QoL evidence is

often a challenge as its assessment is, by definition, subjective and problematic to generalize between different patient populations and countries (12). Another methodological constraint is the fact that oncology trials are frequently open label and information bias becomes a concern (5).

At regulatory level, patient-centered outcomes have been recognized as relevant by the European Medicines Agency (EMA) (13, 14). To a large extent, such acceptance has been fuelled by clinicians, patients and caregivers (15-17). Two different studies found that one third of the EMA reports included patient reported measures among which QoL data, with the latter being more frequently mentioned in reports of antineoplastic agents (18, 19). A similar trend is observed at the Food and Drug Administration (20) where a draft guidance on the use of patient-reported outcomes in industry-sponsored studies was released for public consultation by the FDA in early 2006 and later updated in 2009 (20).

On the pathway for patient access to new drugs, regulatory approval is the first step. Within the European Union, a successful marketing authorization is generally followed by a myriad of health technology assessments (HTAs) at the national level guiding pricing and/or reimbursement recommendations. A relative effectiveness assessment (REA) of a new drug is a particular type of HTA that compares the clinical benefit of a drug with standard treatment. In many European countries, it is a relevant criterion in pricing and/or reimbursement decisions (21). Previous studies have shown that QoL is considered a relevant endpoint in relative effectiveness assessments (REAs) of new drugs (22). On the other hand, there have also been reports about a lack of consensus on which QoL data is to be used (11), indicating that challenges exist in this domain. The aim of this study is to investigate whether the perceived importance of QoL data is reflected in REAs for pricing and/or reimbursement recommendations for oncology drugs in Europe. We want to investigate the relevance of QoL data in European REAs by answering the following questions:

- Which requirements are included in methodological guidelines of different EU jurisdictions on the use of QoL data in REAs?
- Is QoL data included in the REAs of new cancer drugs across different EU jurisdictions? If so, how does it impact on the recommendations?
- Are there differences in the use of different types of QoL instruments and how do these affect the recommendations?

METHODS

Research design

We have conducted a retrospective comparative cross-sectional analysis of publicly available assessments produced by HTA bodies on anti-cancer medicines authorised in the EU between 2011 and 2013. The data presented in this article are part of a larger study on the use of endpoints in REAs of anti-cancer drugs (23). For this article, the data collection focused on the use of QoL data in the assessments and their impact on the recommendation.

Inclusion criteria

HTA jurisdictions

We searched for publicly available reports from HTA bodies involved in drug assessment for pricing and reimbursement decisions in jurisdictions within the EU. Reports were publicly available for nine out of the 29 jurisdictions[1]. From these nine, three were excluded due to insufficient data: Belgium did not publish all the reports they produced, whereas Portugal and Ireland only published brief summaries thus preventing appropriate data extraction and analysis.

- Six jurisdictions and their HTA agencies were included in our study:
- England (EN) - National Institute for Health and Care Excellence (NICE);
- France (FR) - Haute Autorité de Santé (HAS);
- Germany (21) - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG);
- Netherlands (NL) - Zorginstituut Nederland (ZIN);
- Poland (PO) - Agencji Oceny Technologii Medycznych i Taryfikacji (AOTMiT), and;
- Scotland (SC) - Scottish Medicines Consortium (SMC).

HTA Guidelines

National HTA guidelines for medicines' assessment were obtained from relevant HTA agencies' websites. If no guideline was available, grey literature was searched to obtain information on the favoured endpoints in the REAs of anti-cancer medicines. Information on QoL data was retrieved with a special focus on REA sections (and not cost-effectiveness sections).

Anti-cancer medicines and reports

A list of all new anti-cancer drugs approved by the EMA between 1 January 2011 and 31 December 2013 (n=26) was compiled. We then selected those medicines for which ≥ 4 HTA reports had been published by different HTA bodies by April 2015 (n=14).

Reassessments for the same indication (due to changes in price or clinical data availability) were excluded. A total of 72 HTA reports were identified. When an HTA report included separate evaluations and/or recommendations for specific (sub)indications, each (sub)indication was included as an item. The 12 IQWIG reports included a total of 25 (sub)indications with separate recommendations. However, for 7 out of the 25 (sub)indications, data were missing and therefore were excluded from our data set, resulting in a total of eighteen assessments for Germany. One HAS report included 2 (sub)indications with separate recommendations. The final data set included 79 HTAs assessments. A detailed flow chart of the selection process is provided in Kleijnen et al (23).

[1] There are 28 EU member states, however UK was divided into two HTA jurisdictions (England and Scotland) due to extensive experience of the national institute for health and clinical excellence (NICE) and the Scottish Medicines Consortium (SMC).

Data collection and extraction

A structured data collection form was developed and used to extract data from the assessments. The detailed description of the development including validation is described elsewhere (23). This article focuses on a subset of the questionnaire, which is related to the inclusion of QoL data and their impact on the recommendation (Questions 22-25).

Since our focus was on the REAs and not cost-effectiveness, data were extracted from the reports' clinical sections and from the overall recommendations. QoL data were defined as any data measured with validated QoL instruments.

In order to capture the impact of QoL data on the recommendation, statements about QoL data in the recommendation/discussion sections of the assessments were categorized as *positive, neutral, negative, unknown* or *no impact* (not identified). The algorithm for QoL data impact categorisation is presented in Figure 1.

Data were collected between April and May 2015 by four researchers, with data abstraction being conducted by a researcher fluent in the jurisdiction's language.

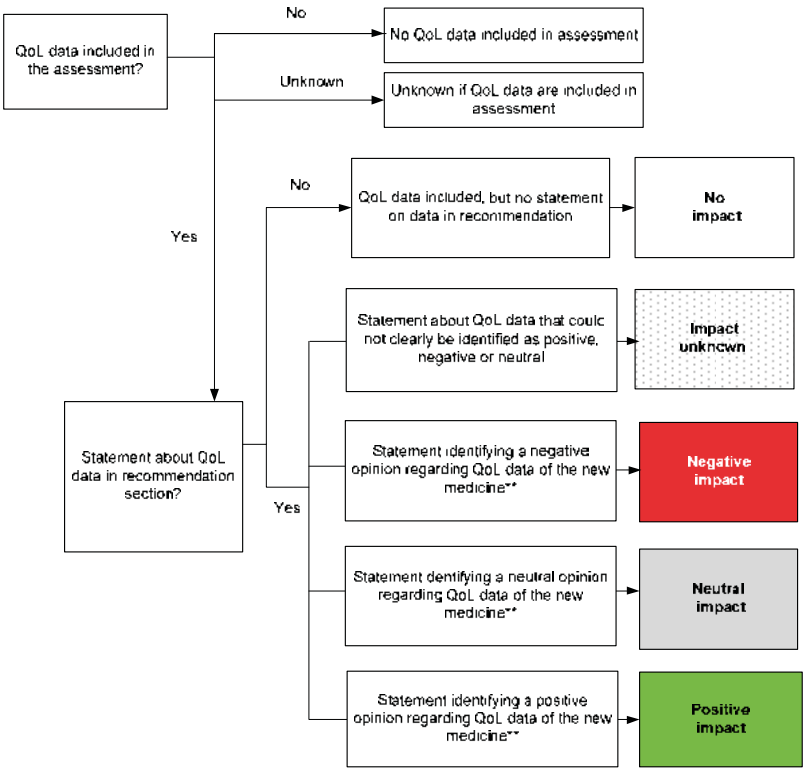

FIGURE 1. Algorithm used to determine the impact of QoL data on recommendation.

To improve consistency among researchers', frequently- used statements were identified. In addition, a quality control was conducted by the first author (i.e. checking eventual errors and overall uniformity). Any disagreements were discussed until consensus was reached among all researchers. Furthermore, an expert panel was invited to clarify pending issues. This panel was composed of six experts (one per agency) who are or have been involved in drug assessments. Their review resulted in changes to the categorisation. We initially presumed that an explicit statement about the absence of QoL data impacted negatively on the recommendation. But based on the input from the experts we changed this into 'no impact'.

Data analysis

Descriptive statistics were used to summarise the following data and to calculate: the percentage of assessments that included QoL data by jurisdiction, drug and instrument type; and the percentage of statements about included QoL data that were classified as positive, neutral, negative, unknown or no impact across the various jurisdictions and also per type of instrument used. Moreover, data and statements were analysed qualitatively to identify commonalities and disparities across jurisdictions.

RESULTS

HTA guidelines

For five out of six jurisdictions HTA guidelines were identified including information on the use of endpoints in drug assessment. No guideline was identified for France but information was retrieved from a published consensus statement and a review of European countries. Table 1 includes the most relevant information on QoL extracted from the guidelines.

QoL was considered a relevant endpoint in all jurisdictions. Most guidelines are general and do not mention oncology medicines specifically. In addition, the majority refers that evidence requirements applicable to QoL data are to be the same as for other health effects, e.g. preferably measured in randomised clinical trials. The German guidelines provide some details on how to handle bias from open studies. Some guidelines provide pointers on the potential influence of QoL data in recommendations. German guidelines indicate that for new drugs the demonstration of an added benefit in terms of QoL alone is insufficient when there is no added benefit either in morbidity or mortality. The Dutch guideline refers: '*Very little research is undertaken that explicitly focuses on quality of life. However, the added value of a medicine may actually be expressed in the form of an improved quality of life. Consequently, it is always worthwhile mentioning relevant data on this aspect.*'

Some jurisdictions (England, Scotland, and the Netherlands) also specify that the well-being of caregivers is relevant. The English guideline states that it is important to "*identify principal measures of health outcome(s) that will be relevant for the estimation of clinical effectiveness. That is, they measure health benefits and adverse effects that are important to patients and/or their carers*".

TABLE 1. Overview of information provided on Quality of Life in guidelines of Health Technology Assessment agencies

Jurisdiction	England/Wales	France[a]	Germany
HTA organisation	NICE	HAS	IQWIG
Separate REA analysis	No, part of cost-effectiveness analysis	Yes	Yes
Patient relevant endpoints	Survival or health-related quality of life	Mortality, morbidity, health-related quality of life	Mortality, morbidity or health-related quality of life
Specific guidance on quality of life	· For the cost-effectiveness analyses health effects should be expressed in QALYs. · EQ-5D is the preferred measure of health related quality of life in adults. · QOL data should be reported directly by patients and/or carers. · Valuation of QoL data should be representative sample of the UK population. · The committee finds it helpful to have the perspective of patients or carers about how relevant the clinical outcomes and the standardised generic instruments for measuring health-related quality of life are to the disease or condition.	· The Commission often bemoans the lack of quality-of-life data: Tools are available in oncology but are difficult to use repeatedly in clinical trials and vary inter-individually, which reduces their relevance for deciding between treatments or therapeutic strategies. As cancers become chronic, other tools such as examining patient preference or utility could be taken into account by the Transparency Commission in oncology.	· Use instruments that are suitable for use in clinical trials. · RCTs are best suited to demonstrate an effect. If not possible, other efforts are required to minimize and assess bias (e.g. blinded documentation and assessment of outcomes). · For particularly serious or even life-threatening diseases, it is usually not sufficient only to demonstrate an improvement in quality of life if at the same time it cannot be excluded with sufficient certainty that serious morbidity or even mortality are adversely affected to an extent no longer acceptable.

[a] **No guideline was publicly available.** Other sources were used.

SOURCES:

England: National Institute for health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Process and methods guide. 4 April 2013. Available from: http://publications.nice.org.uk/pmg9

France: Rima de Sahb-Berkovitch et al. Assessing Cancer Drugs for Reimbursement: Methodology, Relationship between Effect Size and Medical Need. Thérapie 2010 Juillet-Août; 65 (4): 373–377 & Kleijnen S, Goettsch W, d'Andon A, et al. EUnetHTA JA WP5: Relative Effectiveness Assessments (REA) of Pharmaceuticals. Background review. July 2011 (version 5B).

Germany: Institute for Quality and Efficiency in Health Care (IQWIG). General Methods. Version 4.1 of 28 November

Netherlands	Poland	Scotland
ZIN	AOTMiT	SMC
Yes	No, part of cost-effectiveness analysis	No, part of cost-effectiveness analysis
Morbidity, mortality and/or quality of life.	Deaths, cases or recoveries, quality of life, and adverse effects.	Mortality, survival, incidence of disease, morbidity, functional performance, quality of life
· Very little research is undertaken that explicitly focuses on quality of life. However, the added value of a medicine may actually be expressed in the form of an improved quality of life....Firm conclusions cannot always be determined based on the Dutch results of research in which quality of life is a secondary parameter.	· A cost-utility analysis should be used when: the health-related quality of life is one of the significant outcomes or if the compared technologies give very different clinical effects and it is necessary to find a common denominator. · It is admissible to perform the quality of life measurement in the patient population or the preference measurement in the general population. · The preference measurement for utility assessment is possible by using direct or indirect preference measuring methods. It is recommended to use indirect methods for preferences measurement – validated questionnaires in Polish. While measuring preferences with the WuroQol (EQ-5D) questionnaire, it is advised to use the Polish utility standard set obtained by means of the –time trade-off– method.	· Valuing medicines should include gains in length of life and quality of life, as well as adverse effects such as toxicity, which should be included as negative impacts on quality-of-life · SMC prefers generic and validated classification system which reliable and appropriate population preference values (choice-based method such as the time trade-off or standard gamble). · Ideally, these data will be generated through randomised controlled studies. · A higher cost/QALY may be accepted if: more than 3 months survival gain with sufficient quality of life to make the extra survival desirable […] or evidence of a substantial improvement in quality of life (with or without survival benefit). Evidence of a substantial improvement in quality of life (with or without survival benefit); Evidence of a substantial improvement in quality of life (with or without survival benefit).

2013. Available from: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf
Netherlands: Zorginstituut Nederland. Dutch Assessment Procedurees for the Reimbursement of Outpatient Medicines. Joint publication of the Ministry of Health, Welfare, and Sport and CVZ. March 1th, 2010. Available from: http://www.zorginstituutnederland.nl/Dutch_assessment_Procedures_for_the_Reimbursement_of_Outpatient_Medicines.pdf
Poland: Agency for Health Technology Assessment. Guidelines for conducting Health Technology Assessment (HTA). Version 2.1. Warsaw, April 2009. Accessed from: http://www.aotm.gov.pl/www/assets/files/wytyczne_hta/2009/Guidelines_HTA_eng_MS_29062009.pdf
Scotland: Scottish Medicines Consortium. Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF) (October 2014). Accessed from: https://www.scottishmedicines.org.uk/Submission_Process/Submission_guidance_and_forms/Templates-Guidance-for-Submission/Templates-Guidance-for-Submission

The French consensus statement addressed the absence of QoL data, stating: '*The Commission often bemoans the lack of quality-of-life data: tools are available in oncology but are difficult to use repeatedly in clinical trials and vary inter-individually, which reduces their relevance for deciding between treatments or therapeutic strategies. As cancers become chronic, other tools such as examining patient preference or utility could be taken into account by the Transparency Commission in oncology*'.

Inclusion of QoL data in REAs

Figure 2 provides an overview of the QoL data included in REAs, per medicine and per instrument type. There are variations across different drugs as to the inclusion of QoL data and as to the instrument being used. For two drugs no QoL data were included (aflibercept and eribulin) in any of the REAs and for 5 out of the 14 drugs all REAs had QoL data. Also, the type of instrument used (generic vs cancer-specific) varied not only across different medicines but also within the same indication (e.g. cabazitaxel vs enzalutamide for prostate cancer). On average, cancer-specific QoL data were more frequently included in REAs than generic QoL data.

Figure 3 shows the inclusion of QoL data per jurisdiction and type of QoL instrument. The overall percentage of REAs across all jurisdictions in which QoL data were included was 54%; it varied from a lowest of 29% (Poland) to a highest of 67% (England). In what concerns the choice of instrument, Germany stands out with a relatively high percentage of cancer-specific QoL data in its REAs (56%). The Netherlands, on the other hand, only included either generic data or a mix of generic and cancer-specific QoL data.

The most frequently used QoL instruments were the disease-specific FACT questionnaire (included in 24% of the REAs), the EORTC questionnaire (20%) and the generics EQ-5D (10%) and Brief Pain Inventory-Short Form (8%). An overview of QoL instruments retrieved in our sample is presented in Supplementary Table 1.

Impact of QoL data on recommendation

The impact of included QoL data on the recommendation, per jurisdiction, is provided in Figure 4. Overall, QoL data did not impact the recommendation in 26% of the REAs (i.e. we did not find a statement on QoL data in the recommendation). Yet this percentage varied substantially at national level from 0% in France, Germany and The Netherlands to 88% in Scotland. The percentage of REAs in which QoL data had a negative impact was relatively low for all jurisdictions (on average 7%). QoL data had a positive or neutral impact on the recommendation in about one third of the recommendations (respectively 30% and 35%).

Only the lung cancer drug afatinib received a positive recommendation ('*hint*' of added benefit in Germany) for a particular subgroup: patients under 65 years of age with a L858R mutation, primarily based on benefits in symptom relief and QoL. In addition, QoL data seems to have had a positive effect on the recommendation for crizotinib (indicated for lung cancer) across multiple jurisdictions, as well as for abiraterone and enzalutamide (both indicated for prostate cancer). Supplementary Table 2 provides some examples of citations categorized as having had a positive or negative impact on the recommendations.

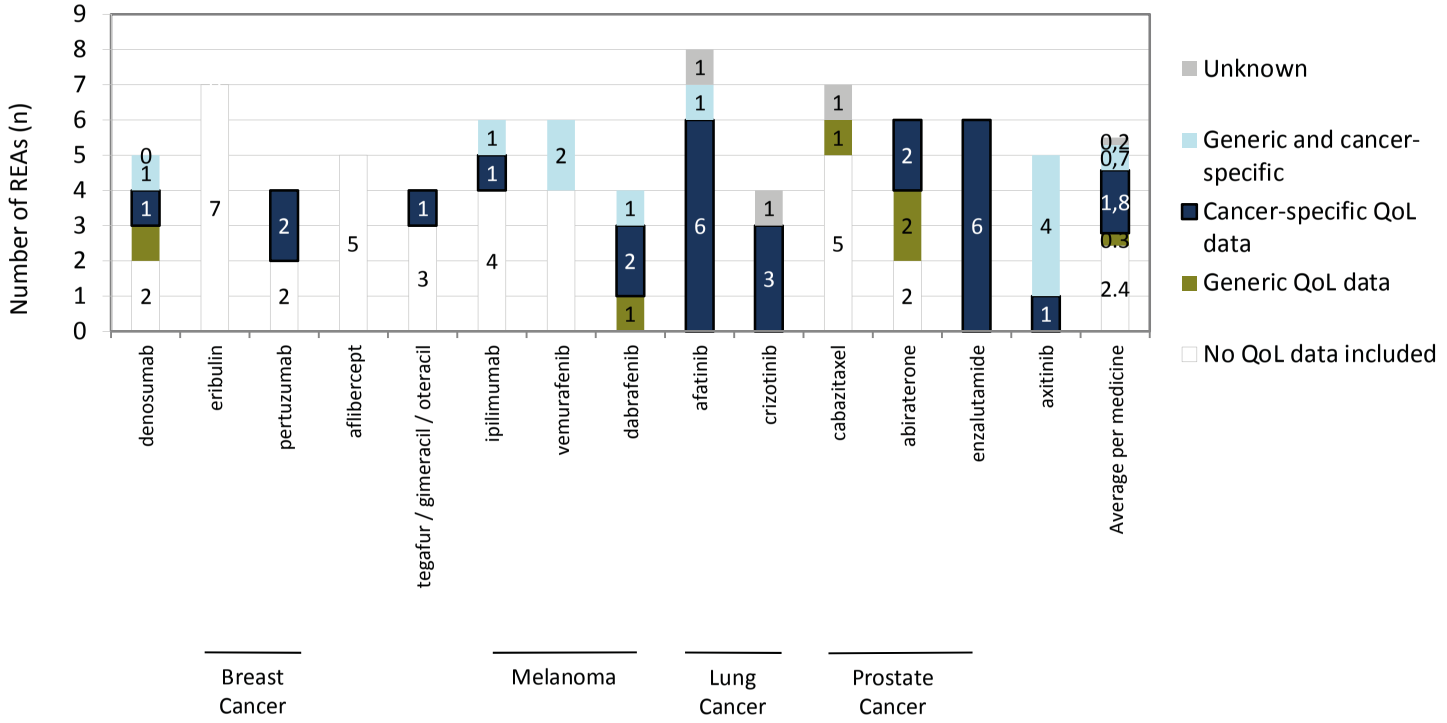

FIGURE 2. Number of REAs (n) in which quality of life data is included per medicine and instrument type

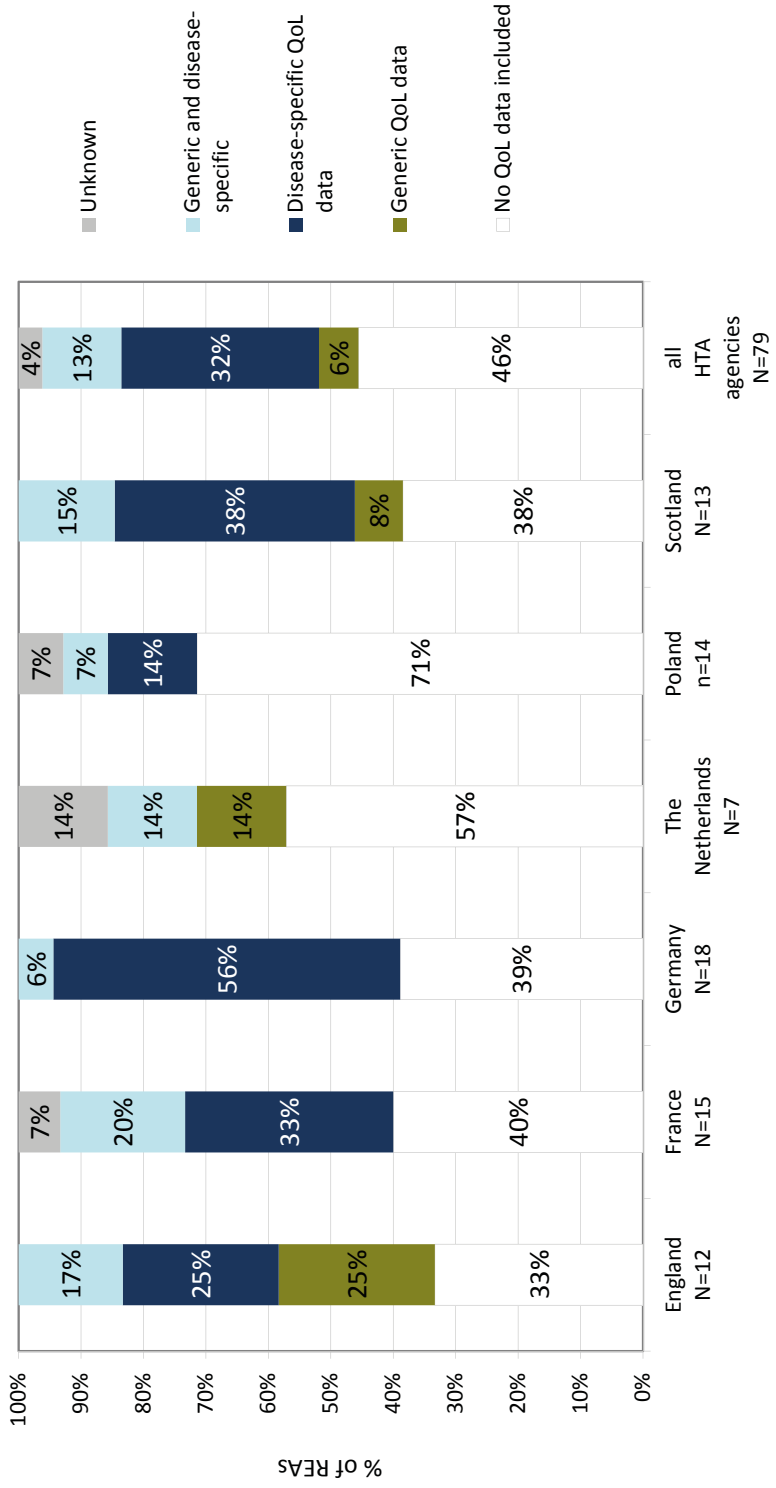

FIGURE 3. Quality of life data and instruments included in REAs per jurisdiction (percentage)

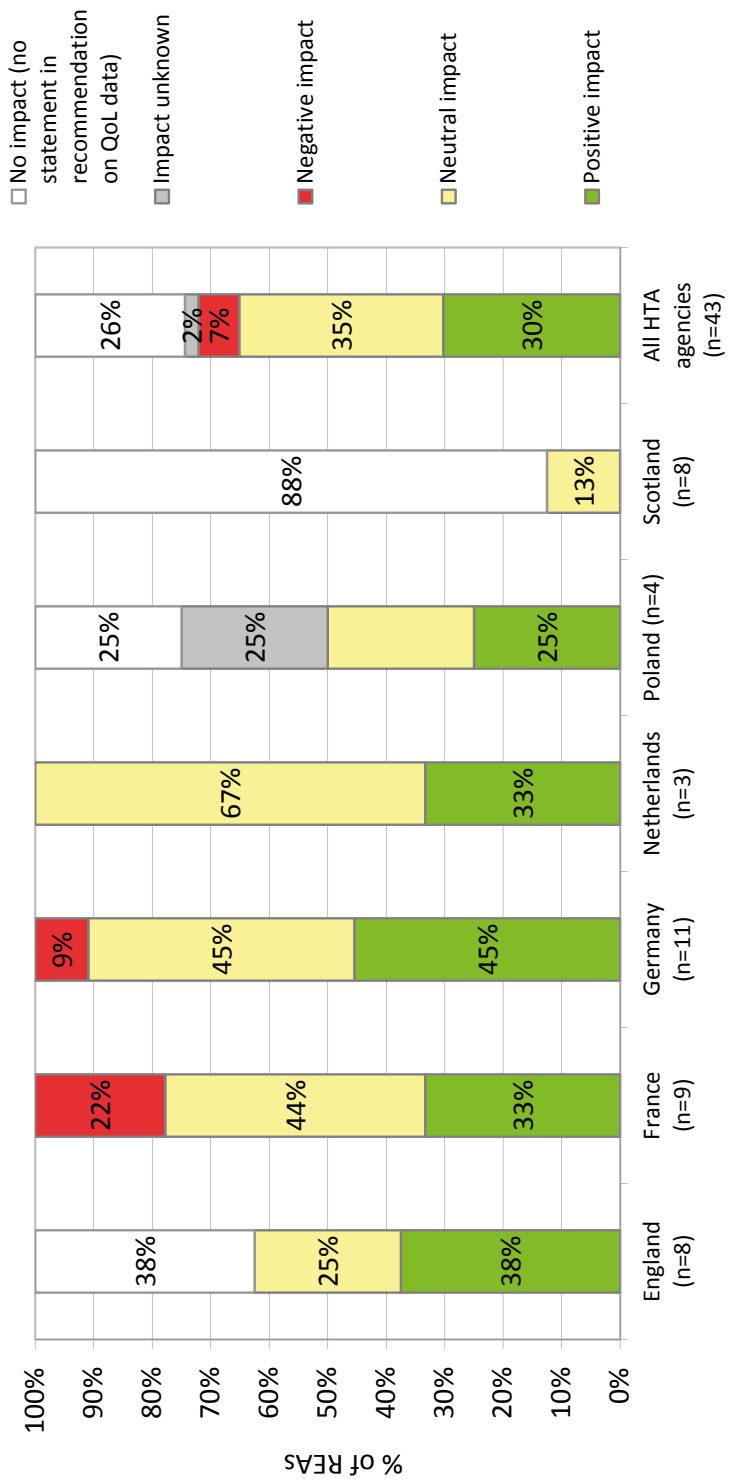

FIGURE 4. Impact of included quality of life data on the recommendation.

TABLE 2. Impact of QoL data on recommendation per type of instrument

Type of QoL data	REAs (n)	Positive impact	Neutral impact	Negative impact	Impact unknown	No impact*	Total
Generic QoL data	5	20%	20%	0%	0%	60%	100%
Disease-specific QoL data	25	44%	24%	12%	0%	20%	100%
Generic and disease-specific	10	0%	70%	0%	0%	30%	100%
Unknown	3	33%	33%	0%	33%	0%	100%

* no statement in recommendation on QoL data

Association between instrument type and impact on recommendation

A higher percentage of cancer-specific QoL data had a positive impact when compared to generic QoL data or cancer-specific & generic QoL data, however, differences in percentages across instrument types were not significant. The majority of generic QoL data seemed to have had no impact on the recommendation whereas the majority of cancer-specific & generic QoL data had a neutral impact (Table 2).

DISCUSSION

This study aimed to explore the role played by QoL data in REAs for HTA recommendations of new cancer drugs in European countries.

Whereas guidelines from HTA agencies indicate that QoL data is to be considered a relevant endpoint in the reimbursement decision-making process of new anti-cancer drugs in Europe, evidence from our study suggests otherwise. QoL data was only included in 54% of the REAs reports. In addition, the impact of the included QoL data was limited as no specific statement on included QoL data was identified in one fourth of the recommendations. Our study also suggests a higher uptake and positive impact of cancer-specific QoL data, when compared to generic QoL data. Moreover, differences exist between countries as to the inclusion and extent of use of QoL data in relative assessments. These differences are indicative of variation across HTA agencies on how they handle and report this type of data.

Other researchers have also reported on the limited availability of (robust) QoL data for oncology medicines (24). Within our sample of HTA reports, stated reasons for non-inclusion of QoL data were either unavailability (i.e. absence) or lack of robustness. The first cause was applicable to eribulin, with the lack of QoL data in the pivotal EMBRACE study being highlighted in the English, French, Dutch and Scottish assessments. QoL data was considered to be insufficiently robust in the German assessments of abiraterone and pertuzumab. Even though the weakness of the QoL evidence is mentioned in several recommendations (e.g eribulin, abiraterone, alfibercept and pertuzumab) we learnt during the expert panel consultation that this shortcoming does not generally negatively impact the final HTA recommendation. Results from a contemporary study indicate that data on other endpoints, such as overall survival and

progression-free survival, play a more decisive role in the recommendation than QoL data (23). *De facto*, within our dataset, only one drug - afatinib - received a positive recommendation for a specific subgroup due to its beneficial effects on QoL and symptom relief.

There is evidence supporting the inclusion of patient-reported outcomes, including health-reported QoL, in regulatory product approvals (15, 17-19). Vodicka et al. (2015) investigated the entries in the US clinicaltrials.gov register between 2007 and 2013 and reported an increase in the collection of patient-reported measures from 2009 onwards, particularly oncology drug trials (25). While this trend might, at first glance, suggest future improvements, there are no guarantees that the endpoint data will be duly collected, reported and of sufficient quality to meet drug regulators' requirements and HTA agencies' needs. Such difficulties in retrieving and valuing patient-reported outcomes within HTA assessments have been reported by Triggs and Howells (2015), who looked into NICE recommendations for new pharmaceutical products over 2014 (26). They concluded that guidance on the use of patient reported outcomes for clinical-effectiveness assessments was vague and thus compliance was very low. They added that a stringent approach was needed when assessing patient reported outcomes data, to ensure accurate measurement of treatment effectiveness.

In those jurisdictions where HTA guidelines indicated a QoL instrument preference (England, Poland and Scotland), generic QoL data seemed to be favoured. Nevertheless, our study indicates that cancer-specific QoL data seems to have greater impact on recommendations than generic QoL data. This confirms previous results from other research on REA methods across 29 jurisdictions, which showed that disease-specific QoL measurements were more widely accepted (21). The guideline produced by the European Network for Health Technology Assessment (EUnetHTA) of the use of QoL data in REAs refers that the choice of the QoL measure is dependent on the purpose of the REA and the decision-making context, but that consensus on QoL evidence is often lacking due to variations in context (11). They recommended that REAs aimed at coverage decisions should include both a disease- or population-specific measurement as well as a generic QoL measure, so that the impact of a disease on daily life can be adequately captured. Within our dataset, this mix of disease and generic measurements was only available in 17% of the REAs reports.

Yet, Cleemput et al. (2015) also emphasise that recommendations informing decisions on resource allocation across various indications should primarily be based on generic QoL data, as only generic instruments enable comparisons between multiple indications and intervention types (11). They indicated that within a given indication, disease-specific QoL data may be suitable, but recommend, in addition to the disease-specific measure, the use of complementary generic QoL data to ensure that all potentially relevant dimensions are included.

Measuring QoL is also relevant to grasp a new drug's safety profile. According to Trask (2009), the inclusion of health-related quality of life in clinical trials can help identify which treatment-related symptoms are having a negative impact on patients, sometimes even before the QoL changes observed are noted as adverse events (7). Recent pharmacovigilance legislation in the European Union also encourages the inclusion of patient-reported data in the assessment of a drug's benefit-risk balance (27, 28).

While the HTA agencies identified in our study considered QoL to be a relevant endpoint to be taken into account during relative effectiveness assessments, they also reported concerns about the methodological constraints of QoL data collection and their subsequent quality. Further steps needed to improve data collection would include reducing providers' inexperience with QoL instruments, tackling methodologic barriers such as the limitations of QoL instruments in detecting clinically meaningful changes and addressing feasibility and logistic difficulties such as time constraints (7). HTA bodies are in a key position to proactively stimulate better collection of QoL data by establishing standardised evidence requirements.

The general limitations of this study include the restricted number of European HTA jurisdictions; the variability in drugs assessed per jurisdiction; as well as challenges faced in the interpretation of value statements from HTA reports and the fact that our study's methods and results somewhat simplify real-world decision making. We have opted to focus on the role of QoL data in REAs, and not on pharmacoeconomic assessments, as relative effectiveness is the most commonly shared criterion for pricing and/or reimbursement recommendations in EU jurisdictions (21). Nevertheless, it is very likely that QoL would have a more prominent role in pharmacoeconomic assessments of oncology drugs given its relevance in utility analysis of quality-adjusted life years. Finally, this research was restricted to oncology medicines and it remains unclear whether our findings would be applicable to other indications. Recent research has shown that the type and frequency of patient reported outcomes used in clinical trials are largely dependent of the disease being studied (29).

CONCLUSION

There seems to be a lack of (robust) QoL data in REAs for oncology drugs. Yet apparently, this current absence of robust QoL data does not impact on the recommendations. Further collaboration is needed to promote the use of robust QoL data and to map strategies to improve the use of this patient-centered outcome in future reimbursement decisions. HTA bodies are in a key position to proactively stimulate better collection of QoL data by establishing standardised evidence requirements for valid and reliable QoL data to be used in REAs. This could potentially encourage pharmaceutical companies to incorporate robust QoL measures in their clinical research and subsequently provide regulatory agencies and HTA institutions with more complete dossiers for assessment.

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SUPPLEMENTARY DATA

TABLE S1. Descriptive table of the quality of life instruments retrieved in our sample

Name of QoL instrument	# of REAs in which was included (total n=79)	Medicines
FACT-(B, FKSI-15, FKSI-DRS, G, Ga, M, P)	18	tegafur/gimeracil/oteracil (FR), denosumab (NL,PO), abiraterone (FR), vemurafenib (GE,SC), axitinib (GE,UK,SC, FR) pertuzumab (FR, SC), enzalutamide (GE, GE, UK, FR, SC, PO)
EORTC-QLQ-(BR23, C30)	15	ipilimumab (GE, FR), axitinib (PO), crizotinib (GE, UK), dabrafenib (GE,FR,SC), afatinib (GE, GE, GE, GE, UK, FR, SC)
EQ-5D	8	Denosumab (UK,NL) axitinib (UK,SC,PO), afatinib (UK), , dabrafenib (UK,FR)
EQ-VAS	2	vemurafenib (GE), afatinib (UK)
BPI-SF	6	Denosumab (NL), abiraterone (NL,EN, SC), enzalutamide (GE,GE)
Pain response* †	2	Cabazitaxel (UK, NL)
SF-36	1	Ipilimumab (FR)
Pain progression †	1	Cabazitaxel (UK)
Time to detoriation †	1	Crizotinib (SC)
Time to developing pain †	1	Denosumab (UK)
Analgesic use †	2	Denosumab (UK,NL)

* Measured with present pain intensity score on the McGill-Melzack scale

† These are also considered to be morbidity-related patient reported outcomes.

TABLE S2. Examples of the positive and negative impact of quality of life data excerpts included in HTA recommendations

Positive Impact			
Medicine	**Indication**	**HTA body and jurisdiction**	**Citation**
abiraterone	Prostate cancer	NICE England	"The patients' quality of life deteriorates less under treatment than with placebo." "The Committee also noted that patients receiving abiraterone were more likely to experience an improvement in symptoms, including pain, functional status and fatigue."
crizotinib	Prostate cancer	HAS France	"In view of the available clinical data, in particular a study versus chemotherapy with docetaxel or pemetrexed showing an absolute increase of 4.7 months in progression-free survival in favour of XALKORI, with a significant improvement in objective response rate as well as quality of life, a moderate additional impact in terms of morbidity, mortality and quality of life is expected in patients treated with XALKORI as a second-line therapy compared with chemotherapy."
enzalutamide	Non-small-cell lung cancer	IQWIG Germany	"FACT-P: Outcome category: non-serious/non-severe symptoms/late complications CI< 0.80 Added benefit, extent: considerable" BPI-SF: Added benefit, extent: non-quantifiable."
Negative Impact			
Medicine	**Indication**	**HTA body and jurisdiction**	**Citation**
afatinib	Lung cancer	IQWIG Germany	"Negative effects: Health-related quality of life (in each case "hint"): "role functioning (≥ 65 years)" improvement; "minor"
enzalutamide	Non-small-cell lung cancer	HAS France	"The fragmented quality of life data cannot quantify the impact of XTANDI on the quality of life of the patients treated."
tegafur / gimeracil / oteracil	Gastric cancer	HAS France	"Available data do not show the impact of TEYSUNO in terms of a reduction in morbidity and mortality or the improvement in quality of life; therefore it is not expected that this medicinal product will have an additional impact compared with current treatments."

CHAPTER 3

STRATEGIES BY THE PHARMACEUTICAL INDUSTRY TO INFLUENCE HEALTHCARE PROFESSIONALS AND THE PUBLIC

CHAPTER 3.1

MEDICINES INFORMATION AND THE REGULATION OF PHARMACEUTICAL PROMOTION

Teresa Leonardo Alves, Barbara Mintzes, Joel Lexchin

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ABSTRACT

Many factors contribute to the inappropriate use of medicines, including not only a lack of information but also inaccurate and misleading promotional information. This review examines how the promotion of pharmaceuticals directly affects the prescribing and use of medicines. We define promotion broadly as all actions taken directly by pharmaceutical companies with the aim of enhancing product sales. We look in greater detail at promotion techniques aimed at prescribers, such as sales representatives, pharmaceutical advertisements in medical journals and use of key opinion leaders, along with the quality of information provided and the effects thereof. We also discuss promotion to the public, through direct-to-consumer advertising, and its effects. Finally, we consider initiatives to regulate promotion that come from industry, government and nongovernmental organizations.

INTRODUCTION

Medicines can cure acute illnesses, treat chronic conditions, relieve symptoms and prevent future ill health. However, any decision to use a medicine involves weighing potential benefits against possible harms. To make an informed decision, a person needs information on the aims of the treatment, how it works, how to use it properly, the likelihood of benefit and harm, and how this medicine compares with other available treatment options or the option not to treat, as well as relative cost-effectiveness. The quality of information that accompanies medicines can make the difference between "a poison and a cure", between a use that leads to better health and a use most likely to lead to harm. Of equal importance to information on medicines, inaccurate information on diseases and disease risks can lead to harm if patients seek medical treatment when it is not needed, leading to unnecessary medicine use and the potential exposure to drug-induced harm.

Irrational use of medicines is widespread. It includes the use when medicines are not needed, use beyond approved indications (off-label), choice of unnecessarily harmful or ineffective options, concomitant use of products that should not be combined, use by patients for whom there is no scientific evidence of benefit, excessive dosing, and the use of the more expensive of equivalent options. Underuse can also be a problem, for example if an inadequate dose or duration of use leads to treatment failure or development of resistance, or if a person fails to adhere or is not provided with the needed therapy, such as for example a patient with atrial fibrillation who does not receive an anticoagulant drug. Many factors contribute to inappropriate medicine use, including not only a lack of information but inaccurate and misleading promotional information.

The World Health Organization (WHO) defines the promotion of pharmaceutical as, *"all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs"* (1). Not all promotion necessarily leads to inappropriate medicine use. However, a tension exists between the competitive pressures that manufacturers face to expand product sales, and support for limited, judicious use of the most cost-effective of available alternatives (2). An analysis of the 25 most heavily promoted drugs in the United States (US) from August 2013 to December 2014 found that only one-third were rated as innovative, and only one was on the WHO's essential medicines list (3).

Many forms of disguised promotion have flourished involving the use of scientific research and educational events to promote medicines' sales (4). US court cases involving multinational pharmaceutical companies have uncovered a range of promotional activities raising strong ethical and public health concerns, such as the hiring of clinical expert 'key opinion leaders' to promote unapproved uses (off-label), ghostwriting of scientific articles, instructions to sales staff not to mention specific evidence of harm (5) and efforts to discredit clinicians who raised safety concerns (6). Healthcare professionals frequently underestimate the extent to which their prescribing decisions are affected by the promotion of pharmaceuticals (7) and most governments devote few resources to the regulation of promotion (8).

The focus of this article is on the promotion of medicines to healthcare professionals and the public. We define promotion broadly as all actions taken directly by pharmaceutical companies with the aim of enhancing product sales. We highlight what is known about the quality of the information transmitted directly to doctors by sales representatives, journal advertising and key opinion leaders and then look at the major effects of these types of promotion on prescribing. We then specifically discuss promotion to the public through direct-to-consumer advertising and its effects. We chose these particular areas to focus on because there is concrete evidence that they affect prescribing patterns. The three authors have in-depth knowledge of the promotion of pharmaceuticals and have chosen representative evidence of key aspects of promotion, based on their expertise. Most, but not all, of the literature we cite comes from developed countries where the bulk of the research has been done. We conclude by reviewing initiatives from the pharmaceutical industry, government and nongovernmental organizations for improvement of the regulation of the promotion of pharmaceuticals.

SPENDING ON DRUG PROMOTION

Global pharmaceutical sales reached $1057.1 billion in 2014 (9). (Unless otherwise stated all monetary amounts are in US dollars.) Medawar and Hardon describe a 'crisis in innovation' within the industry as a key driver of companies' increased dependence on blockbuster drugs to maintain profitability, and hence of increased spending on promotion (10). The marketing focus has recently switched to "niche-busters", or high-priced drugs for smaller markets, but promotion is still needed to drive the sales of these products. Both total numbers of new molecular entities and the number with evidence of therapeutic advantage have declined in the last 50 years, without a decrease in industry profitability (11). Compared with other industrial sectors, the pharmaceutical industry is the highest ranked investor in research and development (R&D) (12). However, a report by the National Academy of Medicine puts marketing spending for the 12 largest pharmaceutical companies above $120 billion in 2016 compared to about $75 billion for R&D (13).

Data on national spending on the promotion of pharmaceuticals are not publicly available in most countries; the US is a notable exception because of freedom of information laws and information that has become public in legal cases. Thus, much of the published research on promotional spending is US-based. Estimates of the amount spent in the US on promotion range from $57.5 billion in 2004 (14) to $27.7 billion in 2010 (15). The 2004 figure was 24.4% of sales revenues, nearly double the amount spent on R&D and even the lower 2010 estimate represented 9.0% of sales. Most activities were directed at physicians and on average companies spent US$61,000 per physician in 2004. A 2014 audit by the market research company Cegedim confirms the primary focus on physician-directed promotion (16)(Mack, 2014 #44;Mack, 2014 #39). Based on data released under the US Sunshine Act, in 2014 and 2015, companies provided US$2 billion in payments to individual US doctors per year, and another $600 million to teaching hospitals (17).

PROMOTION OF MEDICINES TO PRESCRIBERS AND ITS EFFECTS

Sales representatives

While the number of sales representatives of the products of the pharmaceutical companies in the US has dropped from a high of 105,000 in 2006 to 60,000 in 2013, the majority of doctors are still willing to see them (18). In 2015, just over a third of Canadian doctors did not see sales representatives, 11% saw 6 or more a month (19) and in that year there was a total of 3,720,000 visits (20). Studies of oral presentations by sales representatives in Finland, Australia, the US, the Netherlands, and France, have found that information on harm is often omitted, and inaccurate information was consistently favourable towards the promoted product (21, 22,23,24,25). More recently, a study of the frequency of safety information provision in 1,692 promotions to family physicians in four cities in Canada, the US and France found that serious adverse events were rarely mentioned, even for products with US Food and Drug Administration (FDA) "black box warnings" of risks, and the minimum of information judged *a priori* to be needed for patient safety was provided only 2% of the time (26).

Pharmaceutical advertisements in medical journals

There are differences in national regulations concerning the information that must be provided in advertisements of pharmaceuticals, and differences in the extent to which national laws are enforced. However, as highlighted in WHO's Ethical Criteria, specific elements of information should be included in order for advertisements to allow healthcare professionals to have a basic understanding of the promoted product (1). In practice, these elements are often missing even in advertisements in developed countries. A systematic review of the quality of pharmaceutical advertisements in medical journals identified 24 studies, reviewing advertisements from 26 countries, published between 1975 and 2006 (27). Although most of the advertisements provided the product's brand and generic name, other information needed for rational prescribing, such as contraindications, interactions, side-effects, warnings and precautions were less commonly provided, and when supplied, were only available in the fine print. Interestingly, this information is required by the International Federation of Pharmaceutical and Manufacturers Associations (28) and European Federation of Pharmaceutical Industries and Associations (EFPIA) marketing codes (28, 29). Approved indications were stated in more than 70% of advertisements in five studies. However, a 2001 Russian study found that only 45% of advertisements mentioned approved indications (30). This was similar to results for the United Republic of Tanzania (40%) and Italy (34%) in an earlier multi-country study (31). The systematic review of references referred to in advertisements found that few of them that provided supporting claims were methodologically rigorous and most had been funded by the manufacturer (27). Only 38% of the references were to clinical trials, systematic reviews or meta-analyses. References listed 'data on file' were often not supplied on request. The authors concluded that information quality is poor globally, with an impact expected to be greatest where access to high-quality independent pharmaceutical information is most limited. A comparative study of advertisements in medical journals in Australia, Malaysia and the US from 2004 to 2006 revealed that the majority of

claims were vague and of poor quality, with fewer than one third classified as unambiguous (32). This direct comparison found a problem of poor information quality in both wealthy industrialized settings and a middle-income country. By 2008 nearly half of physician-directed advertisements in US medical journals failed to adhere to at least one FDA guideline regulating content. In addition, advertisements did a poor job of conveying basic information necessary for safe prescribing, with most failing to quantify serious risks, more than one quarter failing to quantify benefits and nearly half providing no verifiable references (33).

Unsurprisingly, the situation in low and middle-income countries when it comes to journal advertisements is even more alarming than in high-income countries. A 2006 study in Bangladesh found that 34% of the claims in a sample of 116 brochures for family physicians were misleading (34). In Zimbabwe, less than half of physician and pharmacy brochures for prescription drugs contained information on adverse effects, warnings and precautions, or major interactions (35). Similarly, in Nepal, promotional materials provided to hospital doctors in 2007 failed to mention adverse effects two thirds of the time, and precautions, contraindications or warnings were only included in 36% (36). In Sri Lanka a considerable proportion of drug promotional materials collected in 2015 used poor quality scientific research as references (37). The majority of 200 pieces of drug promotional literature collected from departments in an Indian hospital in 2014 satisfied only half of the WHO criteria for rational drug promotion and none fulfilled all of the criteria (38). The situation in some developed countries was no better. In Germany in 2004, 94% of the claims in brochures directed at physicians failed to be supported by scientific evidence: in 15% no references were cited; in 22% the references could not be found; and in 63% the relevant study was cited but the claim differed from research results (39).

Key Opinion Leaders

One of the practices described by Steinman in 2006, in a report summarizing documents that became public in a legal case concerning off-label promotion, was the funding of clinician "key opinion leaders" (KOLs) to promote products (40). Companies know that messages coming directly from them are likely to be viewed sceptically by physicians. As a result, the concept of using KOLs as an "independent" source of information has significantly expanded since the mid to late 1990s (41). In the US, a 2007 survey found that 16% of physicians, or about 141,000 received payments for serving as a speaker or being part of a speakers' bureau (42). More recently, in just 5 months of 2013, companies made what appear to be speaker payments of $400 or greater to 55,000 doctors (43).

Some KOLs are clinicians who are hired to give small-scale talks, but for major programs KOLs are typically well known and highly respected leaders in their field who are especially effective at transmitting messages to their peers. Pharmaceutical companies hire KOLs to consult for them, to give lectures, to run continuing medication education sessions, to conduct clinical trials, and occasionally to make presentations on their behalf at regulatory meetings or hearings (44).

Although most KOLs are "true believers" in the drugs that they are promoting they also readily acknowledge that there are other factors involved in their decision to work for drug

companies, such as financial compensation, research funding, increase in the number of publications that they author, early knowledge about new drugs, being at the vanguard of their specialty and psychological rewards (44-46).

One way of judging the importance that pharmaceutical companies place on KOLs is the case that roughly one-third of the marketing budget for pharmaceutical companies is spent on KOLs (41, 44). This amounts to an average of about $38 million on each product as it moves from clinical testing to launch (47). Companies are willing to spend this amount of money because of the return that they get. According to an internal Merck document, doctors who attended a lecture by a KOL on Vioxx (rofecoxib) wrote an additional $623.55 worth of prescriptions for the drug over a 12-month period compared with doctors who didn't attend. "After factoring in the extra cost of hiring a doctor to speak, Merck calculated that the 'return on investment' of the doctor-led discussion group was 3.66 times the investment, versus 1.96 times for a meeting with a sales representative" (48). Whereas in 1998, in the United States, the number of talks by sales representatives and KOLs were about equal at just over 60,000 each annually by 2004 there were almost twice as many talks by KOLs compared to sales representatives (48)– a likely reflection of the economic benefits of using KOLs instead of sales representatives.

The talks that KOLs give can be scientifically valid but also deceptive, for example by touting the benefits of the company's drug but not mentioning that other drugs are equally or more efficacious. Alternatively, KOLs may be hired to give presentations or write articles emphasizing the negative aspects of individual drugs or drug classes without ever mentioning the product made by the company paying them (49). Pharmaceutical companies need to maintain the fiction that KOLs are independent sources of information. This supposed independence is the main reason that doctors trust KOLs more than sales representatives. If KOLs are shown not to be independent then they lose their value to the companies. However, it is precisely when KOLs start to act independently and deviate from the messages that companies are cultivating, that their value to the company starts to be questioned (50,51).

Effects of promotion to prescribers

One of the drivers of inaccuracies and omissions in the promotion of pharmaceuticals is the need for each new brand to obtain and maintain market share, despite a frequent lack of scientific evidence of therapeutic advantage over existing treatment options. A French independent pharmaceutical bulletin, la revue Prescrire, evaluates the clinical trial evidence of effectiveness and safety for all new medicines and new indications for existing drugs approved in France. Only 1.3% of 1038 new drugs and/or new indications introduced between 2006 and 2015 were major therapeutic advances; 52% were "nothing new" and almost 17% should never have been marketed in the first place (52).

Although in some instances healthcare professionals admit that their prescribing could be influenced by seeing sales representatives (53), in most cases they deny being affected. For example, in a survey of 446 physicians in Izmir, Turkey, Guldal and Semin (54) found that nearly two thirds of the physicians thought that their prescribing was unaffected, although nearly half reported seeing sales representatives every day for 15 minutes or more. Belief in personal

invulnerability does not necessarily extend to one's colleagues: Steinman et al. found that 61% of US medical residents believed they were personally unaffected by promotion, but only 16% believed that their colleagues were similarly unaffected (40). A study of medical students, interns and residents doing a psychiatry rotation found that the more gifts they reported receiving, the less likely they were to believe that they were affected (55). The feelings of reciprocal obligation brought about by smaller gifts should not be underestimated, as even tokens such as coffee mugs can have a surprisingly large effect (56). In a review of psychological and social science research on the effects of gift-giving, Katz and colleagues commented that, "Those who do not acknowledge the power of small gifts are the ones most likely to be influenced, because their defenses are down" (56).

A body of research evidence has shown a link between a greater reliance on the promotion of pharmaceuticals and less appropriate prescribing (57) (58). A systematic review of empirical studies on the effects of promotion on physician behavior found that physicians with greater exposure had a higher prescription volume, prescribed more costly medicines, had more a rapid adoption of new medicines, including those without added therapeutic value, and made more requests for formulary inclusion of drugs without established therapeutic advantages (58). In 2010, a second systematic review examined the effects of exposure to information from pharmaceutical manufacturers on prescribing drug quality, volume and costs (59). Among the 58 studies that met inclusion criteria, nearly all found either an association with lower quality, higher volume and higher costs, or no significant difference. The authors failed to find any evidence of net benefit from exposure to promotion. A more recent systematic review focusing solely on interactions between sales representatives and practicing physicians in developed countries echoed the findings of the study by Spurling et al. Fifteen out of the 19 included papers found a consistent association between interactions promoting a medication, and an inappropriate increase in prescribing rates, lower appropriateness of the prescribing, and/or increased prescribing costs (60).

More focused research has reinforced the general findings from these systematic reviews. Muijers et al. evaluated prescribing quality using 20 indicators based on Dutch general-practice guidelines, combining physician survey data and administrative records (61). General practitioners (GPs) who saw sales representatives more often were significantly less likely to adhere to these guidelines. A double-blind randomized controlled trial in the US tested the effect on conscious and unconscious attitudes of exposing medical students to small branded promotional items (62). Students' attitudes were affected by the institutional policies of their medical faculties. One of the medical faculties involved in the study had restrictive policies towards the pharmaceutical industry, while the other was more permissive. In the less restrictive environment, small gifts created a more favourable attitude to the brand; in the more restrictive environment, students receiving gifts had less favourable attitudes. Prosser et al. examined the influences on 107 UK GPs' initial prescriptions for 15 new drugs (7). Physicians cited sales representatives as influential 39% of the time, more often than all other influences, including patient-related factors such as suboptimal current therapy. These results reinforce the influence that sales representatives have, even if this influence is rarely cited by doctors

when asked a general question on prescribing. Studies in the US and France similarly found that sales visits were predictive of initiation of psychiatric treatment in primary care (63) (64), and in Denmark, sales visits were associated with a shift in the brand of inhaled corticosteroid prescribed for asthma, but not overall prescribing volume (65).

PROMOTION OF PRESCRIPTION MEDICINES TO THE PUBLIC AND ITS EFFECTS

The prohibition of direct-to consumer advertising (DTCA) in most countries is a health protection measure linked to prescription-only status. Prescription-only medicines generally treat more serious conditions that cannot be easily self-diagnosed and are generally more toxic or have a less well-understood toxicity profile than non-prescription medicines.

DTCA of prescription medicines has grown rapidly in the US and New Zealand, the only two countries where it is legal. In late 1997, the FDA introduced an administrative policy allowing companies to list only major and frequent risks in broadcast advertising as long as sources of more complete information were provided. This shift opened up television to DTCA. By 2000, advertising spending for top 'blockbuster' medicines had surpassed brands such as Pepsi Cola, Budweiser beer or Nike shoes (66). Spending in this area in the US grew by 19% from 2014 to 2015 to a total of $5.4 billion (67).

One of the top five brands, in terms of spending in the early 2000s was Rofecoxib (Vioxx), an arthritis medicine that was later withdrawn in 2004 due to cardiac risks. This was not the first advertised medicine to be withdrawn from the US market since DTCA became widespread. However, because of extensive potential harm from widespread Rofecoxib use (68), some of which was stimulated by DTCA, US DTCA policy began to be scrutinized. Despite congressional hearings, new industry self-regulatory guidelines, and legislative proposals to restrict DTCA in the eight years since the withdrawal of Rofecoxib, the practice has continued largely unchanged (69). The FDA directly regulates advertising content, and regularly finds advertisements to be illegal, generally because of inadequate risk information or exaggeration of benefits. An analysis of 10 years' worth of magazine advertisements indicates that most failed to include basic information needed for shared and informed treatment choices (70). An analysis of DTCA that appeared on television between 2004 to 2007, found frequent use of emotive imagery linking medicine use with happiness and social approval (71), and a review of advertisements airing between 2008-2010 concluded that 55% of claims made for the drugs being promoted were potentially misleading (72). However, according to a 2006 report by the US Government Accountability Office (GAO), the agency was able only to monitor a small – and shrinking – proportion of advertisements, due to the rapid growth in volume (73) and there is no indication that the situation has changed in the decade since the GAO issued its report. New Zealand relies on industry self-regulation, with all advertisements subject to pre-screening, but information criteria are weaker than those applied by the FDA, with little risk information required in advertisements (74, 75).

Proponents of DTCA claim that it helps empower consumers and stimulates discussions with physicians, that it enables patients to obtain needed treatment at an earlier stage and improves adherence. There is no reliable evidence to back claims that DTCA leads to improved access to needed medicines, adherence, or patient and consumer autonomy (76). Manufacturers have also begun to run compliance programmes for patients who are taking a specific brand. This has led to concerns that patient safety may be compromised, particularly if DTCA has led to patients taking a medicine with a poor safety profile or inadequate efficacy (77).

There is evidence that the rates of diagnoses of specific conditions increases during associated advertising campaigns, but the extent to which this is needed treatment or increased use among those unlikely to benefit remains an open question. If the threshold for diagnosis of a health condition shifts to include milder health problems, increased rates of diagnosis and treatment do not necessarily lead to health benefits. Kravitz and colleagues carried out a randomized controlled trial of the influence of patient requests for Paroxetine (Paxil) using standardized patients who described symptoms of depression or of a less severe temporary condition, "adjustment disorder" that is due to life problems and does not require antidepressant treatment (78). If patients requested an advertised brand, they were equally likely to receive an antidepressant prescription whether they had symptoms of depression or "adjustment disorder". A pharmaco-economic model of the effects of antidepressant advertising found a net benefit, although only six of every 100 people treated with antidepressants were expected to have depression (79). However, this model omitted any adverse effects, included unrealistic assumptions of the magnitude of treatment success, and underestimated associated health-care costs. When these were included in a similar model, harm largely outweighed benefit (80). DTCA for testosterone therapies in the US between 2009 and 2013 was associated with increased testosterone testing and more initiation of testosterone use without recent serum testing, contrary to treatment guidelines (81).

In Turkey, the government suspended the market licence for Bupropion (Zyban) for three months in response to an illegal DTCA campaign (82). Turkey represents an example of a middle-income country that has experienced rapid growth in pharmaceutical spending. In 1998, 35% of total health-care spending was on pharmaceuticals, a greater relative proportion than in higher-income countries (83). Prescribing rates are higher than in most industrialized countries, polypharmacy is a serious problem and enforcement of prescription-only status poor. Semin and colleagues discuss the extra vulnerability of countries like Turkey to harm from DTCA both through increased spending in this area and because prescription-only status is poorly enforced, so a person may buy an advertised medicine without visiting a doctor (82).

Canada has been subject to strong pressure to introduce DTCA (84) (85) and US magazines, cable and satellite television reach Canadian audiences with prescription drug advertising that is illegal under Canadian law (86). Researchers compared prescribing rates for three drugs advertised in US media in English-speaking Canada versus Quebec, which is mainly francophone, and thus is less affected by US media. They found an effect on prescribing rates for one product, Tegaserod (Zelnorm), a drug that was since withdrawn from the market for safety reasons (87). No effect on prescribing was seen for the other two drugs: Mometasone, which was

reimbursed without restrictions in Quebec, but not in most English provinces, and Etanercept (Enbrel), a medicine provided in specialist care to a limited group of patients. These findings strongly suggest that the success of DTCA in stimulating sales is mediated by other factors such as reimbursement status (88).

There are many forms of advertising of medicines on the Internet, including sites that directly offer products for sale, with few controls to ensure the quality, efficacy and safety of promoted products, or to ensure the accuracy of promotional claims. A study commissioned in 2009 by the Netherlands Health Inspectorate analyzed 41 web sites offering health information in the Dutch language: 32 were either hosted or sponsored by a pharmaceutical company, and 23 (72%) contravened national regulations by referring directly or indirectly to a specific prescription medicine (89). An analysis of the top 50 web sites on schizophrenia on Google and Yahoo (n=64 in total) identified 58% as pharmaceutical-industry funded (90). Those funded by industry were significantly more likely to support biological or genetic causes and to ignore the role of psychosocial stressors, to emphasize medication rather than psychological treatments, to portray schizophrenia as a more debilitating and chronic illness, and to discuss risks of violence if patients came off medication. John Read, the author of this study, comments: "For the websites examined in this study, perspectives and statements that are likely to increase drug sales are significantly more likely to appear on web sites funded by drug companies." In its warning letters and notices of violations from 2005 through 2014 related to online promotional activities of prescription drugs advertised directly to consumers, the FDA expressed considerable concern over this type of promotion for cancer treatments, which require regular prescriptions for long-term treatment. The most significant finding from an analysis of these documents suggests that the online promotional content of prescription drugs fails to present risks and benefits in a balanced manner (91).

Pharmaceutical companies also target the public directly through disease awareness campaigns or help-seeking advertisements. These materials usually contain health and disease information which focus on symptoms and suggest a visit to the doctor to learn more about new treatments. A study explored examples of such campaigns in printed media in the Netherlands by assessing their compliance with the WHO Ethical Criteria for medicinal drug promotion and the Dutch guidelines for provision of information by pharmaceutical companies. It concluded that although brand names were not mentioned in the campaigns, there was an overwhelming lack of compliance with the regulations mainly due to a lack of balance, absence of a listed sponsor, use of misleading or incomplete information and use of promotional information (92).

INITIATIVES TO REGULATE PROMOTION

Pharmaceutical industry

Most major pharmaceutical companies have their own codes of ethics that, in some countries, involve disclosure of information on payments to third parties. In the US, Eli Lilly discloses both individual and organizational funding on its website (www.lilly.com), and Pfizer discloses funding to organizations (www.pfizer.com) (93). Rothman and colleagues examined

the profile of 'health advocacy organizations' funded by Eli Lilly, including both patient and professional groups (94). The conditions these groups represented were highly correlated with Eli Lilly drug sales; in the case of both groups, neurosciences, endocrinology and oncology conditions predominated. Although the company had disclosed financing, only 25% of funded organizations did so, and only 10% acknowledged Lilly funding of events. This study highlighted the importance of manufacturer disclosure of funding, and the need for concurrent stronger standards for transparency among funded organizations.

National industry organizations in nearly all developed countries and many developing countries also have codes of marketing practice or ethics (95). The 2009 version of the US PhRMA Code of Ethics, still used at present, bans many traditional forms of gifts, such as pens, mugs and other office items. However, it still allows certain types of gifts if considered to be "items designed primarily for the education of patients or healthcare professionals" valued at $100 or less. The Code also allows the provision of meals and free samples (96). Importantly, this is a voluntary self-regulatory code with no provisions for sanctions. Australia relies primarily on industry self-regulation of promotional practices, but ultimately the national government is responsible for upholding the law. In 2006, the Australian Competition and Consumer Commission required changes to the industry's voluntary code of marketing, requiring companies to report details of funding for educational events, including venue, purpose, amount of hospitality provided, number of attendees and total cost. The data must be provided to Medicines Australia, the industry association, every six months, and Medicines Australia is committed to making the information publicly available as well as investigating any potential promotional violations (97). Medicines Australia has also instituted substantial fines for promotions that breach of its Code of Conduct (98). Jane Robertson and colleagues reviewed the experience with mandatory disclosure from July to December 2007, the first period for which the policy was in effect (99). There were nearly 15,000 sponsored events over this period, or around 600 per week, at a cost of approximately $880 thousand per week. The company had some influence on educational content 91% of the time, and two-thirds of the events were for medical specialists. Robertson and colleagues argued that although this is an important shift towards greater transparency – a direction that many more self-regulatory agencies should adopt – more comprehensive reporting is needed. For example, details such as the names of speakers at educational events, whether sponsors selected speakers or influenced the content of the event, and whether there are direct or indirect financial ties between the speakers and the sponsors could allow better assessment of the educational value of the sponsored events.

The next analysis of industry sponsored educational events in Australia was published ten years later, in 2017 (100). This long gap likely occurred because company reports were posted on the Medicines Australia website as separate pdfs, and not in an analysable format. Over a four-year period, from October 2011 to September 2015, pharmaceutical companies hosted over 116,000 events for healthcare professionals in Australia, at a total cost of over AU$286 million. Most events were held in a clinical setting and in nearly all, sponsors provided free food and drink. There were on average just over 600 events per week, as in 2007. This study confirms just how widespread the "drug lunch" is at a national level. From 2015 on, Medicines

Australia removed reporting requirements for food and drink and capped payments at AU$120 per person. Based on the 2011-2015 data, this would mean that two-thirds of events would no longer be reported, as food and drink were the sole expense (100).

Two of the strongest European self-regulatory codes are reputed to come from industry associations in the United Kingdom and Sweden. An analysis of antidepressant advertisements in Swedish medical journals between 1994 and 2003, concluded that companies failed to provide reliable antidepressants information and that this failure may be attributable to lax oversight, combined with the lag between when an advertisement was printed and when the company was censured and low fines for violations (101). The ability of the self-regulatory codes in both countries to adequately monitor and control promotion was further called into question in an examination of code complaints, complainants and rulings for the period 2004-2012. Fines for code violations averaged in total €447,000 and €765,000 per year in Sweden and the UK, respectively, equivalent to about 0.014% and 0.0051% of annual sales revenues of pharmaceuticals, respectively. According to the authors, the prevalence and severity of breaches testifies to a discrepancy between the ethical standard codified in industry codes and the actual conduct of the industry (102).

In Canada, a multi-stakeholder organization that includes not only the industry but also representatives of professional groups, consumers, the media and the advertising industry, the Pharmaceutical Advertising Advisory Board (PAAB), pre-screens all journal advertisements and advertisements in other media including print, audio, visual, audio/visual, and on-line advertising (103). Although the PAAB operates on a voluntary basis all the companies that belong to the research-based pharmaceutical industry association in Canada have agreed to abide by its code. There are some strong features of the code such as the requirement that if relative risk reductions are used to present benefits in advertisements the absolute risk reduction or number needed to treat also needs to be given or there needs to be information in the advertisement to calculate these values. However, the PAAB also has significant weaknesses; 5 out of the 13 members on its board come from associations that directly benefit from pharmaceutical advertising and most others receive pharmaceutical industry funding. Additionally, similar to the PhRMA code, there are no significant sanctions for violating the PAAB code.

In the European Union, the European Federation of Pharmaceutical Industries and Associations (EFPIA) adopted a Code of Practice on Relationships between the Pharmaceutical Industry and Patients Organisations in 2007 (104), which was later amended in 2011 and again at the end of 2013. Under this self-regulatory code, all EFPIA member companies are requested to publish the names of the patient organizations they support. EFPIA hosts a list of their 31 members that voluntarily declare patient group sponsorship and provides links to their web sites (104). An investigation by Consumers International (CI) of the actual promotional practices by 20 large multinationals operating in the European Union in the mid 2000s found that only two, GlaxoSmithKline and Novartis, reported the number of confirmed marketing code breaches and resulting sanctions. CI could not find any information about the European marketing policies for 8 companies. According to CI "[t]he absence of clear marketing policies for these companies is remarkable, given that irresponsible marketing practices form a serious,

persistent and widespread problem among the entire pharmaceutical industry… A particularly worrying trend shown by our research is that the difference between policies and practices is often striking" (105). At the time of writing of this article (February 2018) there is no evidence of any subsequent investigation to ascertain whether the amended EFPIA code has altered the situation.

EFPIA brought in a transparency code in 2013, requiring national member industry associations to implement policies on disclosure of payments to healthcare professionals if they were not already subject to legal requirements to do so (106). However, these policies suffer from several drawbacks such as incomplete reporting because of exclusion of certain payments such as food and drinks, individual healthcare professional consent that amounts to an "opt-out" clause, and in some cases lack of centralized reporting or posting within a searchable database.

The IFPMA updated its 2000 self-regulatory code of marketing practices in 2006, released in January 2007, and later further updated in 2012 (28). The IFPMA Code is the only regulatory standard in countries without government regulation of drug promotion or a national industry association with a self-regulatory code. The 2006 and 2012 versions of the Code are longer than the version they replaced and include more explanatory sections. However, they fail to explicitly cover two promotional activities that were covered in the 2000 code: the activities of pharmaceutical sales representatives, and direct-to-consumer advertising of prescription drugs (107). Neither omission is likely to be an oversight as these are key promotional activities. The 2006 and 2012 versions of the code also lack any provisions for the active monitoring of promotional activities.

Government regulation

When a medicine is approved for marketing, it includes the pharmaceutical product and accompanying packaging, information, labelling and package inserts. Approved product information is prepared by the manufacturers and summarizes the scientific evidence on effects and sets out conditions for use, although it is subject to approval by regulatory agencies. It also sets out a basis for the judgment of which promotional practices are and are not permitted, and criteria they must meet to comply with national law, such as requirements for consistency with approved indications and product information or prohibitions of financial incentives that may influence prescribing.

Governments may take a more or less direct role in the regulation of the promotion of pharmaceuticals. For example, in some countries, the regulatory agency is directly responsible for pre-approval, monitoring, response to complaints, and levying of any fines and other sanctions. In other cases, most of these activities are delegated to an industry self-regulatory body or a multi-stakeholder committee that is independent of government. Others may opt for a co-regulatory approach, in which the government agency has responsibility over certain forms of promotion, the industry self-regulatory body over others. In general, few resources are devoted to the regulation of the promotion of pharmaceuticals in either low- or higher-income countries (8, 108), despite the evidence that promotion strongly affects prescribing and medicine use, and the public health implications and costs to society of these effects (59).

The WHO Ethical Criteria for Medicinal Drug Promotion, published in 1988, remain the global standard for the promotion of pharmaceuticals with an explicit aim to support the rational use of medicines (1). Although new media and marketing techniques have emerged in the 25 years since their development, key criteria still cover the major promotional issues of concern. For example, one such principle is the avoidance of "…misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks".

Since 1999, the WHO has carried out surveys of all United Nations (UN) Member States every four years on the 'structures and process of country pharmaceutical situations', including the regulation of the promotion of pharmaceuticals. Countries are divided into low, middle and high income according to their per capita gross national product. In 2003, 148 (77%) of UN Member States responded, in 2007, 150 (78%) (109). Table 1 presents the key results concerning regulation of drug promotion for these two surveys. The results are not directly comparable, as there were differences in how the questions were posed, and the 2007 survey elicited more detailed information. Most national governments reported that they had national medicines legislation and legislation specifically covering the promotion of pharmaceuticals. Law enforcement varied by income level, with only one third of high-income countries reporting that they relied solely on government regulation, as compared with most low-and middle-income governments. Few national governments reported reliance solely on industry self-regulation. In 2007, nearly 2/3 of high-income country governments reported reliance on co-regulation. The rate was lower in 2003, but there were also fewer survey respondents from high income countries. In most countries that adopt a co-regulatory approach, enforcement of the law is primarily delegated to an industry self-regulatory body. For example, in the UK, the industry association, the Association of the British Pharmaceutical Industry, has a code of practice that is enforced through the Prescription Medicines Code of Practice Authority (see: www.pmcpa.org.uk/). The national regulatory authority is able to step in, should self-regulatory approaches fail or intervention be deemed necessary, for example if an imminent risk exists to public health. In practice, such interventions are infrequent.

There has been little evaluation of the effectiveness of varying approaches to the regulation of the promotion of pharmaceuticals. If there are inadequate resources for monitoring, government involvement in regulatory activities may be minimal to non-existent, both in higher- and lower-income countries. For example, a 2003-2004 parliamentary investigation in Canada noted that no fines had been allocated for any promotional regulatory violations during the past 25 years (110). In contrast, from 2004-2007 Brazil levied fines totaling around $10 million for 959 infringements of the law on pharmaceutical advertising (111). The US has the strongest history of fining pharmaceutical companies; since 1991, they have paid $35.7 billion in civil and criminal penalties (112). However, profits generated through violations far outweigh even these fines (113).

In 2002, WHO published a 10-country comparison of the regulation of medicines, including the regulation of the promotion of medicines (114). The sample included all six WHO regions and a variety of national income levels. In one of the 10 countries, Cuba, no pharmaceutical

TABLE 1. Regulation of pharmaceutical promotion: World Health Organization survey results 2003 and 2007 (all percentages are of column totals)

	Low income (per capita income ≤US$935/year)		Middle income (per capita income US$936-11,455/year)		High Income (per capita income ≥US$11,456/year)	
Number of respondents[a]	**2003 (n=57)**	**2007 (n=47)**	**2003 (n=65)**	**2007 (n=69)**	**2003 (n=18)**	**2007 (n=34)**
National medicines legislation	52 (91%)	41 (87%)	55 (85%)	60 (70%)	18 (100%)	32 (94%)
Law on promotion	47 (82%)	41 (87%)	50 (77%)	59 (86%)	16 (89%)	34 (100%)
Promotion regulated by:						
Government	38 (67%)	40 (85%)	32 (49%)	48 (70%)	6 (33%)	12 (35%)
Industry self-regulation alone	2 (4%)	2 (4%)	1 (2%)	3 (4%)	1 (6%)	0
Co-regulation[b]	6 (11%)	2 (4%)	14 (22%)	11 (16%)	8 (44%)	22 (65%)
NGOs[c] / civil society involved	8 (14%)	6 (13%)	15 (23%)	20 (21%)	8 (44%)	11 (32%)
Types of regulation (2007 data only)	**Low income (n=47)**		**Middle income (n=69)**		**High income (n=34)**	
Advertising pre-approved	26 (55%)		40 (58%)		11 (32%)	
DTCA[d] of prescription medicines banned	36 (77%)		43 (62%)		21 (62%)	
OTC[e] ads regulated	20 (43%)		31 (45%)		15 (44%)	

[a] In 2003, national income level data were available for 140/148 (95%) countries who responded (148/191 (77%) of UN Member States); in 2007 income was available for all 150 respondents (150/192 (78%) of UN Member States). Listed income cut-offs are 2007 criteria.

[b] Co-regulation refers to joint government and industry regulation. In 2003, no direct questions were posed on co-regulation. Countries that reported they relied both on government regulation and industry self-regulation are listed as having a co-regulatory approach.

[c] NGO = nongovernmental organization

[d] DTCA = direct-to-consumer advertising of prescription medicines

[e] OTC = over-the-counter medicines

advertising or promotion was allowed. In the other nine, the authors noted that, "The empirical data for assessing the regulation of drug information [promotion] are highly inadequate. Even records of the number of violations and the percentage of each type of sanction imposed are generally unavailable. So, too, is information on the effectiveness of action to prevent inaccurate and misleading drug information from reaching health care providers and the public."

A 2007 study analyzed the regulation of advertising and promotion of pharmaceuticals in seven countries in Latin America, in relation to the WHO Ethical Criteria. Relevant legislative texts and regulations were collected in Argentina, Bolivia, Brazil, Colombia, Ecuador, Nicaragua and Peru. The aim was to examine the consistency of national approaches to regulation with the WHO Ethical Criteria and to evaluate their content, restrictions and flexibilities. The study concluded that while the Ethical Criteria acted as a reference in the setting of norms, there was a tendency to exclude key concepts necessary to prevent harm and protect health. Ample room was provided for interpretation and there was recurrent use of vague wording, for instance, in the definitions of promotion, advertising and medical information. The latter enabled the dissemination of disguised promotion to the public. In addition, there was little information on enforcement and sanctions or the role to be played by consumers and independent organizations in the monitoring of the promotion of pharmaceuticals (115).

Some governments have introduced improvements in regulation. Initially in 2000 and later in December 2008, Brazil introduced broad changes to the regulation of the promotion of pharmaceuticals aiming to extend the scope of existing regulations. An analysis of over 800 advertisements in Curitiba (the capital of Paraná State), published in 2007, thus predating the 2008 regulatory changes, had found that three quarters failed to comply with regulations and on average there were 4.6 infractions per advertisement (116).The changes included additional controls on advertising of over-the-counter medicines, such as prohibition of celebrity endorsements and product placement in television, radio, films or theatre productions. The active ingredients must be stated and advertisements must include warnings, such as contraindications for use in young children or during pregnancy. These legal changes also introduced limits on the volume of free samples and prohibition of gifts for physicians or pharmacists (117).

In 2010, the Physician Payments Sunshine Act, part of US health reform legislation under the Affordable Care Act, enacted provisions requiring all pharmaceutical industry payments above $10 to physicians to be publicly disclosed. Starting in September 2014 these payments were available through the Open Payments website of the Centers for Medicare and Medicaid Services (118). Some major medical faculties in the US, including Stanford University, have gone further than national governments or industry self-regulatory bodies to implement both full disclosure and limits on the types of industry financing faculty members may accept. For example, participation in industry speakers' bureaus is not permitted (119). The US legislation has allowed researchers to examine the effects of payments to doctors on their prescribing behaviour. One study linked the Sunshine Act data for 2013 with prescribing information obtained from the Medicare Part D database, the US federal program that covers prescriptions for the elderly. The authors found that the receipt of payments was associated with greater prescribing costs per patient, and more prescribing of branded medicines (120). A second study

using the same datasets showed that the receipt of industry-sponsored meals of even $20 or less was associated with increased prescribing of the brand-name medication that was being promoted at the meal (121).

In France, broad regulatory changes were brought in following the Mediator (Benfluorex) scandal, a medicine withdrawn for safety reasons in 2009. Benfluorex was approved for use in type 2 diabetes, but was widely prescribed for weight loss, an unapproved use. Benfluorex causes heart valve abnormalities, similar to two closely related medicines (Fenfluramine and Phentermine) that had been withdrawn from the market globally 12 years earlier. L'inspection générale des affaires sociales, a French regulatory authority, investigated the factors contributing to this long delay in taking action on safety concerns and found that conflicts of interest in regulatory decision-making had played a large part (122).

In Portugal, legislation passed in 2013 requires disclosure by healthcare professionals (individuals or associations), hospitals and other health institutions as well as patient organizations of any subsidy, sponsorship or gift received from the pharmaceutical or medical device industries. Similarly, sponsors are also required to declare any support they provide on the online portal hosted by the Portuguese drug regulatory agency (123). Other European countries with legislation requiring disclosure of industry payments to healthcare professionals include France, Greece, Romania and Latvia (106).

Recent nongovernmental initiatives

As is noted above, academic clinicians have a major role in some of the newer 'non-traditional' forms of pharmaceutical promotion blurring distinctions between science or education and advertising. The financial ties between clinical experts and pharmaceutical manufacturers are often unclear. This has implications not only for clinical practice, but for the roles of researchers and educators within medicine and the other healthcare professions.

Since March 2007, France's public health code has required healthcare professionals to declare their financial links to pharmaceutical manufacturers in any relevant public statements in print or broadcast media (124). Despite this requirement, a physician's organization, Formindep (pour une Formation et une information médicales indépendantes), together with the consumer group Que choisir have filed charges against nine KOLs who are considered leading experts in their field for failing to declare their ties to manufacturers when speaking publicly (118).

In the US, there have been some initiatives to address the influence of pharmaceutical funding of academic physicians. One driving force behind these institutional changes has been the American Medical Students Association (AMSA) PharmFree Scorecard initiative. Since 2007, AMSA has published grades for all medical faculties within the US on conflict of interest policies involving faculty, the presence of sales representatives and free samples in teaching hospitals, and industry financing of educational activities (125). Institutional policies are published on the web in a format that facilitates comparisons and provides full descriptions both of exemplary policies and those judged to be inadequate.

Acción Internacional para la Salud Nicaragua has developed a short module on critical appraisal of the promotion of pharmaceuticals, to be incorporated into workshops and other

educational events outside of the formal curriculum. Together with the Drug Research Utilization Group of Latin America (www.durg-la.uab.es), a working group was created to implement this module in universities across Latin America. Institutions in Argentina and Colombia adapted it and implemented the module as part of their curriculum. The module package includes reference materials (national legislation, WHO Ethical Criteria), tools for critical appraisal (examples of advertisements, frameworks for analysis, independent information and videos), as well as an evaluation tool to measure its impact. Between 2006 and 2009, 1346 medical students and 200 pharmacy students attended the module at five universities in Nicaragua, Argentina and Colombia. A large majority of participants considered the module to be useful and relevant to their education as healthcare professionals and would recommend it to their colleagues. In Nicaragua, the evaluation revealed that the module raised awareness about the interactions between health staff and the pharmaceutical industry but also improved critical appraisal skills during sales representative visits and in the analysis of printed advertising materials (126).

Another initiative has focused on curriculum development and testing to improve training of medical and pharmacy students about the promotion of pharmaceuticals and the ethical choices they will face once in practice concerning relations with industry. A manual was produced in 2009 in English, Spanish and Russian, and in 2013 in French: "Understanding and Responding to Pharmaceutical Promotion, A Practical Guide" (127). This curriculum development is a joint project of WHO and Health Action International, an international NGO. A revised version of this manual was developed specifically for healthcare professional students in the European Union (128).

CONCLUSION

In conclusion, the WHO Ethical Criteria for Medicinal Drug Promotion remain a global gold standard for the regulation of drug promotion, on which national regulations and codes can be based. Unfortunately, the implementation of the WHO Ethical Criteria remains incomplete, and many widespread new forms of drug promotion are in clear violation of the criteria. These include, for example, the use of clinician key opinion leaders, continuing medical education and disease mongering, as vehicles for disguised promotion.

There are some positive trends in the regulation of the promotion of pharmaceuticals, such as rules requiring mandatory disclosure of funding of healthcare professionals and patient groups, but more systemic fundamental changes are still needed. To realize the full potential health benefits of medicines as a social good, expanded professional and public access to accurate information from the industry, as well as independent, comparative information, is needed, with a clearer distinction between commercial activities and health-care provision and use. The industry has a role in ensuring that approved product information is widely available, and that the full protocols and reports of results of all sponsored clinical trials are made public, as well as post-marketing safety and effectiveness information.

There is ample evidence that promotion affects patterns of prescribing and medicine use, with effects on costs and on appropriateness of medicine use. Regulation aims to ensure that

promotional messages are consistent with the scientific evidence and public health objectives, but has been under-resourced, with little to no evaluation of 'best practices' in regulation of promotion, or what does and does not work.

In order to ensure that the needs of patients and the public - the users of medicines – are at the center of medicine use decisions, both better access to high quality independent information and stringent regulation of drug promotion are needed. This can only be accomplished if the political will exists to ensure that national governments give priority to the health needs of citizens over the need for national and international industries to expand their markets. Where self-regulatory bodies exist, they should function in an open and transparent manner, with full publication of complaints and decisions, and include firewalls between member companies and the committees that judge whether or not promotional practices violate industry norms.

For national governments aiming to better manage medicine use so as to maximize health benefits and cost-effectiveness, two complementary approaches to promotion of rational medicine use are needed, ideally situated within a broader national medicines policy. First, improvements in the regulation of the promotion of pharmaceuticals are a necessary precondition to promotion of rational medicine use. These must address both direct and disguised or indirect forms of the promotion of pharmaceuticals, including the use of expert clinicians as key opinion leaders. Second, there is also a need for publicly-financed, independent/non-commercial information to be integrated into health service provision. Even the best-regulated promotion of pharmaceuticals by definition aims to sell a product, and cannot replace independent/non-commercial, unbiased comparative information sources.

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CHAPTER 3.2

FINANCIAL DISCLOSURE AND TRANSPARENCY OF PATIENT AND CONSUMER ORGANISATIONS AT THE EUROPEAN MEDICINES AGENCY: RETROSPECTIVE CROSS-SECTIONAL STUDY

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In preparation for submission

ABSTRACT

Background and Objective

Patient and consumer organisations are becoming more prominent in medicines regulation, yet little research has been done to ascertain the nature and extent of the relationship of such groups with the pharmaceutical industry. This study provides baseline data on levels of corporate sponsorship among the groups eligible to work with the EMA and studies the trends in financial disclosure and transparency over time (2007 to 2011).

3.2

Design

Retrospective cross-sectional study.

Population

Patient and consumer organisations eligible to work with the European Medicines Agency, (N=19 in 2007; N=34 in 2011).

Methods

Financial data were retrieved from organisations' and pharmaceutical companies' websites, as well through direct requests for the years 2007 to 2011. Disclosure practices of eligible groups, as well as corporate sponsorship received were recorded.

Results

Compliance with EMA reporting guidelines decreased slightly from 2007 (N=4/19, 21%) to 2011 (N=6/34, 18%). Twenty out of the 34 groups (59%) received funding from medicines' manufacturers and/or industry associations. Of these 20, 10 (50%) did not publish detailed information on their corporate sponsorship on their websites. Another 6 (30%) failed to report on financing. The median sponsorship received per patient group increased during our study period, both in value and in contribution to the organization's annual revenue. In 2011, the overall sponsorship received from corporate sources amounted to nearly €6,6 million Euro.

Conclusion

This study indicates there is low compliance with the applicable guidelines. Most groups received industry funding (59%) and that proportion remained stable although the median industry contribution increased considerably over time. Independent patient and consumer input is needed for sound regulation of medicinal products in Europe. The extent of pharmaceutical industry sponsorship of groups providing advice to the EMA is a concern, as is inadequate public disclosure of corporate financing.

INTRODUCTION

Patient organisations are a valuable source of information, services and support for those living with a disease and their carers. The rise of the empowered patient concept has encouraged the participation of patients and their representatives in discussions that affect them. The European Medicines Agency (EMA) is responsible for evaluating and supervising the safety, efficacy and quality of medicinal products marketed in the 28 European Union Member States (1). European umbrella organisations representing patients and consumers across the European Union may apply to work with the EMA. From these, a smaller group is invited to join regular meetings of the EMA's Patients and Consumers Working Party (PCWP). The PCWP makes recommendations to the Agency and its Management Board in matters that interest patients and consumers, including product information, transparency and dissemination of information, pharmacovigilance activities, as well as interaction with the EMA Scientific Committees and agency staff (2). Participants are involved in activities to enhance communication to the public about medicines (i.e. to review package leaflets or disseminate publications about the risk of some medicines) and may, on appointment or request, provide advice to the EMA's Scientific Committees on product-related matters (3).

The involvement of patients and consumers as political stakeholders in pharmaceutical debates in the EU policy-making process requires stable and sufficient funding at organizational level. Pharmaceutical, bio-tech and medical device companies are increasingly sponsoring patient organisations, ranging from direct financing (donations and grants) to various forms of in-kind sponsorship (4). There are several reasons for building such a donor-recipient relationship, including the overlapping interest to seek reimbursement for medicines (5, 6).

Despite such convergence, the aims of medicines and device manufacturers can conflict with the best interests of patients and consumers (7). For example, a pharmaceutical company generally strives to obtain and expand market share for its products as quickly as possible to maximise its return on investment. On the other hand, patients and consumers may or may not benefit from a given product, depending on its characteristics, its therapeutic value when compared to existing treatments and its costs. Bearing that in mind, a donor-recipient relationship forged between pharmaceutical companies and patient organisations could lead to conflicts of interest, or could unduly threaten the patient groups' independence. An Institute of Medicine's report described conflicts of interest at institutional level with patient advocacy groups, "*when an institution's own secondary interests [fund raising] or those of its senior officials pose risks of undue influence on decisions involving the institution's primary interests [benefits to their own members]*" (8). The report added that poor oversight of relations between patient groups and their for-profit donors increases the potential for undue influence. The threat that industry funding can pose to an organisation's independence was cited as a 'problem' by one in five patient organisations (22%) surveyed by Hemminki in 2010 (5).

Although the role played by patient and consumer organisations in European pharmaceutical policy-making is becoming more prominent, little research has been done to ascertain

the nature and extent of the relationship of such groups with the pharmaceutical industry (9). The EMA has developed clear guidelines requiring financial transparency from patient and consumer organisations that are eligible to work with the Agency (10). While these guidelines require financial data to be disclosed to the EMA in a format that includes the names of income sources, the absolute amount of support and its value relative to the organisation's budget, that information is not proactively published by the Agency.

Pharmaceutical companies are increasingly publishing the support they provide to patient and consumer organisations (11). In Europe, this trend has seen the introduction of a Code of Practice on Relationships between Pharmaceutical Industry and Patients Organisations, which was initially adopted in 2007 by the European Federation of Pharmaceutical Industry Associations (EFPIA) and later amended in 2011 (12). This self-regulatory code requires all EFPIA member companies to publish the names of the patient organisations and the monetary value of the support provided and/or the total amount paid by the company for services contracted from the patient group (13,14).

This article examines the changes in disclosure practices of eligible organisations and quantifies the annual corporate sponsorship that the patient and consumer groups active at the EMA have received between 2007 and 2011 by addressing the following questions:

1. What are the online disclosure practices of organisations eligible to work with the EMA and how did they change during the study period?
2. How many of the eligible organisations have received corporate sponsorship during the study period and how has this evolved over time?
3. How much corporate sponsorship has each eligible organisation received annually during the study period and how has this evolved over time?

METHODS

Sample

Thirty-four patient and consumer organisations (hereafter called *organisations*) were included for any of the five years (from 2007 to 2011) in which they were either eligible to work with the EMA or involved in agency activities. This information was retrieved from the annual reports of the Patients and Consumers Working Party (15). Two organisations eligible to work with the EMA merged in 2011 and as a result we were unable to retroactively retrieve their data for 2009 and 2010.

Outcomes of interest

Each organisation's disclosure policy, its revenue and self-reported sponsorship from corporate sources, for each study year was recorded.

Disclosure was defined into four categories, considering the Agency's guidelines (11):

- **Met EMA Guidelines:** The names of corporate sponsors and the monetary value of each sponsor's individual contribution as well as the percentage of the organisation's total income represented, is provided on the organisation's website;

- **Partial**: The names of corporate sponsors and the corresponding monetary value of their individual contributions are provided on the organisation's website, but not the percentage of the organisation's income represented;
- **Unspecified**: Only the names of corporate sponsors are provided without the value of their individual contribution OR only the total value of corporate sponsorship without donor-specific details on the organisation's website;
- **Absent**: Neither the names of corporate sponsors nor the value of corporate sponsorship are listed on the organisation's website.

Corporate sources are enterprises and associations within the healthcare sector. These include companies that produce healthcare-related products or services, including pharmaceuticals or medical devices or nutritional products; company-owned foundations, or foundations and associations established by a single company, as well as industry associations representing medical, drug or device companies. Non-profit foundations and consultancies that received some health-sector corporate revenues, but also funding from multiple sources, were excluded.

Revenue was defined as organisational income from all sources in all forms (including but not limited to grants, donations, sponsorships, fees and investment/bank interest) received for all purposes (including but not limited to operational income, restricted financing and project- or activity-specific financing). Other elements contributing to the organisation's annual income such as assets (real-estate), in-kind contributions and volunteer hours (or their assigned financial value) were excluded from this study.

Corporate sponsorship was defined as any restricted or unrestricted financial contribution accepted from a corporate source for all purposes (including but not limited to core/operational work, events, projects, education grants or research initiatives, payment of conference attendance and related travel costs for patient organisation representatives or honoraria).

Data Collection

The assessment of an organisation's type of disclosure was based on the organisation's website and online publications available via the website for each study year. Each organisation's website and online publications were searched for its revenue and the value of corporate sponsorship received (hereafter called *self-reported sponsorship*). When available, organisations' annual financial accounts were retrieved from the UK Charity Commission for England and Wales (16). When relevant documents could not be found, the following Google search term was used: {patient or consumer organisation name} + annual report OR financial report OR finances OR sponsors OR donations + {year}. The first 20 results were investigated.

Each organisation's revenue and self-reported sponsorship were recorded for each study year. If no year was indicated for the data, it was assumed to come from the year of the last webpage update (found at the bottom of the screen). Financial data for the years 2007 and 2008 were retrieved from online sources between January 20 and February 7, 2010 (17). Data for the years 2009, 2010, and 2011 were extracted from online sources between July 15 and October 27, 2012 with an additional final search on 8 October 2013. When the value of corporate

sponsorship could not be derived from the previous steps, pharmaceutical industry funding was calculated by searching the websites of the 35 EFPIA member companies. If relevant data could not be found on company websites, a Google search term was used: {company name} + {patient organisation name} OR patient organisation OR patient group + {year}. The first 20 results were investigated. The sum of the contributions specified by all pharmaceutical companies to a given organisation was calculated (hereafter called *company-reported sponsorship*) for four years (2008-2011) following the introduction of EFPIA's Code of Conduct. Financial data for 2008 were retrieved from online sources between January 20 and February 7, 2010 (17). Data for the years 2009, 2010, and 2011 were extracted from online sources between July 15 and October 27, 2012. Organisations self-reporting corporate sponsorship or for which company sponsorship could be retrieved were considered to be partly or entirely-corporate funded. Organisations whose self-reported revenue did not include corporate sponsors were considered as not receiving corporate sponsorship. Whenever possible, audited financial accounts were used. When these where unavailable, data were retrieved from annual reports.

Data analysis

All values were recorded in Euro and in cases where another currency was reported, the value was converted to Euro using the average annual currency exchange rates on December 1 of the given year using the website Oanda.com. The annual average corporate sponsorship values were adjusted for inflation using the harmonized index of consumer prices, with 2005 as the reference year for the study period, in line with Eurostat's practice of establishing one reference year per decade. Average annual inflation rates for the Euro area (17 countries) were obtained from the Eurostat website (18).

Fisher's exact test was used to compare differences in frequencies in disclosure practices and corporate sponsorship over time (2007 to 2011). Whenever possible, data analysis was conducted using IBM SPSS 23.

RESULTS

The number of eligible organisations increased annually from 19 in 2007 to 34 in 2011. Every year, around four new organisations became involved in the Agency's activities (See Suplementary Information, Table S1).

Disclosure practices

The percentage of groups *meeting EMA Guidelines* decreased from 21% in 2007 to 18% in 2011. (Figure 1) The percentage of groups specifying donors by name and their corresponding contributions (*partial*) decreased from 32% in 2007 to 23% in 2011. The percentage of organisations reporting lump sums of sponsorship (*unspecified*) decreased from 32% of groups in 2007 to 21% in 2011. The percentage of organisations for which little or no data could be retrieved (*absent*) increased more than two-fold from 2007 (n=3, 16%) to 2011 (n=13, 38%)

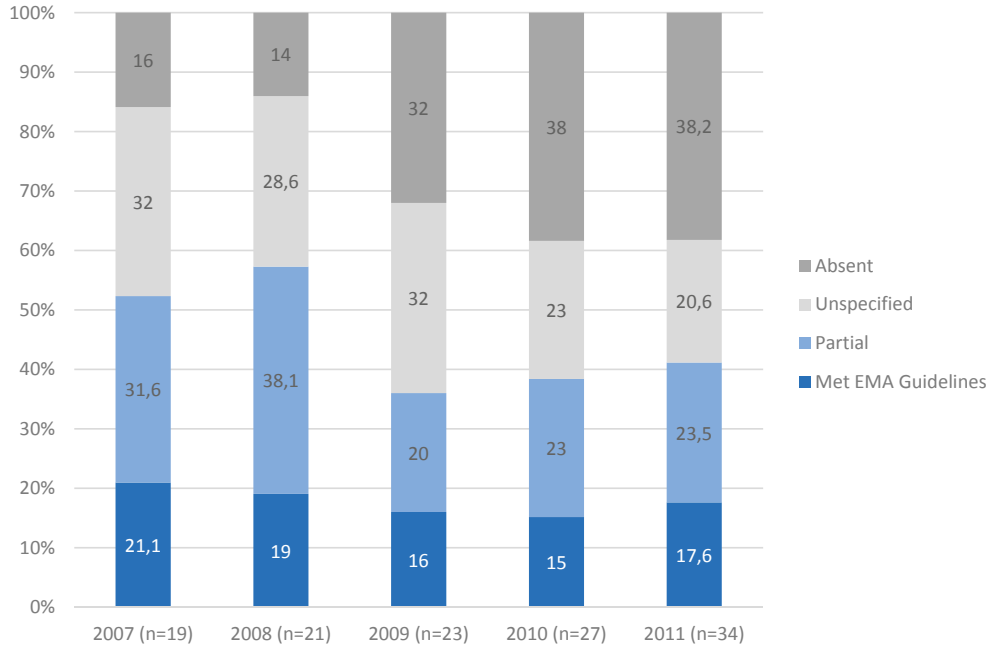

FIGURE 1. Eligible organisations' disclosure practices between 2007 and 2011

(Figure 1). The percentage of organisations for which any donor information could be retrieved decreased from 85% in 2007 (n=16) to 62% in 2011 (n= 21). The trend in frequency of disclosure policies did not differ significantly from 2007 to 2011 (P<0.384). The percentage of eligible organisations partly or entirely funded by pharmaceutical companies which provided detailed information on sources of revenue decreased during the study period (*met EMA guidelines* or *partial disclosure*), whereas only one of the groups refusing corporate sponsorship reported on one occasion unspecified disclosure (Supplementary Information Table S1). The frequencies of disclosure were only significantly different between funded and non-funded groups for 2011 (P<0.005), which suggests a trend in poorer disclosure over time of organisations receiving corporate sponsorship.

Receipt of corporate sponsorship

The proportion of funded organisations remained stable over time. In 2007, 11 of the 19 eligible organisations (58%) received financial sponsorship from corporate sources whilst three (16%) received funding from other sources. It was not possible to retrieve any financial data for 5 organisations (26%) (Figure 2). In 2011, nearly two-thirds of the 34 eligible patient and consumer groups at EMA received partial or entire funding from medicines manufacturers and/or industry associations (n=20, 59%) and seven organisations were entirely funded by non-pharmaceutical sources (21%). No financial data could be retrieved for seven organisations (21%).

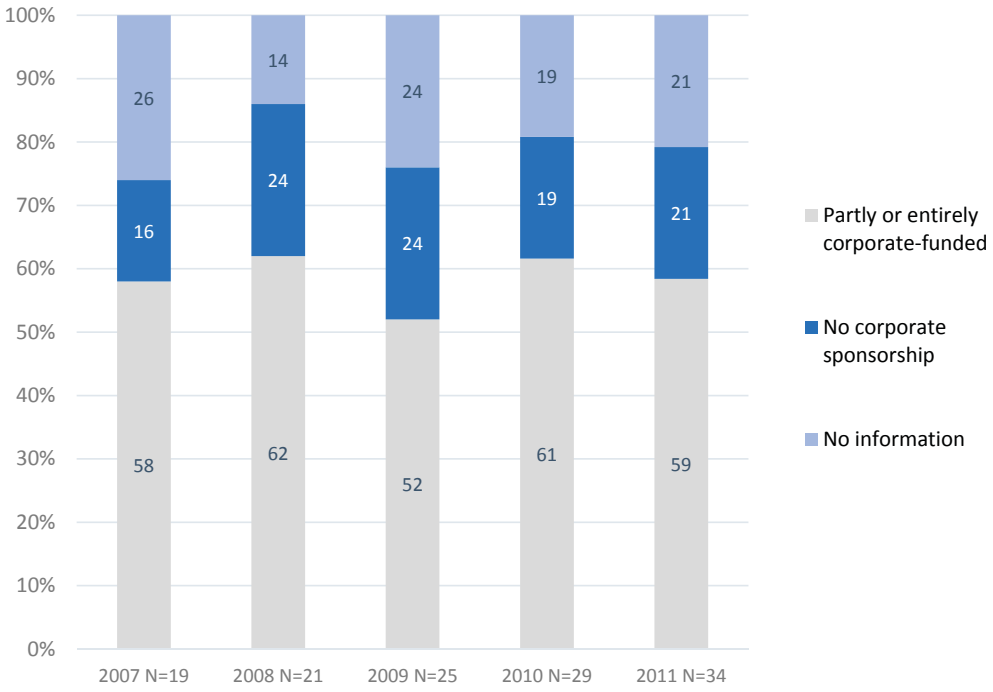

FIGURE 2. Corporate sponsorship of eligible organisations between 2007 and 2011

Sponsorship values and their contributions to annual revenue

The median value of *self-reported corporate sponsorship* (adjusted for inflation) rose from €265,180 in 2007, to €341,309 in 2008, to €386,897 in 2009, to €508,841 in 2010, to €452,013 in 2011 (Table 1). These amounts correspond to a median corporate contribution to the organizational annual revenue of 43%, 44%, 73%, 71%, 66% respectively. The percentages were not significantly different between study years. The total value of *self-reported corporate sponsorship* received by all eligible organisations increased annually from €3,250,965 in 2007 to €4,985,517 in 2011 (Figure 3). The median values for *company-reported sponsorship* varied from €315,151 Euro in 2008, to €345,618 Euro in 2009, €238,950 Euro in 2010, to €220,971 in 2011 (Table 2). These amounts correspond to a median corporate contribution to the organizational annual revenue of 37%, 67%, 56% and 64% respectively. These percentages did not differ significantly between study years. The total value of *company reported-sponsorship* for all groups combined increased from €3,855,764 in 2008 to €6,597,850 in 2011 (Figure 3). The number of organisations for which data about sponsorship and revenue could be retrieved varied across our study period (Tables 1 and 2). Pharmaceutical companies' websites provided evidence of financing more organizations than patient organisations' websites, especially for the years 2010 and 2011.

TABLE 1. Trend of self-reported and company-reported sponsorship over time (median)

	Year N= Eligible organisations for which data was available and/or retrieved				
Type of report (sponsorship)	**2007** **N=10**	**2008** **N=10**	**2009** **N=8**	**2010** **N=8**	**2011** **N=10**
Self-reported sponsorship					
Median Self-reported sponsorship (EUR)	**265.180**	**341.309**	**386.897**	**508.841**	**452.013**
25% percentile (EUR)	152.717	255.769	349.659	284.913	186.505
75% percentile (EUR)	534.941	506.84	538.589	640.231	750.488
Company-reported sponsorship		**2008** **N=12**	**2009** **N=13**	**2010** **N=16**	**2011** **N=19**
Median Company-reported sponsorship (EUR)		**315.151**	**345.618**	**238.950**	**220.971**
25% percentile (EUR)		177.49	123.531	111.704	126.687
75% percentile (EUR)		470.658	462.103	601.421	588.438

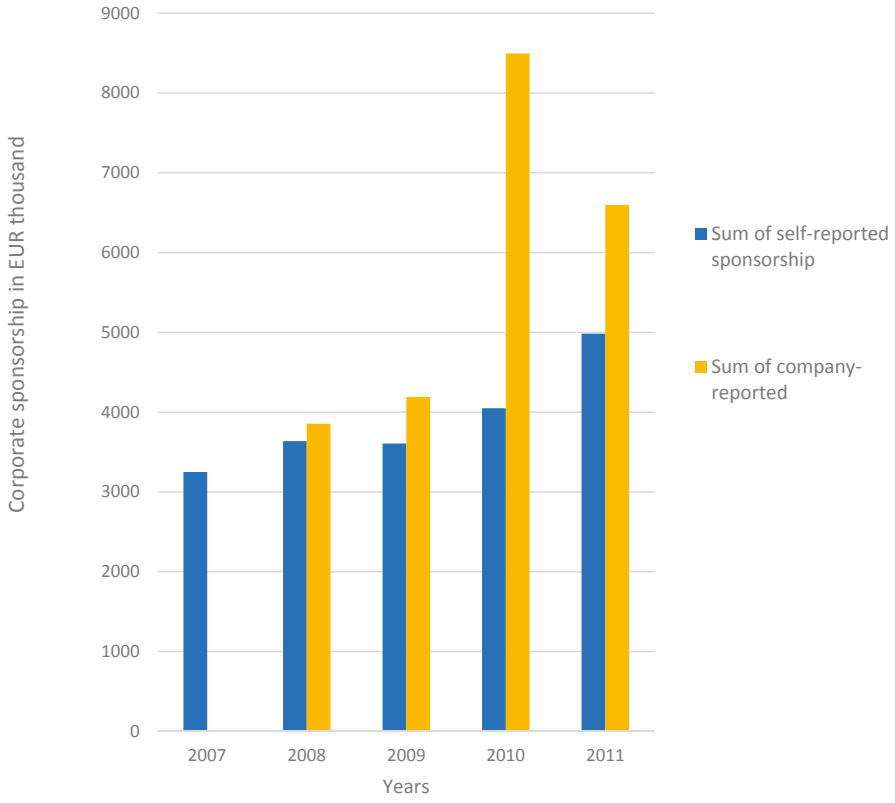

FIGURE 3. Corporate sponsorship (sum) received by organisations eligible to work with EMA between 2007-2011.

TABLE 2. Trend over time of the proportion of annual revenue from sponsorship (self-reported and company-reported) over time (median)

Year	Eligible groups in analysis (sponsored and for which information is available)	Median % of annual revenue from self-reported sponsorship	25% percentile of the median	75% percentile of the median
2007	10	42.94	26.13	93.79
2008	10	43.68	31.56	84.31
2009	8	72.65	32.03	81.27
2010	8	70.68	33.14	83.90
2011	8	66.45	20.36	91.00
Year	**Eligible groups in analysis (sponsored and for which information is available)**	**Median % of annual revenue from company-reported sponsorship**	**25% percentile of the median**	**75% percentile of the median**
2008	12	36.45	31.4	81.83
2009	10	66.84	30.8	80.5
2010	11	55.62	25.65	77.85
2011	13	63.79	25.87	91.00

Trend in disclosure per funding policy

The percentage of eligible organisations partly or entirely funded by pharmaceutical companies which provided detailed information on sources of revenue decreased during the study period (*met EMA guidelines* or *partial disclosure*), whereas only one of the groups refusing corporate sponsorship reported on one occasion unspecified disclosure (Table S1). The frequencies of disclosure were only significantly different between funded and non-funded groups for 2011 ($P<0.005$).

DISCUSSION

Our findings indicate that the prevalence of good disclosure practices declined slightly during the study period. In 2007, 53% of all eligible organisations disclosed at least partial information about their sponsors and contributions, whereas in 2011 only 41% did so. By 2011, thirteen, i.e. 38% of eligible organisations, disclosed little or no information about their funding sources, although six (46%) from these were sponsored by the pharmaceutical industry. There was low compliance with the applicable EMA guidelines for financial disclosure and public transparency of the organisations working with the EMA. The proportion of patient and consumer groups with adequate disclosure declined over the study period, with only 18% of the organisations publishing financial information in line with the EMA's guidelines in 2011.

This study found that 59% of the patient and consumer organisations eligible to work with the European Medicines Agency had received corporate sponsorship from the pharmaceutical

or medical devices industries between 2007 and 2011. Our findings raise questions about the ability of these groups to represent an independent patient voice.

Despite the economic crisis in Europe, the median amount of corporate sponsorship reported per organization increased from €265,180 in 2007 to €452,013 in 2011, at a rate greater than that of inflation. The sum of corporate sponsorship as reported by companies and received by groups eligible to work with the EMA also increased, amounting to €6,597,850 Euro in 2011.

Although several studies have reported on industry funding of patient advocacy organisations (4, 5, 11,19,20,21,22) no research has, to the authors' knowledge, systematically investigated the levels of corporate funding of European patient and consumer advocates active in EU pharmaceutical policy.

Evidence of corporate sponsorship of patient organisations increased markedly when pharmaceutical company websites were consulted in addition to the organisations' own webpages. These results corroborate those of another study that suggests that patient groups' websites give insufficient information about corporate donors to assess whether their interests might conflict with those of their pharmaceutical and other corporate funders (4). By 2011, only six out of the 34 eligible organisations proactively disclosed their funding sources in line with the EMA's financial transparency criteria. Our findings are also consistent with those of an Italian study, which found disclosure of funding to be more complete in pharmaceutical companies' websites than in patient and consumer groups' websites (19). Nevertheless, some pharmaceutical companies may not be EFPIA members and/or may not disclose financial sponsorship to patient organisations at European level.

There is currently no register of pharmaceutical or medical devices industry sponsorship to patient organisations or professional societies at European level. This study aims to shed light on the disclosure practices of organisations active at the EMA and to estimate the annual sponsorship received, based on publicly available information. The fact that little or no information could be retrieved about 2010 and 2011, either directly or indirectly, for seven eligible organisations could have affected the study results.

Our findings are a conservative estimate of the true value of sponsorship. The evidence was largely self-reported and retrieved according to objective criteria from the public domain and is verifiable by third parties. Two information sources were used to optimize data collection and maximize data reliability. The EFPIA code of conduct sets a standard of disclosure of funding to patient organisations for the EFPIA member companies at European level (11). Similar standards are not available for the nutritional and medical devices industries, although these donors might have also contributed to the revenue of sponsored groups. Therefore, our results likely underestimate the extent of overall corporate funding.

In-kind contributions were excluded from our study to enable data comparison between different organisations, as they varied greatly in type and reporting format. Most notably, there is no common standard on how such donations should be declared by patient and consumer organisations.

Disclosure of all sponsorship sources, the intended purpose of the funding, its value and the proportion of organisational revenue that it represents, is important as it provides

a qualitative and quantitative evidence base from which to assess potential conflicts of interest. According to Fung and colleagues, "*disclosure must provide meaningful information and be easy to interpret so that the public can make their own valid judgments about whether or not to trust the institution*" (23). Our study demonstrates that the value of corporate sponsorship of patient and consumer groups is increasing, while health researchers, peer-reviewed journals, physicians and bioethicists are questioning conflicts of interest arising from pharmaceutical company funding of their communities (7,8, 24,25,26). Not surprisingly then, the policy on Conflicts of Interest of Experts at the EMA considers sponsorship of an organisation by a pharmaceutical company to be a conflict of interest, albeit indirect (27). A 2012 report by the European Court of Auditors also exposed the limitations in the EMA guidelines, underlining the need for clear standards and the annual disclosure of sources of funding of patients and consumers (28). The eligibility criteria of patient and consumer organisations have since been reviewed. These new criteria establish a mandatory annual disclosure to the EMA of "*sources of funding both public and private by providing the name of the bodies and their individual financial contribution, both in absolute terms and in terms of overall percentage of the organisation budget*". Nonetheless, the agency does not foresee making available the detailed information on the EMA's website (10). This decision stands out from that of drug regulatory authorities in France, the Netherlands and Portugal which have started to collect and publish online funding information about patient and consumer organisations involved in their activities (29,30,31).

As time elapses, the EMA's policies and rules of engagement may have important implications as patient and consumer representatives participate more frequently in a wider scope of agency activities among which the Management Board, the Pharmacovigilance Risk Assessment Committee, and other meetings at committee level (32,33,34,35). The role of patients and consumers at the EMA is arguably becoming more influential as consultations and public hearings take place during CHMP discussions and at the EMA's Pharmacovigilance Risk Assessment Committee, respectively. During such meetings patients are invited to discuss a drug's harm-benefit balance and to share their experiences on its therapeutic effects (36,37). This enables patient representatives to affect Committee's decisions about how that pharmaceutical product is regulated, also in recommendations to grant or withdraw marketing authorisations. Given that most eligible groups at the EMA are sponsored by the pharmaceutical industry, as demonstrated by this study, prudence is advised as the EMA implements patient and consumer participation in such gatherings (38).

The low rates of financial transparency observed could be due to several inter-related factors, such as an organisation's relatively recent establishment, its lack of resources or experience as policy advocates, or the low priority it places on maintaining up-to-date public records. These reasons do not detract from the imperative of complete financial transparency for organisations representing a public interest in an official capacity with a regulatory authority (39).

The trend of poorer disclosure practices as observed in our study suggests that new groups joining policy debates should be encouraged to adopt transparency policies. Support mechanisms and regular reviews can maximize the full and transparent participation of patients and consumers in policy-making. Public financing initiatives could enhance the impartiality of

civil society representatives at the EMA. A pooling mechanism through which various revenue sources could be combined and awarded to patient and consumer organisations based on merit would create greater distance between recipients and corporate donors.

This study identified an absence of a uniform and detailed financial reporting system applied to civil society groups active in European pharmaceutical policy making. Similar problems in ascertaining the financial support received by patient-advocacy organizations in the United States have been identified by McCoy et al who then advocated for the creation of a *sunshine law* to cover industry support to these groups (23). Clear, complete and public disclosure of the sponsorship received from the pharmaceutical industry and other corporate donors must be an imperative. A stronger drive towards the harmonization and publication of financial disclosure criteria not only at the EMA, but also within the European Commission and across EU agencies is needed.

This study has focused on corporate sponsorship in relation to patient and consumer organisations active at the EMA. However, these organisations represent but a selection of all non-governmental stakeholders active in health policy in Europe. Thus, further research is crucial on financial transparency and the nature of corporate sponsorship and conflicts of interests of civil society representatives in European health policy making.

CONCLUSION

The extent of pharmaceutical industry sponsorship of groups providing advice to the EMA is a concern, as is inadequate public disclosure of corporate financing. Independent patient and consumer input is needed for sound regulation of medicinal products in Europe. Clear, complete and public disclosure of the sponsorship received from the pharmaceutical industry and other corporate donors must be a prerequisite for any interest representative in official capacity.

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SUPPLEMENTARY DATA

TABLE S1. Disclosure and funding policies of organisations eligible to work with the EMA

Eligible organisations	2007 N= 19 (%)***	2008 N=21 (%)	2009 N=25 (%)	2010 N=29 (%)***	2011 N=34 (%)
Included in study	19	21	25**	26**	34
Disclosure policy by funding policy					
Disclosure: Met EMA guidelines	4 (21)	4 (19)	4 (16)	4 (15)	6 (18)
Partly or entirely corporate-funded	3	3	2	2	4
No corporate sponsorship	1	1	2	2	2
No information	0	0	0	0	0
Disclosure: Partial	6 (32)	8 (38)	5 (20)	6 (23)	8 (23)
Partly or entirely corporate-funded	4	4	2	3	3
No corporate sponsorship	2	4	3	3	5
No information	0	0	0	0	0
Disclosure: Unspecified	6 (32)	6 (29)	8 (32)	6 (23)	7 (21)
Partly or entirely corporate-funded	4	5	6	6	7
No corporate sponsorship	0	0	1	0	0
No information	2	1	1	0	0
Disclosure: Absent	3 (16)	3 (14)	8 (32)	10 (38)	13 (38)
Partly or entirely corporate-funded	0	1	3	5	6
No corporate sponsorship	0	0	0	0	0
No information	3	2	5	5	7

**Two patient organisations eligible to work with the EMA from 2007 until 2010 merged into a single eligible organisation in 2011. Data collection for the years 2009-2011 commenced in 2012 and it was not possible to retroactively retrieve data for the two organisations for the years 2009 and 2010 prior to their merge.

*** Percentages do not equal 100 due to rounding.

CHAPTER 4

PROMOTIONAL INFORMATION TO THE PUBLIC ABOUT HEALTH AND TREATMENT AND ITS IMPACT

CHAPTER 4.1

UNBRANDED ADVERTISING OF PRESCRIPTION MEDICINES AND ATTITUDES, KNOWLEDGE, HEALTH SERVICES USE, COSTS AND HEALTH OUTCOMES [PROTOCOL]

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Cochrane Database of Systematic Reviews 2017, Issue 7.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows: to assess the effects of unbranded advertising of prescription medicines, conducted by or on behalf of pharmaceutical companies, on consumers' attitudes, knowledge, behaviour, health services use, health outcomes and costs.

BACKGROUND

Direct advertising of prescription drugs to the public, also known as direct-to-consumer advertising (DTCA) (Table 1), is permitted only in the USA and New Zealand. Advertising of products that have prescription-only status is prohibited in the European Union as a public health protection measure. The rationale for prohibition is linked to prescription-only status. These medicines generally treat more complex or serious conditions and have potentially greater toxicity than over-the-counter medicines (1, 2). Because the assistance of a health professional is needed to ensure appropriate use, manufacturers may not sell or advertise these products

TABLE 1. Glossary of key terms

Key term	Definition
Branded direct-to-consumer advertising of prescription medicines (DTCA)	Advertising that includes a product's brand name. In the USA, this includes two types of advertising described by the Food and Drug Administration: 1) 'full product advertising', which includes the product name and health claims. Such advertising must also include information on the drug risks; 2) reminder advertising, which states the product's name but makes no health claims. In the USA, this advertising is not allowed for drugs with boxed warnings of serious risks.
Unbranded advertising of prescription medicines	Any paid advertising campaign, in any media, by a pharmaceutical manufacturer, with a focus on a condition treated by one or more of its products, but without any mention of brand or generic names.
Off-label promotion	The term 'off-label promotion' refers to promotion of a medicine for an unapproved use. This type of promotion is generally illegal. Physicians may prescribe a medicine for any use, whether it is approved or not, but manufacturers may not promote medicines for off-label use.
Mixed promotion (both on- and off-label)	'On-label promotion' refers to promotion for approved uses. 'Off-label promotion' is for unapproved uses. Mixed promotion is for both types of uses.
Generic drugs or generics	Generic drugs or generics are medicines that have no brand name or registered trademark. Once the patent for a medicine expires, other manufacturers may produce the medicine, and these products are generic drugs.
Direct-to-consumer advertising	Direct-to-consumer advertising (DTCA) refers to advertising of prescription-only medicines aimed at the public. Such advertising is fully legal only in two countries, the USA and New Zealand.
Non-commercial information sources	We define a non-commercial information source to be any public or private entity, institution, non-government organisation, foundation or society involved in distributing information about health and treatment which does not derive a commercial gain from inducing the prescription, supply, purchase and/or use of pharmaceutical products, either directly or indirectly.
Third party acting on behalf of pharmaceutical company	Any public relations consultancy, marketing company, professional society, think tank, patient and consumer group, key opinion leader, medical practice or hospital, which has been hired or funded by a pharmaceutical company to promote specific pharmaceutical products.

directly to the public. Nevertheless, manufacturers are using an increasing array of techniques to advertise prescription-only medicines to the public both directly and indirectly (3-5).

There is also evidence of promotional influence on how the media covers health topics (6) and on how the media can play an important role in influencing decisions on health and treatment (7), shaping consumers' information base and opinions about therapeutic options (8), and also affecting public policy. Striking examples include, among others, policy decisions being reversed, such as negative reimbursement recommendations for certain cancer drugs after public outcry; or alterations to government priorities and expenditure following intense media coverage of problems in health services provision (such as waiting lists) (9).

4.1 Description of the condition

According to European Union legislation, pharmaceutical companies are permitted to provide general information on health and diseases, but there cannot be any reference, even indirectly, to a specific medicine, unless it is a vaccine (10). This provision offers companies an alternative promotional approach (11), that of unbranded advertising (Table 1), also known as 'disease-awareness', 'help-seeking' or 'condition-oriented' advertisements, which discuss a condition but do not mention a specific brand of medicine (12). The available evidence suggests that these materials draw attention by generating demand for treatments for non-life threatening conditions, by focusing on symptoms and encouraging viewers to see their doctor to obtain further treatment information (13) or seeking diagnostic testing that will later be associated with a decision to use a medicine. Despite their nature and content, these unbranded campaigns are not governed by specific regulations on pharmaceutical promotion, and regulators are often reluctant to consider them as advertising unless explicit links to branded product information are included (14).

Proponents of unbranded campaigns claim these have an educational role in raising awareness about untreated, underdiagnosed health problems at an earlier stage and prompting consumers to seek care (15, 16). However, questions have been raised about the effects of industry-funded unbranded advertising on healthcare use and health outcomes: such campaigns can increase product awareness and increase physician visits, prescribing and sales, thereby burdening health systems (11, 17). By generating demand among those who do not necessarily need medical treatment and supporting the use of newer, more expensive products, these campaigns can encourage irrational medicines use and divert resources away from more important conditions, negatively affecting quality and costs of care (11, 13). In doing so, these campaigns may also inadvertently disadvantage patients and consumers who are in genuine need of treatment (either for the specific disease covered in the campaign, or for other more serious conditions) (11).

While much research has been done in other areas of traditional drug promotion (e.g. physician-directed, product detailing, drug samples, DTCA), far less is known about how these unbranded campaigns influence both health practitioners and the public. A systematic review can add to a better understanding of the effects of these campaigns by synthesising existing research evidence and providing a comprehensive overview both of what is known about the outcomes of such advertising campaigns and gaps in research evidence.

Any condition affecting consumers for which there is a pharmaceutical treatment available can be the object of unbranded advertising. Any member of the public can be affected. Therefore, this review is not restricted to specific diagnoses, symptoms and consequences. A glossary of key terms is available (Table 1).

Description of the intervention

This review will assess the effects of unbranded advertising involving mass media channels of communication and conducted by sponsors, namely the pharmaceutical company that manufactures produces or distributes a medicine or a third party acting on their behalf, for a condition treated by a pharmaceutical product (Table 1).

Mass media channels of communication are intended to reach large numbers of people, as defined by Brinn 2010 (18), Bala 2013 (19) and Mosdøl 2015(20), and are not dependent on person-to-person contact. Unbranded advertising interventions may be made up of one or more components and/or formats. Different formats include: print media (newspapers, magazines, booklets, leaflets, posters and pamphlets), online media (websites and social media), digital technology, and broadcast media (television and radio) as well as outdoor advertising (billboards and banners). Different components include: statements on diagnostic criteria, health outcomes, prevalence rates and symptom recognition; normative statements; images; interactive content such as questionnaires, screening tools or symptoms checkers that a consumer can fill in; recommendations for action (suggestions to seek further information and treatment, e.g. see your doctor); as well as sources substantiating the message being conveyed. The condition highlighted may represent an approved or unapproved (off-label) use of the advertiser's pharmaceutical product (Table 1).

Unbranded advertising generally targets the whole population, but can also focus on specific audiences within the population, such as women (via magazines that target women, for example). There may be differences not only in targeting specific groups but also in responses by gender (men or women), age (older or younger, adults, children), health status (patients with chronic conditions versus other population groups) or socio-economic status. There may also be differences between such advertising in higher-income countries versus low- to middle-income countries, and the characteristics of unbranded advertising may vary across different settings or jurisdictions.

We will analyse, when possible, differences in the effects of unbranded advertising among different target groups. We will compare how the use and effects of unbranded advertising differ between men and women, as there is evidence of greater marketing exposure and effectiveness among women due to their 'healthcare gatekeeper' role in the family (21). In addition, women may be particularly vulnerable to harm arising from prescription drug advertising both for social and biological reasons, as they are more often prescribed drugs and are more susceptible to some harms associated with specific prescription drugs (2). It will also be relevant to compare the use and effects of the intervention between different types of patients, as patients with chronic conditions have specific information and treatment needs that differ from other target groups. Since there are reports of promotional activities encouraging the use of medicines outside their

approved indications (off-label) (22), we also plan to carry out a subgroup analysis comparing the effects of unbranded advertising encouraging on- and off-label use (23).

We will compare unbranded advertising with other information or education activities conducted by non-commercial information sources (Table 1); or with no intervention. Non-commercial information or education activities will not be limited to any specific media, but will include print media (newspapers, magazines, leaflets, posters, pamphlets), online media (websites and social media), broadcast media (television and radio) as well as outdoor advertising (billboards and banners). When possible, we will also compare different types of unbranded advertising (for instance traditional media versus social media).

4.1 How the intervention might work

Unbranded disease awareness campaigns are often developed and carried out using the concepts and tools from social marketing. Pharmaceutical companies, or third parties acting on their behalf, have an underlying commercial intent to drive the choice for a particular treatment. This unbranded advertising is part of a broader and integrated marketing campaign that aims to increase sales of prescription-only medicines (17).

Existing studies describe a model whereby advertising to the public affects consumers' awareness of and knowledge about a condition. Consumers are exposed to the unbranded advertising and are stimulated to seek further medical care by consulting their doctors and requesting a pharmaceutical treatment. Consumers' requests trigger the prescription for the advertiser's product by the physician, who has previously been subject to targeted branded advertising (24-27). Figure 1 presents a logic model.

Advocates of disease awareness campaigns claim these can educate the public, make consumers aware of otherwise untreated health problems and help them seek effective care at an earlier stage (15, 16). However, concerns have been raised about the content and nature of such campaigns and their potential negative effects. One hypothesis that has been put forward is that advertising campaigns are more misleading than informative (28, 29).

Unbranded advertising can transform ordinary life experiences into conditions that require medical diagnoses, encourage consumers to seek further medical tests, and misinterpret the evidence about drug benefits and harms (30) (31). Also, if such campaigns support the use of newer, more expensive products with least well understood benefit-harm profiles over cheaper, well-known, older medicines, they can encourage irrational medicine use, affecting equity, quality and costs of care (13).

Campaigns can take place at a single time point, or may be sustained over a longer period. They can also vary in intensity (e.g. extent and frequency of advertising) and reach (e.g. proportion of intended population who see the advertisements).

There are also equity issues associated with the use of unbranded advertising. Gender can influence healthcare access, service utilisation and treatment implementation in different ways, depending on the particular socio-cultural context and region (e.g. lower- and middle-income countries or higher-income countries), and may contribute to the differential impact

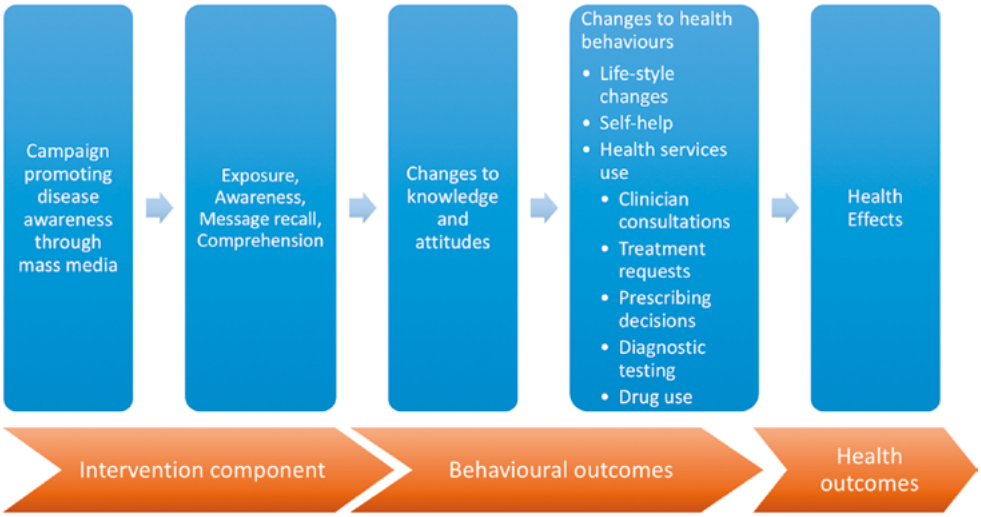

FIGURE 1. Logic model (based on Mosdøl 2015) (20)

of unbranded advertising on men and women. In higher-income countries, women may use more health services than men (32-34). A similar trend is observed in medicines use, with women using more pharmaceutical products than men and gender targeting in DTCA further reinforcing sexual stereotypes (17). There is also evidence of a greater exposure to DTCA, along with self-reporting of greater influence, among lower socio-economic groups (35). Impact may also be influenced by ability to pay for expensive medicines or available insurance/low co-payments, which differ across socio-economic groups in some countries. It is possible that within lower socio-economic groups, the potential increase in costs resulting from unbranded advertising's encouragement of inappropriate or more expensive treatment choices will have the greatest impact.

Why it is important to do this review

Unbranded advertising of prescription medicines is a grey area in pharmaceutical regulation. Even in countries with strong enforcement of prescription-only status, companies are increasingly running condition-oriented advertising campaigns that aim to stimulate sales of prescription-only medicines. These advertisements do not mention the product's brand name but suggest to viewers to 'ask your doctor'. Unbranded advertising may or may not include that a pharmaceutical company is sponsoring the campaign.

The quality and nature of the information provided in such campaigns is very relevant to inform current and future discussions on pharmaceutical regulation. A proposal for a European directive on information to the general public on medicinal products subject to medical prescription, presented in December 2008, foresaw changes to the regulations on medicines advertising (36). The proposal contemplated an expanded role for the pharmaceutical industry

in the provision of information on prescription medicines directly to the public through the Internet and health-related publications.

The ever-increasing scope and complexity of digital advertising and its span across various media outlets poses a challenge to authorities, which are faced with regulatory frameworks that have not kept abreast with these developments (37).

This systematic review will provide needed evidence to inform current policy discussions on the impact of public unbranded campaigns by the pharmaceutical industry in terms of the research evidence and gaps in knowledge about effects on consumers' attitudes, knowledge, health services use, costs and health outcomes. It is important for these discussions to be informed by the existing body of research evidence, including an understanding of current gaps in knowledge about the effects of this intervention.

There is a Cochrane review on mass media interventions and their effects on health services utilisation (38). The review, however, does not mention unbranded advertising by sponsors and excludes the effects on patient and public attitudes, awareness and knowledge. Moreover, the review also excluded online interventions.

We intend to investigate a specific type of intervention both in terms of the agent that is carrying out the intervention (pharmaceutical manufacturers or other entities or actors that are funded by pharmaceutical manufacturers) and the link to marketing of health products. Due to their commercial intent these interventions are likely to differ systematically from mass media interventions by public health agencies.

Additionally, a systematic review specifically focusing on disease-awareness advertising would provide important background information for regulatory decision-making in this domain. The European Commission has carried out public consultations to canvas opinions on potential legislative changes including on the use of different tools to inform the public about prescription-only medicines; such tools included disease-awareness campaigns. However, no evaluation of the responses to those consultations was produced. The only report published made many assertions concerning outcomes based on varying levels of evidence, contained serious methodological flaws (non-representative sampling; selection bias) and was incomplete (39). A rigorous systematic review is therefore needed to shed light on the effects of unbranded advertising.

There are no systematic reviews specifically on this topic as the existing Gilbody 2005 review - now outdated - included both branded and unbranded advertising. The authors did not find any studies that assessed health outcomes. They concluded that while it was clear that DTCA increased prescriptions and market share, there was a void in research of its wider effects. The authors also added that further research on disease awareness campaigns was justified. A number of narrative reviews have examined the issue of disease mongering, including unbranded pharmaceutical advertising (17, 40).

OBJECTIVES

To assess the effects of unbranded advertising of prescription medicines, conducted by or on behalf of pharmaceutical companies, on consumers' attitudes, knowledge, behaviour, health services use, health outcomes and costs.

METHODS

Criteria for considering studies for this review

Types of studies

We anticipate that few if any randomised controlled trials (RCTs) will have assessed the influence of mass media unbranded advertising sponsored by pharmaceutical companies, especially under conditions of usual advertising exposure. We will therefore include a broader range of study designs in this review, including non-randomised studies, guided by the recommendations from Cochrane Effective Practice and Organisation of Care (41) (41).

We will include the following types of studies:

1. Randomised studies:
   - RCTs; and
   - cluster-randomised trials, in which the unit of allocation is a specific unit, such as a regional district or institution, rather than an individual.
2. Non-randomised studies:
   - quasi-RCTs; these trials attempt randomisation but a non-random type of sequence generation is used, such as day of the week, date or birth, or sequence of entry into trial; and
   - controlled before-after (CBA) studies, in which:
     - there are at least two intervention sites and two control sites
     - the timing of the periods for study for the control and intervention groups is comparable (that is, the pre- and post-intervention periods of measurement for the control and intervention groups should be the same); and
     - the intervention and control groups are comparable on key characteristics.
3. Interrupted time series (ITS) studies in which:
   - the intervention occurred at a clearly defined point in time, as described by the researchers; and
   - there were at least three data points before and three data points after the intervention was introduced.
4. Observational studies:
   - controlled cohort studies, in which:
     - a concurrent control group is selected from a similar or the same population as the group with exposure;
     - some form of matching or statistical adjustment is used to minimise the influence of factors other than the exposure of interest; and

- the cohort consists either of a specific population (e.g. residents of a specified region with advertising exposure; a health insurance database) or of a random sample of a population.

We will only include studies from 1990 onwards as mass media channels have diversified quickly over the last 25 years, changing their nature and type of interventions.

Types of participants

Participants will be members of the public (e.g. consumers) who are exposed to specific unbranded advertising campaigns, with subgroup analyses when possible per demographic group (sex, age, setting), as well as per patient group (people diagnosed with a specific condition). We will exclude studies of health professionals since the regulations governing advertising of prescription-only medicines to health practitioners are substantively different from those governing advertising to the general public.

We will exclude studies on individual patient information provided by healthcare professionals (at a doctor's office, clinic, hospital, health centre, pharmacy) for individual patient information purposes; as well as any material or information provided by a pharmaceutical manufacturer to a healthcare professional for use only by the professional. In addition, unbranded advertising by companies that do not sell prescription-only medicines (e.g. medical device manufacturers, natural health product manufacturers, and food, infant formula, and nutritional supplement companies) will be excluded. Moreover, unbranded campaigns about vaccines will also be excluded.

Types of interventions

We will include all types of mass media unbranded campaigns conducted by sponsors where there is no direct reference to a pharmaceutical product's brand name. To be eligible, the information provided must be produced by or on behalf of a pharmaceutical company and the intervention must:

1. include mention of a therapeutic drug class; and/or
2. include mention of a condition or disease to be treated with a product; and/or
3. include other information suggesting a visit to a physician to request a treatment with a pharmaceutical product; and/or
4. stimulate diagnostic testing of a condition for which a pharmaceutical treatment is available.

We will define mass media as in other Cochrane reviews (18-20): "Mass media is defined here as channels of communication such as television, radio, newspapers, billboards, posters, leaflets or booklets intended to reach large numbers of people and which are not dependent on person-to-person contact". As recommended by Mosdøl 2015, we will also include other channels such as campaigns delivered through the Internet, social media and mass distribution through mobile phones.

We will consider a sponsor as any pharmaceutical company that manufactures, produces or distributes a medicine.

We will define advertising as: communication on behalf of a sponsor, or third party acting on its behalf which aims to raise awareness about a specific condition and/or promote or encourage the use of pharmaceutical product(s). This includes both traditional forms of paid communication such as television commercials, and communication in which payment is less explicit, such as online media postings. Advertising is thus not limited to any specific media, but includes print media (newspapers, magazines, leaflets, booklets, posters, pamphlets), online media, broadcast media (television and radio) as well as outdoor advertising (billboards and banners).

We will only consider including studies about hypothetical (i.e. theoretical or experimental, not implemented) unbranded advertising campaigns in our review if the studies are produced or carried out by or on behalf of pharmaceutical companies. Likewise, if the information provided in the study enables us to ascertain that the third party implementing the unbranded advertising campaign is acting on behalf of the sponsor (for instance a patient or user group funded by the sponsor), then that study will be included provided it meets the other inclusion criteria.

We will include studies that compare unbranded advertising with:

- no intervention;
- any information or education activities provided by non-commercial sources;
- branded advertising; or
- another type of unbranded advertising.

We will set no requirements on the minimum length of intervention.

We will exclude:

- interventions by healthcare professionals (at a doctor's office, clinic, hospital, health centre, or pharmacy) for individual patient information purposes;
- any material or information provided by a pharmaceutical manufacturer to the healthcare professional;
- campaigns focusing on vaccination;
- campaigns focusing on medical devices containing no prescription medicine;
- campaigns focusing on over-the-counter medicines (medicines not subject to medical prescription); and
- disease-oriented advertising by companies promoting natural health products, food, infant formula, and nutritional supplements.

Types of outcome measures

We anticipate that the studies included in this review will report a wide variety of outcome measures. The following outcome categories have been identified.

1. Consumer attitudes. This would include positive or negative effects; stigma/acceptance; anxiety/reassurance.

2. Consumer knowledge. This would include accuracy of assessment of disease risks, prognosis, prevalence; knowledge of treatment availability and estimated benefit and harm.
3. Consumer behaviour. This would include both information- and care-seeking behaviours, such as seeking medical advice or visiting the GP or pharmacist), as well as undertaking lifestyle modifications (e.g. quitting smoking, exercise, dietary change).
4. Health services use. This would include effects on health services utilisation such as rates of diagnostic testing (e.g. plasma testosterone levels; bone density; plasma glucose levels); consultations or discussions with healthcare professionals; physician visits in total; physician visits for the advertised condition; other health professional contacts (including pharmacist consultations, mental health professionals etc.); requests for medicines; medicine switches (changes to the pharmaceutical product prescribed).
5. Health service costs, such as: overall costs; medicine use rates (changes in frequency of initiating a new prescription; costs associated with switching from one product to another; changes to the sales volume and to the prescribing volume).
6. Health outcomes associated with a shift in health services use. The outcomes to be assessed include serious adverse events (including hospitalisations and emergency visits); adverse events associated with specific treatments; condition-specific adverse events. No direction of effect is prespecified; shifts in health services use may be associated with either a reduction or an increase in these adverse events.

If more than one outcome measure is available from a study for the same outcome, we will consider the following criteria when selecting an outcome measure.

1. We will select the outcome that has been defined as primary by the study authors.
2. If no primary outcome has been identified, we will choose the outcome measure used in sample size calculations.
3. If no outcome measure is mentioned in the sample size calculations, we will select the most appropriate or relevant outcome measure for the given intervention. This will most likely require further discussion among the authors responsible for data extraction.

Primary outcomes

We have opted to focus mainly on the outcome category of health services use and to select primary outcomes that are objective (not self-reported) and clearly linked to advertising campaigns. Each of these endpoints is also measurable and could be easily combined in a meta-analysis:

1. measures of consumer knowledge;
2. rates of consultations with health professionals; and
3. prescribing rates (including initiation, switching and discontinuation rates).

These outcomes will be measured in terms of the level of change observed and the lag time between the media intervention and the observed effect.

Secondary outcomes

As secondary outcomes of interest, we will include:

1. measures of consumer attitudes on diagnosis and treatment;
2. diagnostic testing rates;
3. fatal and non-fatal serious adverse events, including hospitalisations and emergency visits; and
4. health service costs.

Timing of outcome assessment

We have not established a minimum duration of follow-up for the outcome measures. If data are available, we will present outcomes separately for shorter-term (less than six months) and longer-term follow-up.

Main outcomes for 'Summary of findings' tables

Bearing in mind their relevance to stakeholders and to decision making, we have opted to select outcomes that are clearly linked to advertising campaigns. These endpoints are also measurable and could be easily combined in a meta-analysis. They are:

1. measures of consumer knowledge of diagnosis criteria, disease prognosis, and treatment outcomes;
2. rates of consultations with health professionals;
3. diagnostic testing rates;
4. prescribing rates;
5. fatal and non-fatal serious adverse events, including hospitalisations and emergency visits; and
6. health service costs.

Search methods for identification of studies

We will obtain the assistance of a research librarian with expertise in Cochrane systematic reviews to prepare the electronic search.

Electronic searches

We will start our electronic search from 1990 (as explained in Types of studies). We will search the following electronic databases:

- The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, latest issue)
- MEDLINE (OvidSP) (1990 to present)
- Embase (Embase.com) (1990 to present)
- PsycINFO (OvidSP) (1990 to present)
- SCOPUS (1990 to present)
- CINAHL (EBSCOhost) (1990 to present)

There will be no language restrictions during the electronic searches; translation will be organised as needed through university and Cochrane network contacts. We present the strategy for MEDLINE in Appendix 1. We will tailor strategies to other databases and report them in the review.

Searching other resources

We expect that many of the studies examining the effects of unbranded advertising will be unpublished, internal market studies held by pharmaceutical companies; therefore the usual strategies to find unpublished studies via clinical trial registries, pharmaceutical company websites and regulatory documents are not likely to be successful. We will search the drug industry documents database (www.industrydocumentslibrary.ucsf.edu/drug) and search studies via US court cases on marketing activities from 1990 onwards as well as Lexis Nexis using the following keywords:

- unbranded AND advert*
- (disease OR condition) AND aware*
- condition-oriented campaigns
- disease-oriented campaigns
- disease awareness campaigns
- unbranded acquisition campaigns
- consumer relationship marketing of prescription-only medicines.

We will search reference lists of included studies and relevant systematic reviews. We will also contact experts in the field and authors of included studies for advice as to other relevant studies. Grey literature search methods will include: searching abstracts of world pharmaceutical marketing conferences; contacting industry bodies in key regions (such as EFPIA, IFPMA and PhRMA) as well as searching websites of governmental and non-governmental organisations (in English, French, Spanish, Portuguese, Dutch, Latvian, German and Russian); and citation forward checking from included studies using the Web of Science and Scopus databases.

Data collection and analysis

Selection of studies

Two authors will independently screen all titles and abstracts identified from searches to determine which meet the inclusion criteria. We will retrieve in full text any papers that are identified as being of potential or uncertain relevance by at least one author. Two review authors will independently screen full-text articles for inclusion or exclusion, with discrepancies resolved by discussion and by consulting a third author if necessary to reach consensus. We will list all potentially relevant papers excluded from the review at this stage as excluded studies, and will provide reasons in the 'Characteristics of excluded studies' table. We will also provide citation details and any available information about ongoing studies, and collate and report details of duplicate publications, so that each study (rather than each report) is the unit of interest in

the review. We will report the screening and selection process in an adapted PRISMA flow chart (42).

Data extraction and management

Two review authors will extract data independently from included studies. Two authors will independently assign the outcomes reported in each included study included to the review's outcome categories (see Types of outcome measures) and resolve any differences in categorisation, if they occur, by the involvement of a third author. We will develop and pilot a data extraction form using the Cochrane Consumers and Communication Group data extraction template, and incorporate elements of EPOC data extraction guidance as necessary.

Data to be extracted will include the following items: details of the study (aim of intervention, study design, description of comparison group, participant characteristics and demographics), details of the intervention - such as country, media outlets used, condition/diagnostic/treatment covered, related drug or therapeutic class, duration, primary and secondary outcomes as well as their data and results, sponsorship status (any private funding received by pharmaceutical companies or third parties acting on their behalf, including the name of sponsor, when available), declaration of interests of the authors.

If the focus of a study is an intervention by a patient, consumer or special interest group, we will try to ascertain whether the group receives core or unrestricted funding from a pharmaceutical company, funding for related projects (by subject area), or if the specific campaign is explicitly referred to as being funded by the sponsor, even if conducted by the patient and/or consumer group. If additional information is provided about the details of the funding such as amount or type (core or project funding), these data will be extracted.

Since the quality and accuracy of the information being conveyed is also an important component of the intervention to be taken into consideration, we will also extract, when possible, additional descriptive information, such as numerical data being disseminated, types of risks mentioned and evidence cited to support claims. In addition, should studies examine effects of relevant policy or regulation shifts, these will be noted and extracted.

Outcome data and results of studies will be extracted from included studies during this process. One review author will enter all extracted data into RevMan (43), and a second review author, working independently, will check them for accuracy against the data extraction sheets. We will present details of the included studies in the 'Characteristics of included studies' section.

Assessment of risk of bias in included studies

We will assess and report on the methodological risk of bias of included studies in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (44) and the guidelines of Cochrane Consumers and Communication, which recommend the explicit reporting of the following individual elements for RCTs: random sequence generation; allocation sequence concealment; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; and funding/sponsorship. We will consider

blinding separately for different outcomes where appropriate (for example, blinding may have the potential to affect differently subjective versus objective outcome measures). We will judge each item as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins 2011, and provide a quote from the study report and a justification for our judgement for each item in the 'Risk of bias' table.

RCTs will be deemed to be at the highest risk of bias if they are scored as at high or unclear risk of bias for either the sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias (44).

We will assess and report quasi-RCTs as being at a high risk of bias on the random sequence generation item of the 'Risk of bias' tool. For cluster-RCTs we will also assess and report the risk of bias associated with an additional domain: selective recruitment of cluster participants.

4.1

EPOC guidance recommends using the same nine criteria for assessment of risk of bias for RCTs, non-randomised controlled trials, and controlled before-after studies (45). In addition to the above domains identified in the RCT 'Risk of bias' tool, as per EPOC guidance, we will assess the following: whether baseline outcome measurements are similar, whether baseline characteristics are similar, and whether the study was adequately protected against contamination.

We will report CBA studies as being at high risk of bias on both the random sequence generation and allocation sequence concealment items. We will exclude CBA studies with sites that are not reasonably comparable at baseline.

We will assess and report on the following items for ITS studies: intervention independence of other changes; prespecification of the shape of the intervention effect; likelihood of intervention affecting data collection; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; and other sources of bias such as seasonality.

Other methodological aspects to consider in ITS that could lead to biased results are autocorrelation and non-stationarity. Autocorrelation measures whether data collected close together in time are correlated with each other. For instance, prescription patterns closer to each other may be more similar. Non-stationary data show an underlying trend that is unrelated to the intervention. We will identify both aspects and when present, we will assess whether they have been adjusted for.

For controlled cohort studies, we will use the recently developed Cochrane 'Risk of bias' assessment tool for non-randomised studies of interventions (46). This includes an assessment of whether or not the study authors have adequately adjusted for a set of prespecified confounders. Potential confounders are defined as factors associated both with likelihood of exposure to unbranded advertising and to measured outcomes. Based on research on branded DTCA (17), key identified confounders include age (younger versus older adults), sex, and socio-economic status and/or insurance status/price sensitivity.

We will also include risk of bias associated with the source of funding (47). This is especially important in an analysis of unbranded advertising by pharmaceutical companies as a commercial sponsor may have a strong incentive for a specific result.

Should any of the studies to be included be authored or co-authored by members of the review author team, data extraction and assessment of risk of bias of those studies will be undertaken by two members of the author team not involved in the primary publication.

In all cases, two authors will independently assess the risk of bias of included studies, with any disagreements resolved by discussion to reach consensus or by third review author adjudication if consensus is not reached. We will contact study authors for additional information about the included studies, or for clarification of the study methods as required. We will incorporate the results of the 'Risk of bias' assessment into the review through standard tables, and systematic narrative description and commentary about each of the elements, leading to an overall assessment the risk of bias of included studies and a judgment about the internal validity of the review's results. We will report risk of bias for multiple study designs (RCTs, CBA studies, ITS studies) using EPOC's suggested table (48). ROBINS-I 2016 (46) will be used for controlled cohort studies.

Measures of treatment effect

In RCTs, for dichotomous outcomes, we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the risk ratio (RR) and 95% confidence interval (CI), using a random-effects model for meta-analysis. For rare outcomes (< 1%) a Peto odds ratio (OR) will be used. For continuous measures, we will analyse data based on the mean, standard deviation (20) and number of people assessed for both the intervention and comparison groups to calculate mean difference (MD) and 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in Review Manager 5.

For CBA studies, we will calculate effect measures for dichotomous outcomes (RR) and for continuous outcomes (relative % change post intervention).

For ITS studies, we will look into the change in level of the outcome at the first point after the introduction of the intervention, and the post-intervention slope minus the predicted outcome based on the pre-intervention slope only (49). We will calculate these estimates from regression models adjusting for autocorrelation. If an ITS study has not reported an appropriate analysis but provides the data points, we will consider re-analysing the data using segmented time series regression techniques (49, 50).

For controlled cohort studies we will use generic inverse variance analysis, based on the logs of hazard ratios (HR) and OR and the standard error of log HR or OR, adjusted for confounding factors.

Unit of analysis issues

If cluster-RCTs are included we will check for unit of analysis errors. If errors are found, and sufficient information is available, we will re-analyse the data using the appropriate unit of analysis, by taking account of the intracluster correlation (ICC). We will obtain estimates of the ICC by contacting authors of included studies, or impute them using estimates from external sources. If it not possible to obtain sufficient information to re-analyse the data we will report effect estimates and annotate 'unit of analysis error'.

Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome, or summary data). Unsuccessful attempts to retrieve data will be duly reported (i.e. no data available; did not reply; did not provide data). For participant data, we will, where possible, conduct analysis on an intention-to-treat basis; otherwise data will be analysed as reported. We will report on the levels of loss to follow-up and assess this as a source of potential bias. For missing outcome or summary data we will impute missing data where possible and report any assumptions in the review. We will investigate, through sensitivity analyses, the effects of any imputed data on pooled effect estimates.

Assessment of heterogeneity

We will report on the rationale behind any decision to pool or not to pool studies after assessing clinical and methodological heterogeneity, and considering characteristics of participants, interventions, comparisons and outcomes.

Where studies are considered similar enough (based on consideration of populations, interventions and outcomes, and study methodology) to allow pooling of data using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots and by examining the Chi^2 test for heterogeneity. Heterogeneity will be quantified using the I^2 statistic. An I^2 value of 50% or more will be considered to represent substantial levels of heterogeneity, but this value will be interpreted in light of the size and direction of effects and the strength of the evidence for heterogeneity, based on the P value from the Chi^2 test (44).

Where we detect substantial clinical, methodological or statistical heterogeneity across included studies we will not report pooled results from meta-analysis but will instead use a narrative approach to data synthesis. In this event we will attempt to explore possible clinical or methodological reasons for this variation by grouping studies that are similar in terms of populations, intervention features and outcomes, and study methodology to explore differences in intervention effects.

Assessment of reporting biases

We will assess reporting bias qualitatively based on the characteristics of the included studies (e.g. if only small studies that indicate positive findings are identified for inclusion), and if information that we obtain from contacting experts and authors or studies suggests that there are relevant unpublished studies.

If we identify sufficient studies (at least 10) for inclusion in the review we will construct a funnel plot to investigate small study effects, which may indicate the presence of publication bias. We will formally test for funnel plot asymmetry, with the choice of test made based on advice in Higgins 2011, and bearing in mind when interpreting the results that there may be several reasons for funnel plot asymmetry.

Data synthesis

Studies of different designs will be analysed separately. When possible, we plan to analyse RCTs, quasi-RCTs and cluster-RCTs jointly. We will decide whether to meta-analyse data based on whether the interventions in the included trials are similar enough in terms of intervention type, comparison and outcome measures to ensure meaningful conclusions from a statistically pooled result. Due to the anticipated variability in populations and intervention types of included studies, we will use a random-effects model for meta-analysis.

We plan to meta-analyse the data obtained from CBA and/or ITS studies, whenever possible, using a generic inverse-variance weighted average. If we are unable to pool the data statistically using meta-analysis we will conduct a narrative synthesis of results. We will group the data based on the category that best explores the heterogeneity of studies and makes most sense to the reader (i.e. by interventions, populations or outcomes). Within each category we will present the data in tables and narratively summarise the results.

We will carry out separate meta-analysis of controlled cohort data if these are possible, for example if studies with similar enough designs, interventions, and outcomes are found for results to be meaningfully combined. In this case we will use generic inverse variance to combine OR or HR and maintain the authors' adjustments for potential confounders.

Should meta-analysis not be possible, we will provide descriptive statistics for CBA, ITS and controlled cohort studies. Descriptive statistics could include median effect sizes, inter-quartile ranges or other measures, and this information could be presented graphically using bar charts or other approaches.

We plan to conduct the following comparisons:

- Unbranded advertising versus no advertising
- Unbranded advertising versus branded advertising
- Unbranded advertising from sponsors or parties acting on their behalf versus information and education activities from non-commercial sources
- Comparisons between different types of unbranded advertising (for instance, traditional unbranded advertising versus unbranded advertising in social media)
- Comparisons between unbranded advertising campaigns for two different drugs.

Subgroup analysis and investigation of heterogeneity

In the presence of sufficient numbers of studies, subgroup analyses may be conducted to explore heterogeneity, using a significance test for interactions for subgroup differences and an I^2 statistic. We plan to carry out a priori subgroup analyses for effects of on- and off-label campaigns if possible, and will contact authors to obtain additional data to carry out these

subgroup analyses if the results have not been reported separately in the primary study. Mixed (on and off) campaigns will be subject to a second level of coding for primary message on- or off-label and will be classified based on the primary message. We will test for interaction effects between subgroups of on- and off-label use, and present the results of subgroup analyses. If outcomes do not differ, however, we will calculate the combined effects as well and will present these outcomes. If there are significant interaction effects (Chi^2 for interaction effects < 0.05), we will present subgroup outcomes separately.

The other factors we may also consider for exploratory subgroup analyses are:

- intervention characteristics
  - type of media used (online versus all other types of media);
  - length and intensity of intervention;
  - multiple media versus single media; and
  - setting (lower-/middle-income countries versus high-income countries, as per World Bank country income levels);
- influences of age and gender;
- chronic conditions versus other conditions; and
- influence of type of prescriber (medical practitioners versus other healthcare professionals).

In the event that substantial clinical, methodological or statistical heterogeneity across studies precludes meaningful combining of data, we will attempt to explore possible clinical or methodological reasons for this variation by grouping studies that are similar in terms of target groups, intervention characteristics, methodological features or other factors to explore differences in intervention effects.

Sensitivity analysis

Sensitivity analyses will be conducted to determine the robustness of the results. These may include but are not restricted to undertaking both fixed-effect and random-effects meta-analyses, excluding outlier studies or excluding poorer quality studies to explore the robustness of results. In addition, any methodological decisions undertaken during the course of the review (e.g. combining different study designs; imputation of missing data) will be subjected to sensitivity analyses.

'Summary of findings' table

We will prepare a 'Summary of findings' table to present the results of meta-analysis, based on the methods described in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions (51). We will present the results of meta-analysis for the major comparisons of the review, for each of the major primary outcomes, including potential harms, as outlined in Types of outcome measures. We will provide a source and rationale for each assumed risk cited in the table(s), and will use the GRADE system to rank the quality of the evidence using

the GRADEprofiler (GRADEpro) software (51). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format, such as that used by Chan 2011.

Ensuring relevance to decisions in health care

The review will inform current policy discussions on the impact of public unbranded campaigns by the pharmaceutical industry in terms of the research evidence, and gaps in knowledge, about effects on consumers' attitudes, knowledge, health service use, costs and health outcomes. It is important for these policy discussions to be informed by the existing body of research evidence, including an understanding of current gaps in knowledge about effects of this intervention.

The review will receive feedback from at least one consumer referee in addition to a content expert as part of Cochrane Consumers and Communication's standard editorial process. This protocol has also been reviewed by members of an advisory consumer panel - Ilaria Passarani and Signe Mezinska - whom we thank for their input and contribution.

ACKNOWLEDGEMENTS

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SUPPLEMENTARY DATA

APPENDIX 1. MEDLINE search strategy

1. prescription drugs/
2. (prescription adj (drug* or medicin* or medication* or pharmaceutic*)).ti,ab,kw.
3. drug industry/
4. (sponsor* or awareness or campaign*).ti,ab,kw.
5. (1 or 2 or 3) and 4
6. ((compan* or corporat* or industry) adj10 sponsor*).ti,ab,kw.
7. (drug* or medicin* or medication* or pharmaceutic* or prescription*).mp.
8. 6 and 7
9. 5 or 8
10. exp marketing/
11. (market* or adverti*).ti,ab,kw.
12. (health adj (promotion or education or communication)).mp.
13. campaign*.ti,ab,kw.
14. public relations/
15. persuasive communication/
16. (public relation* or publicity or public information or (communication adj (program* or strateg*)) or positive framing).ti,ab,kw.
17. mass media.mp.
18. or/10-17
19. 9 and 18
20. (prescri* and (market* or adverti* or promot* or campaign* or public relations or publicity or mass media or sponsor*)).hw,ti.
21. disease awareness.ti,ab,kw.
22. (unbranded or nonbranded or non-branded or condition brand* or condition orient* or disease orient*).ti,ab,kw.
23. (consumer relation* marketing or sponsored advert*).ti,ab,kw.
24. ((disease specific or informational or help seeking) adj5 (adverti* or DTC* or campaign*)).ti,ab,kw.
25. (drug* or medicin* or medication* or pharmaceutic* or prescription*).mp.
26. or/21-24
27. 25 and 26
28. 19 or 20 or 27

CHAPTER 4.2

COMPLIANCE OF DISEASE AWARENESS CAMPAIGNS IN PRINTED DUTCH MEDIA WITH NATIONAL AND INTERNATIONAL REGULATORY GUIDELINES

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ABSTRACT

Background

The European legislation prohibits prescription-only medicines' advertising but allows pharmaceutical companies to provide information to the public on health and diseases, provided there is no direct or indirect reference to a pharmaceutical product. Various forms of promotion have become increasingly common in Europe including 'disease-oriented' campaigns.

Objectives

To explore examples of disease awareness campaigns by pharmaceutical companies in the Netherlands, by assessing their compliance with the World Health Organization (WHO) Ethical Criteria for medicinal drug promotion and the Dutch guidelines for provision of information by pharmaceutical companies.

Methods

Materials referring to health/disease and treatments published in the most widely circulated newspapers and magazines were collected from March to May 2012. An evaluation tool was developed based on relevant underlying principles from the WHO ethical criteria and Dutch self-regulation guidelines. Collected disease awareness advertisements were used to pilot the evaluation tool and to explore the consistency of information provided with the WHO and Dutch criteria.

Findings

Eighty materials met our inclusion criteria; 71 were published in newspapers and 9 in magazines. The large majority were news items but 21 were disease awareness advertisements, of which 5 were duplicates. Fifteen out of the 16 disease awareness campaigns were non-compliant with current guidelines mainly due to lack of balance (n=12), absence of listed author and/or sponsor (n=8) , use of misleading or incomplete information (n=5) and use of promotional information (n=5). None mentioned a pharmaceutical product directly.

Conclusion

Disease Awareness Campaigns are present in Dutch printed media. Although no brand names were mentioned, the lack of compliance of disease awareness campaigns with the current regulations is alarming. There were information deficiencies and evidence of information bias. A key concern is that the context in which the information is provided, mostly through indirect referral, is likely to support treatment with the sponsor's product.

INTRODUCTION

In 1988, the World Health Organization established the Ethical Criteria for Medicinal Drug Promotion, defining promotion as "all informational and persuasive activities of manufacturers and distributors that affect the prescription, supply, purchase and/or use of medicinal drugs" (1). While not legally binding, these criteria include a set of guiding principles that can be adapted to national circumstances.

Advertising of prescription drugs to the public – also known as direct-to-consumer advertising (DTCA) – is controversial and only allowed in the United States and New Zealand. European legislation prohibits advertising of products that have prescription-only status, aiming to protect public health. Despite this prohibition, however, manufacturers are using an increasing array of techniques to advertise these medicines to the public both directly and indirectly (2).

Media and communication channels are key influencers of consumer decisions, helping to shape consumers' information and options, also on health and treatment (3). Media can also exert a powerful influence over human behaviours and public policy (4). Health topics are often covered in printed media and they can include factual information on diseases and conditions but also treatment information of promotional nature (5,6).

In Europe, pharmaceutical companies are explicitly allowed to provide general information to the public on human health and diseases, as long as there is no reference, even indirectly, to a specific medicinal product (7). This provision enables companies to run unbranded 'disease-awareness' or 'help-seeking' advertisements (8). These materials draw viewers' attention to certain health conditions by focusing on symptoms and suggesting the public to 'ask their doctors' for newly available treatment information (9). Such campaigns are not subject to any specific regulations governing pharmaceutical promotion, nor pre-clearance. They represent a grey area in regulation since regulators are reluctant to consider them to be product-specific promotion unless they include explicit links to branded information (10).

Disease awareness campaigns (DACs) can educate the public about disease, make consumers aware of untreated health problems and lead them to seek effective care at earlier stage, thus leading to better health (11). Advocates consider disease awareness campaigns to be particularly important for under-diagnosed diseases (12). However, concerns have been raised about the quality and nature of the information being provided to the public in disease awareness campaigns (13). Proponents of direct to consumer advertising claim that it empowers consumers by stimulating discussions with physicians, enabling patients to obtain needed treatment at an earlier stage and improving adherence. Evidence shows, nevertheless, that exposure to advertisements increases prescribing volume and patient demand and that it shifts prescribing into less cost-effective choices. In addition, there is no evidence of improved adherence, nor treatment quality or early provision of needed care (14). In a similar trend, albeit scarce, there is evidence that disease awareness campaigns can lead to increases in consultation rates and prescriptions for the advertisers' product (15). If campaigns support use of newer, more expensive products with least well understood benefit-harm profiles, over cheaper, well-known,

older medicines, they can lead to increases in consultations, inappropriate prescribing and more adverse drug reactions and drug-induced harm, as well as increases in hospitalisations, thus affecting both quality and costs of care (9). While much research has been done in other areas of traditional drug promotion, far less is known about how these campaigns influence both physicians and the public, or on their compliance with the current regulatory framework (16).

In the Netherlands, a self-regulatory approach is used to oversee medicines' advertising (17). In April 2011, the Foundation for the Medicinal Products' Advertising Code (CGR) published a set of guidelines on the provision of disease and treatment information about prescription-only medicines by pharmaceutical companies to the public, thus aiming to define the boundary between information and advertising (18).

Nevertheless, there is no instrument available to assess the compliance of disease awareness campaigns with the provisions included in the WHO Ethical Criteria for Medicinal Drug Promotion or in the Dutch self-regulation guidelines.

Evaluating the quality and nature of the information provided in disease awareness campaigns is very relevant to policy discussions at European level. The proposal for a European directive on information to the general public on medicinal products subject to medical prescription, presented by the European Commission in December 2008, foresaw changes to the regulations on advertising. It contemplated an expanded role for the pharmaceutical industry in the provision of information on prescription medicines directly to the public (19). This study aims to inform future European policies regulating the dissemination of disease and treatment information to the public by the pharmaceutical industry. This article assesses the frequency of occurrence of disease awareness campaigns in printed media in the Netherlands and measures their compliance with current guidelines.

OBJECTIVES

The aim of our research was threefold:

1. To assess the frequency of occurrence of medicines' promotion and disease awareness campaigns in printed media in the Netherlands.
2. To develop a user-friendly instrument to assess the compliance of disease information campaigns.
3. To use this instrument to measure compliance of disease information campaigns, including those disseminated by pharmaceutical companies, in Dutch printed media.

METHODS

Assessing disease-awareness campaign frequency in major print media

We examined high-circulation print media, which included three paid daily newspapers, three free daily newspapers and eight paid monthly magazines (20). Data collection took place over three months (March to May 2012 inclusive). The three free newspapers were collected at train stations whereas the 14 paid publications were accessed in public libraries. Two authors (AMF

and TLA) independently selected materials based on the inclusion criteria outlined below. If there were disagreements, these were to be resolved by consensus. Consensus was reached in all cases.

Our **inclusion criteria** were based on an interpretation of legal provisions, which prohibit direct and/or indirect reference to a pharmaceutical product. Firstly, we included all materials which addressed health and treatment issues. Materials on nutraceuticals, homeopathic products, over-the-counter medicines and vaccines were excluded, as they are governed by different legislation. Secondly, we selected all materials which covered one or more of the following four sets of linked information: (1) symptoms/health issues (for prevention purposes)/diseases/ conditions AND a specific prescription-only medicine or a therapeutic drug class; (2) symptoms/ health issues (for prevention purposes)/diseases/ conditions AND a doctor or website referral / a description of a drug's mechanism of action or a suggestion to seek further treatment; (3) name or the logo of a pharmaceutical company AND mention of a symptom/problem/condition or referred to a website; and (4) reference to disease management programmes and discussion of adding another medical product to the ongoing treatment regimen. Finally, materials were then separated into two groups: disease awareness campaigns (Group I) – which included no author and were to be assessed using the instrument – and news items (Group II) – editorial content which included an author or was attributable to the news desk.

Additional descriptive data which were also recorded included: type of publication where materials were found (Paid or Free); printed media frequency; topic; reference to non-pharmaceutical interventions; reference to changes in the quality of life (either positive or negative); referral to visit a physician; reference to a clinical expert; referral to a website; reference to a patient organization or support group; reference to a brand-name, use of company's name or logo, and reference to the availability of a new medicine or treatment option.

Instrument development

The instrument (originally developed in Dutch and then translated into English) is based on seven relevant criteria from the WHO Ethical Criteria for Medicinal Drug promotion (1) and the KOAG/CGR guidelines (17). These were identified by overlapping the relevant provisions within the two sets of regulatory guidelines that can be used to judge the content and quality of disease-oriented information (Table 1). These are promotional information, misleading or incomplete information, use of fear, inadequate language, lack of balance, use of testimonials and absence of listed author and/or sponsor. These criteria were translated into evaluation statements to judge whether or not a principle is being adequately applied (compliant, non-compliant and not applicable). An option to insert additional comments was also included. A reference to a company's name or logo in a disease awareness campaign was not considered sufficient for a material to be deemed non-compliant.

Three external reviewers (pharmaceutical policy researchers) tested the instrument using three examples of disease awareness campaigns by the pharmaceutical industry, previously published in European printed media. As a result, five statements were altered. Changes included merging, division or rewording of statements. The final instrument is included as Table S1.

TABLE 1. Overlap between relevant provisions within the WHO Ethical Criteria for Medicinal Drug Promotion and the CGR Guidelines for provision of information on prescription medicines

WHO Ethical Criteria	CGR Guidelines	Relevant criteria identified
Article 6. Definition of promotion: "all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs."	Introduction. Definition of promotion: "all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs."	Promotional information
Article 7. "Promotional material should not be designed so as to disguise its real nature."	Introduction. "Instances whereby prescription medication or pills are being mentioned without indicating the drug's brand name or company name" are considered indirect reference, for example when naming the active ingredients or the drug's mechanism of action.	
Article 9. "Scientific and educational activities should not be deliberately used for promotional purposes."	Article 5. "Information may not encourage irrational use of prescription medicines nor the search for unnecessary treatment."	
Article 14b. "Advertisements to the public should not generally be permitted for prescription drugs or to promote drugs for certain serious conditions that can be treated only by qualified health practitioners."	Article 6. "Information may not directly or indirectly lead to the choice of a particular medicine from different a vailable treatments."	
Article 7 . "Advertisements may claim that a drug can cure, prevent, or relieve an ailment only if this can be substantiated. … All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks."	Article 3. "Information may not be misleading. The information provided must comply with the most recent evidence and practice standards. The information must be factually correct and may not contain any misleading elements."	Misleading or incomplete information

TABLE 1. (continued)

WHO Ethical Criteria	CGR Guidelines	Relevant criteria identified
	Article 17. "No comparison is allowed between relevant treatments and medicines that suggests that the effects of a treatment with a prescription drug are better or equal than those of another relevant treatment or drug." 21.2 b) "No single option for treatment is to be highlighted, for instance by using words, colours or images, different font types, markings or any other elements. " Article 21.2 d) "Treatments should be cathegorised based on acceptable formats. For instance using therapeutic classes or categories, or through therapeutic guidelines. Using expressions such as "most recent, or new is better, most commonly used, is not allowed." Article 23. "Information should be displayed objectively and neutrally and must not contain information which relates directly to a specific treatment. When reference is made to specific treatment guidelines, the source must be listed…References to scientific literature should also be published…"	
Article 14: "While they [advertisements] should take account of people's legitimate desire for information regarding their health, they should not take undue advantage of people's concern for their health."	Article 9."Information should not aim nor encourage the public to seek unnecessary treatment, advice or further examination; nor on the other hand refrain the public from seeking treatment, advice or further examination." Article 5. "Information may not encourage irrational use of prescription medicines nor the search for unnecessary treatment."	Use of Fear
Article 15. "Language which brings about fear or distress should not be used."	Article 4. "Information should not boost or amplify feelings of fear and superstition and should be displayed realistically."	

TABLE 1. (continued)

WHO Ethical Criteria	CGR Guidelines	Relevant criteria identified
	Article 20. "The information may not be unjustified, unnecessarily alarming or misleading images of changes to the human body resulting from illness or disease."	
Article 29. "The wording …if prepared specifically for patients, should be in lay language on condition that the medical and scientific content is properly reflected."	Article 7. "Information should be tailored to the average consumer and have understandable language. Medical and scientific terms should be avoided as much as possible, to avoid confusion."	Inadequate Language
Article 7. "All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks… Comparison of products should be factual, fair and capable of substantiation".	Article 9."Information should not aim nor encourage the public to seek unnecessary treatment, advice or further examination; nor on the other hand refrain the public from seeking treatment, advice or further examination." Article 17. "No comparison is allowed between relevant treatments and medicines that suggests that the effects of a treatment with a prescription drug are better or equal than those of another relevant treatment or drug." Article 21. "Information should be as balanced and complete as possible. It should reflect the state-of-the-art. When providing information, all relevant factors should be taken into account. All information should be equally displayed both in content and layout, with the same amount of detail." Article 21.2 c) "The positive and negative effects of a treatment are not to be emphasized in such a way that the pros or the cons of a given treatment are highlighted".	Lack of Balance

TABLE 1. (continued)

WHO Ethical Criteria	CGR Guidelines	Relevant criteria identified
	Article 21.2 d) Information about different therapeutic interventions can be provided. In that case, all relevant treatments should be named, including pharmacotherapy and other interventions, such as adjustments to lifestyle, nutrition and habits. Relevant treatments are the standard of care provided, as per treatment guidelines. Completeness ensures that no information is deliberately omitted. When enumerating all the pharmacotherapeutic options for treatment, all the relevant prescription drugs for the specific treatment are to be mentioned."	
Article 7. "Promotional material should not be designed so as to disguise its real nature." Article 9. "Scientific and educational activities should not be deliberately used for promotional purposes."	Article 18. "Testimonials should portray the opinion or experience of the user truthfully (not that of a professional or any other public figure). They should not include any comparison of the user's situation before and after drug treatment…Before/after testimonials are not allowed because they can lead the public into false expectations regarding the speed of the treatment's effects".	Testimonials
Article 7. "Advertisements may claim that a drug can cure, prevent, or relieve an ailment only if this can be substantiated. … All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks."	Article 22. "Each message is to contain the name of the person responsible for the information".	Absence of Source/ Author

TABLE 1. (continued)

WHO Ethical Criteria	CGR Guidelines	Relevant criteria identified
	Article 23. "Information may refer to scientific studies and results…The source must always be included. The studies and the results that are mentioned must always come from other sources than the medicine's producer and should be verifiable…" "Information should be displayed objectively and neutrally and must not contain information which relates directly to a specific treatment. When reference is made to specific treatment guidelines, the source must be listed…References to scientific literature should also be published…"	

Assessing compliance of disease awareness campaigns with guidelines

As the instrument is based on legal guidelines, the existence of a single non-compliant statement is sufficient to consider the material to be non-compliant. Two authors (TLA and AMF) independently assessed each of the seven criteria for all disease awareness campaigns and differences in scoring were discussed and resolved by consensus. Any remaining disagreements were then adjudicated to a third author (AMT). The frequencies of the information provided in both groups were measured using the risk ratio (RR). When information was absent, a cell in Table 2 obtained a zero and no RR could be calculated. This was dealt by adding 0.5 to every cell in Table 2 to be able to calculate an estimate of the RR (21). Whenever possible, data analysis was conducted using SPSS version 20.0 (SPSS Inc. Chicago, Illinois, USA).

RESULTS

Assessing disease-awareness campaign frequency

On average six materials covering disease and treatment information were published per week. A total of 80 materials were collected, 59 of which were news items (73,8%), whereas 21 were disease awareness campaigns (26.3%) (Table 2). Five of these disease awareness campaigns were duplicates - published in different printed media - leaving 75 materials for further description and 16 materials for the compliance analysis.

Overall (n=80) the seven most commonly mentioned conditions were: allergies and respiratory diseases (n=22; 28%), diabetes (n=7; 9%), cardiovascular diseases (n=5; 6%), cancer (n=5; 6%), contraception (n=4; 5%), Attention Deficit Hyperactivity Disorder (ADHD) (n=4; 5%) and pain (n=4; 5 %). Within disease awareness campaigns, allergies and respiratory diseases, and contraception were common topics. Most notably, all the disease awareness duplicates regarded allergies and respiratory diseases. One disease awareness campaign was sponsored by a patient organisation.

Disease awareness campaigns were significantly more frequent in free publications (RR = 2.8, 95% CI 1.7; 4.5) and in health-related supplements (RR = 3.4, 95% CI 1.9; 5.6). When comparing news to disease awareness campaigns as to the information provided, the latter were more likely to mention a pharmaceutical company (RR = 2.8, 95% CI 1.1; 6.8), a website (RR = 5.3, 95% CI 2.8; 10.1) or a visit to the general practitioner (RR = 2.2, 95% CI 0.9; 5.16) but less likely to include a brand-name (RR = 0.3, 95% CI 0.04; 2.2) (Table 2).

Assessing compliance of disease-awareness campaigns with guidelines

The initial inter-rater agreement in the assessment of overall compliance was of 88%; disparities between assessors were arbitrated by the fourth author. Fifteen out of the sixteen materials assessed were non-compliant with the guidelines. Non-compliance was more frequent due to lack of balance, absence of listed author and/or sponsor, use of promotional information or use of misleading or incomplete information (Table 3, Figure 1). Interestingly, most instances of non-compliance with the misleading or incomplete information criterion involved a lack of references.

TABLE 2. Material Characteristics

Type of publication	Group 1 Disease awareness campaigns (n=21) (% within group)	Group 2 News items (n=59) (% within group)	Risk Ratio (95% CI)
All publications			
Paid	5 (24%)	43 (73%)	
Free	16 (76%)	16 (27%)	**2.8 (1.7; 4.5)**
Publication frequency			
Daily	5 (24%)	38 (64%)	
Weekly	2 (9%)	3 (5%)	
Monthly	0 (0%)	4 (7%)	
Occasionally	14 (67%)	14 (24%)	
Health Supplements	15 (71%)	13 (22%)	**3.4 (1.9; 5.6)**
Information included			
Non-pharmaceutical interventions in addition to therapy	5 (31%)	19 (32.2%)	0.9 (0.4; 2.2)
Suggestion to visit the general practitioner	6 (37%)	10 (17%)	2.21 (0.9; 5.1)
Reference to a Clinical expert	3 (19%)	14 (24%)	0.8 (0,3; 2.4)
Website	13 (81%)	9 (15%)	**5.3 (2.8; 10.1)**
Patient or support group	6 (37%)	9 (15%)	2.45 (1.0; 5.9)
Pharmaceutical company	6 (37%)	8 (8%)	**2.8 (1.1; 6.8)**
Brand name	0 (0 %)	10 (17%)	**0.3* (0.0; 2.2)**
New medicine or treatment option	2 (12%)	15 (25%)	0.5 (0.1; 1.9)

* RR calculated by adding 0.5 to all cells.

TABLE 3. Examples of non-compliance per key criteria from the disease awareness campaigns

KEY criteria	Problem identified	Example *(CONDITION)*
Promotional information	Reference to pharmaceutical products to treat a condition or disease in combination with: the name, logo and website of a pharmaceutical company; or a website for a disease awareness campaign; or quick response codes to dedicated websites.	"We are an international company with expertise in lung diseases…we develop innovative pharmaceutical solutions…" *(Respiratory diseases)* A dedicated website is mentioned in big and bold typeface, as well as the name, logo and website of a pharmaceutical company. (*Contraception)* "X strives respond to challenging medical conditions through innovative approaches. Pain treatment is one of our priorities… physical and emotional challenges borne by pain patients are key. Our R&D programme seeks alternative solutions to fight pain." *(Pain)* "Our website helps you to choose the best treatment for your lifestyle. You will be able to find information about all therapies…and also do a test to help you select a suitable treatment." *(Kidney Failure)*

TABLE 3. (continued)

KEY criteria	Problem identified	Example *(CONDITION)*
		"Do you have, or someone close to you has, urinary incontinence? Have a look at our different links: (company) website; your digital logbook for your mobile phone; your online digital logbook to share with your doctor." *(Urinary incontinence)*
Misleading or incomplete information	No reference is provided on the sources of information provided about prevalence of disease.	"One out of every 8 adults in the Netherlands has high cholesterol". (*Cardiovascular diseases)* "One out of each 10 Dutch has asthma …"one out of every 5 Dutch has hay fever". *(Allergies)* "More than 5000 people get post-traumatic dystrophy every year." *(Post-traumatic dystrophy)* "Approximately 40.000 Dutch suffer from renal disease. There are several treatments available for this debilitating disease." *(Kidney Failure)* "One third of those who suffer from migraine in the Netherlands do not get the appropriate treatment…2.5 million Dutch suffer from migraine." (*Migraine)*
Use of fear	Reference to disability caused by the disease, either through text or picture.	An image of a disabled hand is used. *(Post-traumatic dystrophy)* "Besides the pain…migraine also has implications for society…it costs the Netherlands 1.7 billion per year… I have seen people who cannot fulfil their dreams…. That is terrible… *(Migraine)*
Inadequate language	Uses medical terminology	"Perinasal inflammation…abscesses…metabolic diseases…" *(Alarm signals)*
Lack of balance	More emphasis on the benefits of pharmaceutical treatment than risks. Symptoms are accentuated by layout and/or enumeration. Risk factors are portrayed as diseases. Treatment is accentuated.	"This disease can have a great impact on the individual and its environment. It disturbs your daily life. It is important to diagnose it at an earlier stage, so that treatment can begin quickly. Therapy includes anti-inflammatory drugs and painkillers." *(Post-traumatic dystrophy)* "These symptoms can seem mild, but they can have a great impact on your daily life, at school or at work, and even disturb your sleep patterns". "Symptoms such as shortness of breath, cough and wheeziness result in an asthma attack...Red and itchy eyes, running nose, stuffy nose, sneezes and tiredness can have serious implications." *Allergies)* Symptoms are referred to in headings in big and bold typeface. *(Allergies) (Alarm signals) (Urinary incontinence)*

TABLE 3. (continued)

KEY criteria	Problem identified	Example *(CONDITION)*
		"…when you have high cholesterol, you have a higher risk of developing cardiovascular diseases… you can reduce that risk by…treating your high cholesterol levels. Have a look at our new website about healthy living with lower cholesterol". (*Cardiovascular diseases)* "Now women are able to choose a pill that contains a natural hormone and a progestogen. This natural hormone is easily absorbed by the body…this pill has a neutral effect on acne, weight-gain and blood pressure…your periods will be shorter and lighter..." *(Contraception)* Contraception is mentioned on six occasions in big and bold typeface. *(Contraception)* The sentence: "I (do not) want a pill" and the address of a dedicated website are included in big and bold typefaces. *(Contraception)* "…suffering from migraine, days in a row, a pain impossible to bear…with nausea, and sensitivity to light and noises…seek a good treatment…Medicines play an important role…we advise patients to try two different triptans…" (*Migraine)*
Use of testimonials	Specialist mentions treatment and specific drug classes A comparison is made of the patient's experience before and after treatment with a specific drug.	"The doctor can prescribe anti-histamines…or corticosteroids… immunotherapy can be considered an option". (*Allergies)* "I had tummy and back aches with another pill. I visited my doctor and together we have chosen a new pill with a different ingredient. That has helped". " The first pill I took caused weight-gain and emotional changes. My GP then prescribed a lighter pill and I am feeling fine". *(Contraception)*
Absence of author and/or sponsor	No author and/or sponsor identified.	(Allergies), (Alarm signals), (Cardiovascular diseases), (Contraception), (Migraine)

Most notably, five out of the sixteen materials included the logo or name of a pharmaceutical company, referred to a particular condition and mentioned a treatment indirectly. Other four materials discussed a condition and indirectly a treatment, while including a referral to a website sponsored by a pharmaceutical company. Table 3 provides examples of non-compliance aggregated per key criteria and disease awareness campaign topic.

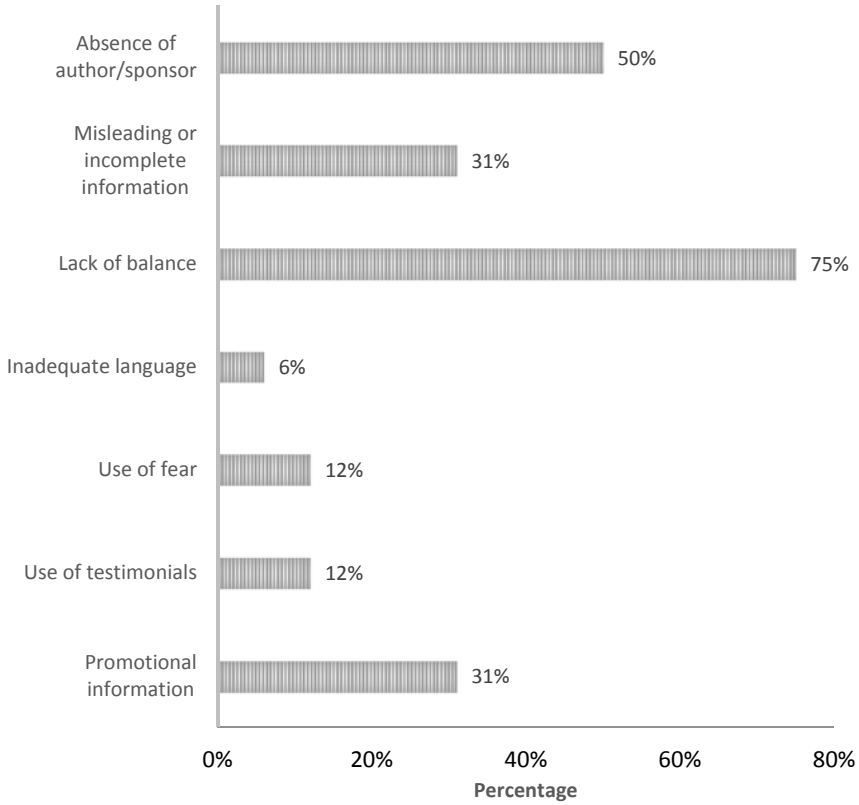

FIGURE 1. Non-compliance of disease awareness campaigns (n=16) per key criteria. Fifteen out of the sixteen materials assessed were non-compliant with the guidelines. Non-compliance was more frequent due to lack of balance, absence of listed author and/or sponsor, use of promotional information and misleading or incomplete information.

DISCUSSION

In this study we have shown that there is a focus on disease and treatment information in printed media in the Netherlands, both through news items and disease awareness campaigns. The majority of disease awareness campaigns identified during our study period did not comply with the WHO ethical criteria nor with the current Dutch self-regulation guidelines.

Most collected materials on health and treatment were news items (74%). On average there were at least five news items published every week and seven disease-awareness campaigns published every four weeks. Our results seem to indicate that pharmaceutical companies often opt to reach a wider audience by publishing their unbranded product advertisements in free media outlets, most notably in dedicated health-supplements. The frequency of occurrence of disease awareness campaigns observed in our study is consistent with the results of an Australian study, where a total of sixty campaigns were identified in popular women's magazines

over eleven months (22). From these, fifteen contained a corporate brand or logo – a result also similar to ours.

The findings on low compliance are worrying, since serious information deficiencies in disease awareness campaigns result in information bias. A key concern is that the context in which the information is provided will be biased towards supporting treatment with the sponsor's product. One third of the disease awareness campaigns in our study referred readers to their physicians. Disease awareness campaigns can stimulate patients' intentions to make requests to doctors for prescription medicines products, increase consultation rates as well as prescriptions for the advertiser's product (15,23). A survey in Australia has shown that 26,9 % of the 800 patients enquired had approached their GP to discuss a treatment they had heard about in the media. Half of the patients reported that their inquiry had resulted in a treatment; more than forty-eight percent of those receiving treatment, reported being prescribed a medicine (5). This has serious implications for general practitioners and regulators.

There is evidence that self-regulation of drug promotion is ineffective. A recent Swedish study demonstrated an overall system failure compounded by lax oversight, regulation lags, and low fines for violations (24). The authors concluded that the current regulatory regimes have failed to deter industry from providing unreliable information. Researchers have raised concerns in the United States about the effects of indirect medical advertising, claiming that medical decisions based on such influences, as manipulated by advertisers, are likely to result in worse outcomes for patients, and have called for indirect advertising to be curtailed (25).

In contrast, researchers in Australia have concluded that the value of disease awareness campaigns could be improved if regulations and guidelines stipulated disease information requirements (23). Our research suggests that in the Netherlands – where such guidelines do exist – pharmaceutical companies are aware of the regulatory grey area that disease awareness campaigns represent – and of their subsequent limited regulatory response – thus circumventing the law and exploring new avenues in unbranded product advertising.

The indirect reference to a treatment in association with the name or the logo of a pharmaceutical company – observed in five disease awareness campaigns – constitutes unbranded product advertisement and seems to be in contravention of European law (7,17). Our results are consistent with those of a 2009 study in the Netherlands which analysed 41 websites offering health information in the Dutch language: 32 were either hosted or sponsored by a pharmaceutical company, and 23 (72%) contravened national regulations by referring directly or indirectly to a specific prescription medicine (26).

The absence of an identifiable advertiser or sponsor was one of the main factors of non-compliance in our sample. This might be deliberate, as pharmaceutical companies face a real threat of litigation from unsubstantiated marketing claims. Their goal is to raise awareness about a condition and the availability of a treatment, but to leave the responsibility for a decision to the patient, who should "talk to the doctor the advantages and disadvantages of this new therapy"(27). There is evidence that the rate of diagnoses of specific conditions increases during associated advertising campaigns (14). A randomized controlled trial using standardized patients found that if patients requested an advertised brand, they were as likely to receive

a prescription whether they had the condition that the product treated, depression, or milder life problems not requiring a medicine ('adjustment disorder') (28).

More than half of the disease awareness campaigns in our study (62%) referred to websites, some of which seemed independent at first glance, but were sponsored and/or maintained by one or more pharmaceutical companies. Bearing in mind the growing interest in online health information and that consumers are more likely to seek out more prescription drug information after exposure to advertising, as well as to engage in more communication with doctors about prescription drugs, the evaluation of the content and quality of disease awareness websites should also be envisaged (29).

Disease awareness campaigns have been identified as a form of disease mongering or "widening the boundaries of treatable illness in order to expand markets for those who sell and deliver treatments" (30, 31). A recent commentary by Schwartz and Woloshin provides a template for how disease awareness campaigns work, using three basic strategies: lowering the bar for diagnosis (turning ordinary life experiences into conditions that require medical diagnoses), raising the stakes so that people want to get tested, and spinning the evidence about drug benefits and harms (16).

While seasonality might have influenced the conditions being mentioned in the materials – namely allergies and respiratory diseases - it is unlikely that it would have affected their quality. Contraception was one of the key topics covered in disease awareness campaigns. A new contraceptive pill was launched into the EU market in May 2012 (32). This might indicate a potential marketing strategy of the marketing authorisation holder to draw attention to their new product. Newspaper readers were also amply exposed to information on diabetes. This might have been related with the inclusion of linagliptine into the Dutch reimbursement list (33).

One of the main limitations of our study has been the small sample of unique advertisements, due to the monitoring and inclusion process. A longer data collection window of a full calendar year would have allowed better sampling and extended statistical analysis.

The dynamics of disease awareness campaigns are intricate and deserve closer scrutiny by physicians, consumers and regulators (27, 34). While our proposed instrument has not been systematically evaluated, it represents an attempt to translate the relevant provisions included in the WHO Ethical Criteria for Medicinal Drug Promotion and the Dutch self-regulation guidelines into measurable operational components (1,17,18). Further validation and testing are needed, to verify our tool's consistency and reliability.

CONCLUSIONS

We have demonstrated that disease awareness campaigns are present in Dutch printed media. Their compliance with current self-regulation guidelines is low, which warrants the need for further research into the effects of these campaigns. The use of our instrument could help identify disease awareness campaigns of promotional nature and further encourage effective monitoring and implementation of the regulation by competent authorities.

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TABLE S1. INSTRUMENT to assess the compliance of disease and treatment information disseminated by pharmaceutical companies to the public with the WHO Ethical Criteria on Pharmaceutical Promotion and the Dutch 'KOAG/CGR guidelines for information on prescription medicines

Criteria	Compliant (C)	Non-compliant (NC)	C	NC	Not applicable	Comments
1.Promotional information	NO (in)direct reference to a pharmaceutical intervention, by for example: Naming a therapeutic class *or* Naming or displaying a specific medicine *or* Using a picture and/or link suggesting intervention (ex. "stop-now.com") *or* Naming a treatment in general for which only one drug is available AND/ OR NO reference to a pharmaceutical company is made	(In)direct reference to a pharmaceutical intervention, by for example: Naming a therapeutic class *or* Displaying a specific medicine *or* Using a picture and/or link suggesting intervention (ex. "stop-now.com") or Naming a treatment in general for which only one drug is available IN COMBINATION WITH: A reference to a pharmaceutical company *OR* Naming a drug by brand name (e.g. company's logo or name mentioned in the text)				
2. Misleading or incomplete information	The information about pharmaceutical treatment meets national clinical guidelines OR Both a new therapy AND old therapy (in line with national clinical guidelines) are mentioned. (If the new therapy is the only one mentioned and no suggestion is made about its superiority, select N.A)	The treatment presented is off label *and / or* does not meet national clinical guidelines OR A comparison is made between several pharmaceutical treatments, highlighting the superiority of a given treatment, which does NOT meet clinical guidelines. (Additional information: a treatment is portrayed in a positive light and adjectives such as 'new', 'spectacular' and 'effective' are used)				
	Claims or statements made about Prevalence *or* Incidence *or* Costs *or* Disease gravity *or* Disease burden are accompanied by reference(s) to available evidence (e.g. current guidelines and peer-reviewed journals)	NO reference is provided on the sources of the information provided about: Prevalence *or* Incidence *or* Costs *or* Disease gravity *or* Disease burden				

TABLE S1. (continued)

Criteria	Compliant (C)	Non-compliant (NC)	C	NC	Not applicable	Comments
3. Use of Fear	There is NO reference to fatal events or disability caused by not treating the disease (through a pharmaceutical intervention)	The text *and/ or* a picture refers fatal events or disability resulting from the non-treatment on the disease				
4. Inadequate Language	Medical and scientific terminology are correctly described and interpreted.	Use of medical and scientific terminology without providing a (correct) explanation or interpretation				
5. Lack of Balance	Treatment benefits and harms are accurately and proportionally portrayed. (Additional information: Benefits referred can include symptom control or elimination, prevention of recurrence, or eliminating disease. Harms/ Risks can include side effects, complications and adverse drug reactions) Sufficient and correct information is provided to clearly distinguish between a condition requiring drug treatment and normal health and/or milder conditions not requiring drug treatment	More emphasis on the benefits of pharmaceutical treatment than on its risks. (Additional information: Benefits referred can include symptom control or elimination, prevention of recurrence, or eliminating disease. Harms/Risks can include side effects, complications and adverse drug reactions) Non-pharmaceutical interventions are erroneously omitted OR Risk factors are portrayed as disease(s) OR Natural ageing processes such as osteoporosis (at 50 +), menopause, arteriosclerosis etc. are portrayed as disease(s)				
	Symptoms *and/or* treatment are not emphasized	Symptoms *and/ or* treatment are accentuated by layout *and/ or* enumeration				

TABLE S1. (continued)

Criteria	Compliant (C)	Non-compliant (NC)	C	NC	Not applicable	Comments
6. Use of Testimonials	There is no professional, scientist or public figure supporting the treatment with a specific drug AND/ OR NO before / after treatment comparison involving an individual patient	The opinion or experience of a professional, scientist or a public figure is given in support of treatment with a specific drug AND/ OR A comparison is made of the patient's experience before and after treatment with a specific drug				
7. Absence of Author/sponsor	The author and/or sponsor is /are clearly stated.	The author and/or sponsor is/are not mentioned.				

The following questions are considered additional information and therefore do not affect the material's assessment.

Descriptive characteristics:	Yes	No	Comments
Website	Is there a reference to a website?		
Treatment	Is the public being referred to visit their GP/ medical specialist/ pharmacist for additional information, a diagnosis and/or possible treatment?		
Self-diagnosis	Is there any reference to a symptom check-list or questionnaire?		

CHAPTER 4.3

COMPLIANCE OF DISEASE AWARENESS CAMPAIGNS IN PRINTED AND ONLINE MEDIA IN LATVIA WITH NATIONAL AND INTERNATIONAL REGULATORY GUIDELINES

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Submitted

ABSTRACT

Background

To measure the frequency of disease awareness campaigns by pharmaceutical companies in Latvian media and assess their compliance with international and European guidelines.

Methods

Materials on health/disease and treatments were collected between April and September 2015 from 12 newspapers and magazines and six online portals. Disease awareness advertisements were assessed using a previously developed instrument based on the WHO Ethical Criteria for Medicinal Drug promotion and a European self-regulatory guideline. Collected materials were used to examine the information provided on medical conditions and their diagnosis and treatment. The inter-rater reliability was calculated.

Results

We collected 263 materials from print (n= 149) and online media (n=114); 94 were news items and 169 were disease-awareness advertisements. Cancer, cardiovascular problems, allergies and respiratory diseases were common topics. Of the 157 campaigns assessed, non-compliance was identified in 149 cases (inter-rater reliability 90%), mainly due to misleading or incomplete information, lack of balance and the absence of a listed author/sponsor. Six disease awareness campaigns directly mentioned a pharmaceutical product by brand name and other four included the logo or name of a manufacturer, referred to a condition and indirectly mentioned a treatment, all in contravention with European law.

Conclusions

The compliance of disease awareness campaigns in Latvian media with international and European guidelines is low. This raises concerns about the nature of information being conveyed. Through lack of balance, missing sponsorship information, and misleading or incomplete information, these campaigns could contribute to inaccurate self-diagnosis and generate demand among those who might not need medical treatment.

BACKGROUND

In countries where full direct to consumer (DTC) advertising of prescription medicines is banned, companies are testing the limits of regulatory systems with disease oriented advertising, public relations campaigns and unbranded advertising to the public (1-3). The approach behind such activities is that mass media expands the patients' disease and/or drug awareness and motivates them to visit physicians for previously untreated conditions (4). Promotional campaigns aimed at physicians are often run concomitantly so that practitioners have a specific product in mind when patients ask about new treatments (5).

Proponents of direct-to-consumer communication highlight the need to empower the patient by facilitating access to information which increases knowledge about medicines, diseases and therapeutics (2). A greater involvement of patients in their treatment could be regarded as contributing to safer consumer choices and improved patient autonomy (6). Similarly, greater awareness about diseases could lead to better detection, diagnosis and treatment (7). On the other hand, consumers might not always be able to judge the information conveyed (2) and campaigns could encourage healthy people to seek unnecessary tests or medication (8). Campaigns at the time of launch of a new drug could have negative implications if the drug's risk profile is not fully known. Moreover, if the information provided is portrayed as a community service, the public might remain unaware of its commercial intent (5).

One key concern is that campaigns could contribute to overdiagnosis which occurs when people are labelled with or treated for a disease that would never cause them harm, leading to the overuse of further tests and treatments (9). Overdiagnosis happens in a range of common conditions and appears to be increasing (10). One of the drivers of overdiagnosis is the pharmaceutical industry which aims to maximize health, but also has a conflicting interest in expanding product sales (1, 9).

Disease awareness or condition-oriented campaigns can be effective tools in familiarizing consumers with a disease and a specific pharmaceutical intervention and raise therefore ethical and public health questions similar to those of direct-to-consumer drug promotion (11). Bearing this in mind, it is pertinent to explore whether the information conveyed in such campaigns is meeting current legal and ethical standards and to distinguish legitimate health information from promotional activities.

Drug manufacturers are legally prohibited from communicating directly with consumers about their prescription-only products, except in New Zealand and in the United States of America (12). European Union (EU) legislation prohibits direct-to-consumer advertising of prescription medicines as a public health protection measure (13). However, campaigns to the public about diseases and health from drug manufacturers are allowed, provided there are no direct or indirect references to medicines (14). Each member state is then responsible for transposing and implementing the directive. In Latvia, legal provisions on medicines' advertising define pharmaceutical promotion as "*any form of notification, activity, and measure if the purpose thereof is to promote the prescription, distribution, or use of medicinal products*"

(15) but there is no specific guidance about the provision of health and treatment information. The same applies to the voluntary code of conduct published by pharmaceutical manufacturers' associations on which national self-regulation mechanisms are based.

While the literature on disease awareness campaigns is relatively scarce, there is some evidence that such activities increase awareness of the advertised conditions, as well as rates of consultations and prescriptions of the sponsored product (16-18). Research in Australia and the Netherlands also suggest that exposure to this type of campaigns is relatively common (19, 20). In a previous study, we developed an instrument to assess the compliance of printed disease awareness campaigns in the Netherlands with international and Dutch regulations (20). Although this was a small pilot study over a short study period, it identified an alarming lack of compliance of disease awareness campaigns in Dutch printed media with the WHO Ethical criteria for medicinal drug promotion (21) and with national self-regulation guidelines (22).

We aim to use that same instrument over a longer period in another EU member state – Latvia - where significantly less resources are devoted to health and out-of-pocket payments for health are among the highest when compared to other countries in the Organisation for Economic Cooperation and Development (23). This study measures the frequency of health and treatment information in printed and online media in Latvia and compares the information provided in news items and disease awareness campaigns. It also assesses the compliance of disease awareness campaigns with the WHO Ethical Criteria and self-regulation guidelines for Information on Prescription-only medicines. This is the first study to examine disease awareness campaigns in the Baltic Region.

METHODS

Selection and coding of materials

Data collection took place from April to September 2015. We selected print and online media based on high circulation and subscription numbers (24-26). These included: three daily and three weekly newspapers; three monthly and three health magazines; three news and three health portals (see Table S1). All were accessed at public libraries and available either in Latvian or Russian. In Latvia, 37.2 % of the population are Russian-speaking and media are available in both languages (27).

From all the items covering health topics identified in the various media, we selected materials which mentioned conditions or symptoms or manufacturers and provided treatment suggestions (either directly or indirectly). These **inclusion criteria** were based on EU legal provisions (14) and are described in Table S2. Nutraceuticals, homeopathic products, over-the-counter medication and vaccines were excluded as they are governed by different regulations. Prior to data collection, a training session was conducted on application of inclusion criteria and the instrument, with methods piloted during late 2014 and early 2015. Three researchers (EP, SM, LA) then selected materials published between April and September 2015, with duplicate independent screening of all included media and any disagreements resolved by consensus.

Technical information

We separated the collected materials into two groups:

- Group I were news items with listed authors or attributed to a news desk. These were not assessed using the tool as press reports are not subject to regulations or guidelines on pharmaceutical promotion.
- Group II were disease awareness campaigns without a listed author. These were scored using the instrument described below.
- We extracted general and key content characteristics for both Group I and Group II materials on the following factors:
- *Publication type:* subscription status (paid or free); language; frequency;
- *Author* (yes/no);
- *Content*: non-drug options mentioned; physician referral; reference to clinical expert or spokesperson; referral to patient organization or support group; one or more brand-name drugs recommended; availability of new treatment noted; referral to a website; company's name or logo listed; sponsored by a clinic or hospital.

Assessing compliance of disease awareness with guidelines

We applied an instrument developed in a previous study (20) and based on seven relevant criteria from the WHO Ethical Criteria for Medicinal Drug Promotion (21) and Dutch self-regulation guidelines (22). These include use of: promotional information; misleading or incomplete information; fear; inadequate language; lack of balance; testimonials; and absence of source/author. Dutch and Latvian self-regulatory guidelines are subject to EU regulations (14) and are similar in approach. Table S3 describes the overlap between relevant provisions in international guidelines and the instrument's domains. Websites mentioned in disease awareness campaigns were assessed separately. Three authors (EP, LA, ISK) independently pilot tested the instrument on a sample of materials (n=20). Materials were duplicate coded and differences in scoring resolved through consensus.

Statistics

Descriptive statistics are presented and risk ratios (RR) were calculated comparing frequencies of information provision in news items (Group I) and disease awareness campaigns (Group II). Inter-rater reliability was measured using the intraclass correlation coefficient two-way random effects model (28). We used chi-square to test for differences by language (reported jointly if similar). Data analysis was conducted using SPSS version 24.

RESULTS

Assessing disease-awareness frequency in media

A total of 263 materials were collected, 94 (35.7%) of which were news items (Group I) and 169 (64.2%) were disease awareness campaigns to be scored by the instrument (Group II)

(see Figure 1). This means that on average, ten materials covering disease and treatment topics were published in print or online media every week, 6 of which were disease awareness campaigns. We identified 12 duplicate disease awareness campaigns within Group II, which were excluded for all other analyses. Three media sources (n=3) contained no materials on health and treatment. Results are presented jointly for Latvian and Russian media as information frequency did not differ significantly by language.

The most common topics in news items were dermatological problems (12.8%), cancer (11.7%), cardiovascular diseases (9.6%), pain (9.6%), and gastrointestinal disorders (5.3%). Within disease awareness campaigns, the most frequent themes were cardiovascular diseases (10.7%), dermatological problems (8.3%), cancer (7.7%), urological problems (7.7%), and pain (7.1%).

As is described in Table 1, news items included quotes from key opinion leaders more often, and mentioned the availability of a new treatment, whereas disease awareness campaigns were more likely to refer viewers to a website (RR=4.04, 95%CI 1.46;11.19) or a pharmaceutical company (RR=7.78, 95%CI 1,03;58.55). These disease-awareness campaigns were also often sponsored by a hospital or clinic (RR=3.29, 95% CI 1.17;9.26). Nearly all the materials recommended seeing a physician. Quoted key opinion leaders were most frequently general practitioners and leading specialist physicians from academic hospitals, such as cardiologists and gastroenterologists. Non-drug or lifestyle interventions were mentioned over half the time, although this occurred more often in news items than in disease awareness campaigns. The type

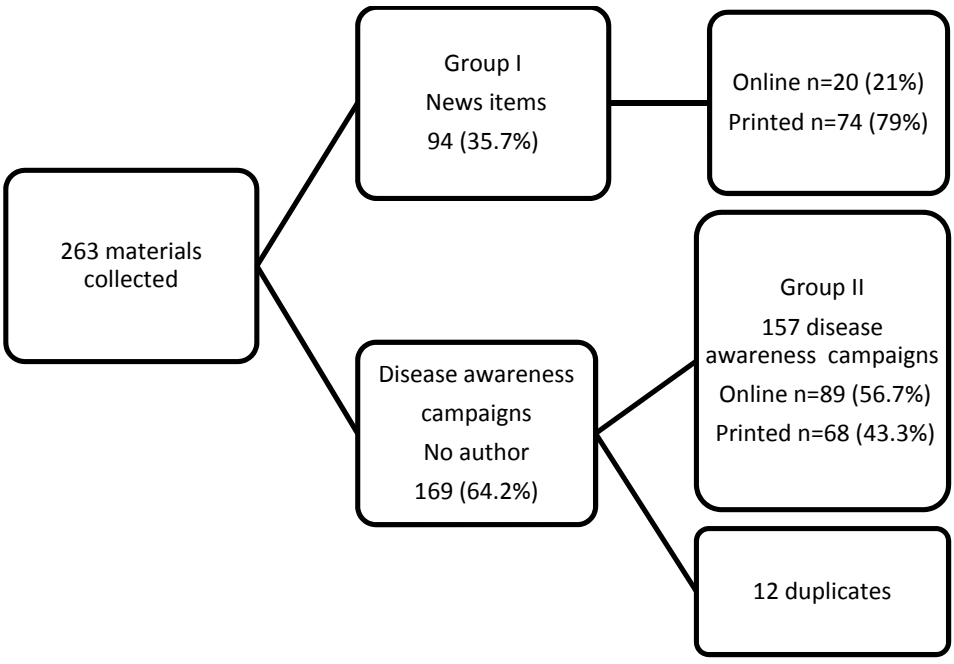

FIGURE 1. Materials collected and their allocation per type of media

TABLE 1. Frequency of information provided across materials and their Risk Ratio

Information included	Group I News Items (n=94) (% within group)	Group II Disease Awareness Campaigns (n=157) (% within group)	RR Frequency in disease awareness campaigns versus news items (95% CI)
Suggestion to visit a physician	86 (91.5%)	132 (84.1%)	0.92 (0.883;1.01)
Key opinion leader or public figure quoted	89 (94.7%)	94 (59.9%)	0.63 (0.55;0.72)
Non-pharmaceutical interventions in addition to therapy	67 (71.3%)	86 (54.8%)	0.77 (0.63;0.93)
Referral to a website	4 (4.3%)	27 (17.2%)	**4.04 (1.46;11.19)**
Sponsorship by specific clinic	4 (4.3%)	22 (14.0%)	**3.29 (1.17;9.26)**
Mention of availability of a new medicine or treatment option	17 (18.1%)	16 (10.2%)	0.56 (0.30;1.06)
Pharmaceutical company name or logo	1 (1.1%)	13 (8.3%)	**7.78 (1.03;58.55)**
Patient organization or support group	4 (4.3%)	9 (5.7%)	1.35 (0.43;4.25)
Brand-name pharmaceutical product	5 (5.3 %)	6 (3.8%)	0.72 (0.22;2.29)

of lifestyle interventions mentioned most frequently were exercise (e.g. for depression, varicose veins, pain, urological problems); and psychotherapy (e.g. in cases of depression, compulsive eating, vegetative dystonia).

Compliance of the disease awareness with guidelines

Of the 157 diseases awareness campaigns assessed, 149 (94.9%) were non-compliant. Inter-rater agreement for independent coding of judgments of compliance with guidelines was high: 0.906 [95% CI 0.877; 0.929]. Non-compliance was most often due to the absence of author or source, lack of balance, or use of misleading or incomplete information. In total, 29.9% of campaigns were non-compliant with two criteria and 19.1% with three criteria. Table 2 provides some examples of non-compliance per key criteria and campaign topic. Figure 2 provides an overview of compliance levels per key criteria, and compares results with those obtained in the Dutch study (20). The Latvian campaigns seem overall more compliant with regulations than the Dutch but were more likely to contain misleading or incomplete information, inadequate language and not to mention an author/sponsor.

Twenty-three of the 157 campaigns (14.6%) listed dedicated websites, 20 (86,9%) of which were also non-compliant with guidelines. Eight of these websites were sponsored by a pharmaceutical company. Ten disease-awareness campaigns (6.4%) were likely in contravention of European law: four included the logo or name of a pharmaceutical company and both referred to a condition and mentioned a treatment indirectly; six mentioned a medicine by its brand name.

TABLE 2. Examples of non-compliance per key criteria from the disease awareness campaigns

KEY criteria	Problem identified	Example (CONDITION)
Promotional information	Reference to pharmaceutical products to treat a condition or disease in combination with: · the name, logo and website of a pharmaceutical company; · or a website for a disease awareness campaign; · or quick response codes to dedicated websites.	"For example, one of the current treatments recommended by doctors for premature ejaculation is a serotonin reuptake inhibitor which prolongs intercourse for men older than 18 for up to 200-400%". The name and logo of a pharmaceutical company as well as a dedicated website are mentioned. (Premature ejaculation) (30) "My doctor informed me about a compassionate use program in which 17 patients with hepatitis C had an opportunity to receive the new non-interferon therapy for free, which guaranteed 97-100% cure rate. […] The program was supported by pharmaceutical company X. " (Hepatitis C) (20) A website about upper respiratory tract conditions states: "inhaled corticosteroids are the most effective bronchial asthma therapy". The website includes the logo and the name of an asthma medication manufacturer (Asthma, website, LV). "Selective progesterone receptor modulator is the approved pharmaceutical treatment for uterine fibroids. It reduces bleeding and fibroid volume." The website includes the logo of a pharmaceutical company, as well as a section for specialists where the product's brandname is mentioned (Uterine fibroid, website, LV)
Misleading or incomplete information	No reference is provided to the sources of information provided about prevalence of disease.	"Approximately 90% of the world population suffers from lower back, neck line and muscle pain…" (Back pain, RU) "Every 30 seconds someone has a fracture due to osteoporosis". (Osteoporosis, RU) "After reaching 60 years of age, approximately 60% of population suffers from venous insufficiency" (Varicose veins, LV) "It is possible that you are among the 90% of the population who suffer from herpes blisters. Here is the information that you need to know about the herpes virus." (Herpes, LV)
Use of fear	Reference to disability caused by the disease, either through text or picture.	"Approximately half of ovarian cancer cases are lethal. This is due to the asymptomatic nature of the cancer and delayed diagnosis" (Cancer, LV) "If left untreated hemorrhoids will only get worse – inflamation will develop into abcess, pain will increase, bleeding and prolapse will form thrombs." (Hemorrhoids, RU)

TABLE 2. (continued)

KEY criteria	Problem identified	Example (CONDITION)
Inadequate language	Uses medical terminology	"If Lyme disease is not diagnosed and treated in a timely manner, other symptoms of Lyme disease can develop several weeks, months or years after the tick bite, such as arthritis, nervous system or cardiovascular disorders" (Lyme disease, LV) "[High blood pressure] also increases the risk of heart diseases - ischemic heart disease, cardiomyopathy, development of infarction and stroke." (Cardiovascular disease, LV)
Lack of balance Use of testimonials	More emphasis on the benefits of pharmaceutical treatment than risks. Symptoms are accentuated by layout and/or enumeration. Risk factors are portrayed as diseases. Treatment is accentuated. Specialist mentions treatment and specific drug classes. A comparison is made of the patient's experience before and after treatment with a specific drug.	"Botulin injections are one of the most effective methods to fight excessive sweating. […] The effect will appear on the 4th to 6th day after the injection and will last six to nine months. " (Excessive sweating, LV). Symptoms are referred to in headings in big and bold typeface. (Diabetes, Nr 105, LV) (Asthma, Nr 30) (Alzheimer, Nr 138, LV) "There are several tablets you can use for the treatment of erectile dysfunction. […] There is a high chance that treatment will work (in 8 cases out of 10 treatment is effective). Please discuss the advantages and disadvantages of these treatments with your doctor." (Erectile dysfunction website, LV) Quote from a general practitioner "If you have frequent and pronounced herpes infections you will need to use acyclovir [tablets] – a serious medication in high doses." (Herpes simplex infection, Nr. 9, LV) "I trust my doctor a lot but I was still worried that [with a new therapy] I would experience the same side effects I had before... This time everything was different! I only had to worry about taking my pills on time. " (Hepatitis C, Nr 52, LV)
Absence of author and/or sponsor	No author and/or sponsor identified.	Conditions or Symptoms where this non compliance was identified: Anemia Alzheimer Diabetes Cancer (breast, cervical, colorectal, melanoma) Cough Contraception Glaucoma Gout

TABLE 2. (continued)

KEY criteria	Problem identified	Example (CONDITION)
		Excessive sweating
		Eye infection
		Eating disorders
		Female sexual dysfunction
		fibromioma
		Heart failure
		Heart attack
		Hemorrhoids
		Hepatitis C
		Herpes simplex
		Hypertension
		Lyme disease
		Migraine
		Nail fungus
		Osteoporosis
		Pain
		Parkinson
		Psoriasis
		Pulmonary arterial hypertension
		Seasonal affective disorder
		Smoking cessation
		Sport related injuries
		Stroke
		Seasonal allergy
		Trophic ulcers
		Varicose veins
		Warts

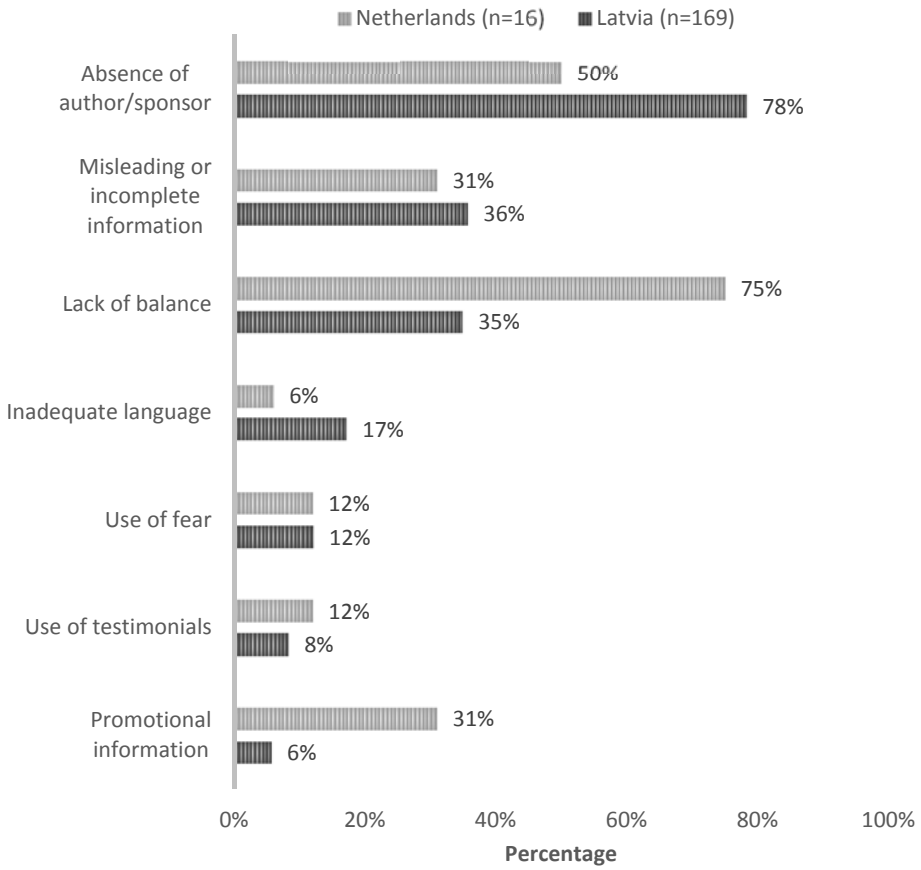

FIGURE 2. Non-compliance of disease awareness campaigns per key criteria*
*See Supplementary Data Table S3 for operational definitions of the key criteria.

DISCUSSION

Our study confirms that there is a strong focus on health and treatment information in Latvian media with more than ten items being published every week covering various topics, including both health-related news items and disease-awareness campaigns. An average of six disease-awareness campaigns were published per week, which is a higher frequency than that reported in similar studies in the Netherlands and in Australia (19, 20).

In this sample, the overwhelming majority of Latvian disease-awareness campaigns (94.9%) did not comply with the WHO Ethical Criteria for Medicinal Drug Promotion (21) nor with self-regulatory standards (22). The overall compliance results seem somewhat more positive than those obtained in the Dutch study (20), but 58.6% of the campaigns included in our Latvian sample failed to comply with two or more of the WHO Ethical Criteria.

According to the WHO *'promotion' includes all informational and persuasive activities of manufacturers and distributors, that affect the prescription, supply, purchase and/or use of*

medicinal drugs"(21). Although disease awareness campaigns can contain information which might be of potential value to the public, they also have many characteristics that would make them promotional and are, in some cases, clearly designed to support treatment with the sponsor's product as part of a marketing campaign. They are not subject to the same type of regulatory oversight in Latvia as other types of promotion. Generally, if the product name is not mentioned, these are not considered to be pharmaceutical advertising, even if the sponsor has a product on the market to treat the condition that is under discussion.

In 78% of the cases we were unable to identify the author or sponsor of the campaigns. This means that the target audience might remain unaware of the intent of the information conveyed (5) and of its commercial source. Ebeling describes 'condition branding' as an essential component of direct-to-consumer marketing of pharmaceuticals in the United States, with the definition of symptoms associated with a specific treatment being a key focus of activities aiming to create a market for newly developed products (29). In a randomized trial of a fictitious advertising campaign, consumers tended to perceive disease awareness campaigns more positively than branded advertisements, and stated their intent to seek information and treatment more often after viewing disease awareness campaigns (30).

The information provided in the disease awareness campaigns collected in our study was often incomplete or misleading about the presentation of benefits and harms of medicines and lacked balance. Prevalence rates were often inaccurate and suggested nearly everyone had the health problem, such as a 90% cited rate of neck and back pain (Table 2). Our results are consistent with reports in other settings (31, 32) of striking statistics, exaggerated stated incidence, prevalence or condition severity (33) (34). They also mirror existing evidence of the display of striking visuals (1) and use of emotive messages to build brand loyalty (19). Inaccuracies and information imbalance can lead to increased health care costs if new more expensive drugs are used instead of equally effective lower-cost drugs or non-drug treatments, and even to avoidable injury or death if patients are encouraged to ask for drugs that are less safe than alternatives (35). For serious conditions, an additional concern is that patients may seek less effective treatments, again leading to avoidable harm.

Concerns have been raised about campaigns' potential to exaggerate the risks of a condition, which may result in increased anxiety and unnecessary visits to doctors (34). When adoption of newer more expensive products without established advantages over cheaper alternatives is encouraged, this can lead to more doctor visits and inappropriate prescribing (16, 36, 37), shifting both the quality and the costs of care (3). This is particularly critical in Latvia with its under-resourced health system (23). Latvian public expenditure on health is remarkably low when compared with neighbouring countries with similar economic development, and out-of-pocket payments are amongst the highest in the European Union (23). This might explain why 14% of the disease awareness campaigns were sponsored by private clinics. The commercial imperative behind these campaigns may be fuelling unnecessary health anxieties. Such strategies do not comply with the WHO Ethical Criteria which clearly outlines that promotional activities should *"not take undue advantage of people's concern for their health"* (21).

We found several disease awareness campaigns that referred directly to a specific brand and/or to a pharmaceutical company (either by name or logo), in contravention of the EU directive prohibiting direct-to-consumer advertising of prescription-only medicines. The Latvian Health Inspectorate reported that 15% of the contraventions to advertising regulation in 2016 were direct-to-consumer advertisements for prescription-only medicines (38). However, despite this experience, the Inspectorate does not actively monitor disease awareness campaigns. There is a contradiction between prescription-only status, requiring provision by clinicians with specialised training and knowledge, and allowing those same drugs to be marketed to people who lack that specialised knowledge (39). The overall lack of compliance with current guidelines points to the need for more active monitoring and enforcement.

We found many non-compliant websites in disease awareness campaigns. Websites pose several challenges to regulators, including difficulties ascertaining the source of available information, frequently changing content, and global access to websites that are covered by differing national regulations, including those originating in countries where direct-to-consumer advertising of prescription medicines is legal (5). Nearly any user worldwide can encounter unregulated and unmonitored pharmaceutical information online (1).

Some of the conditions mentioned in non-compliant campaigns in our sample have been highlighted in the medical literature as subject to overdiagnosis: female sexual dysfunction, overactive bladder, erectile dysfunction, nail fungus, seasonal affective disorder and excessive sweating (16, 40). Under the guise of education, companies define conditions and their associated symptoms in the minds of physicians and patients while predicating the best available treatment (29).

Our study had some limitations. As the study period covered six months, seasonality is likely to have influenced the content of campaigns. We would not expect an effect on quality, however. As one of our aims was to probe the campaigns' compliance with the guidelines, we opted to include all types of campaigns. Not all were necessarily sponsored by pharmaceutical companies. Additionally, while we did not use the instrument to assess news items, we found some features consistent with drug promotion in news coverage of specific conditions and new treatments, such as use of key opinion leaders and lack of information balance. Further application of the instrument in other jurisdictions could shed light on the enforcement status of disease awareness campaigns and inform future policy about adequate measures to respond to the challenges raised by this type of promotional activities.

CONCLUSION

Disease awareness campaigns are present in Latvian printed and online media. Their compliance with national and international regulatory standards is low. This raises concerns about the nature of information being conveyed. Through lack of balance, missing sponsorship information, and misleading or incomplete information, these campaigns could contribute to inaccurate self-diagnosis and generate demand among those who might not need medical treatment. We have implemented an instrument to systematically evaluate the information content of disease

awareness campaigns. The use of this instrument may help identify promotional campaigns and encourage the effective monitoring and implementation of the regulations.

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SUPPLEMENTARY DATA

TABLE S1. Data collection: list of publications included

Format	Title	Type of Media	Language/frequency
Print	Latvijas Avīze (Latvian Newspaper)	Newspaper	LV daily
	Diena (Daily)		LV daily
	MK Latvija (MK Latvia)	Newspaper	RU daily
	Privātā dzīve (Private Life)	Tabloid	LV weekly
	Kas Jauns (What's New)		LV weekly
	Rīgas Santīms (Riga's Santim)	Free	RU weekly
	Santa (Santa)	Lifestyle magazines	LV monthly
	Klubs (Club)		LV monthly
	Lilit (Lilita)	Lifestyle magazine	RU monthly
	Ievas veselība (Ieva's Health)	Health magazines	LV bi-weekly
	Ko ārsti tev nestāsta (What doctors Don't Tell You)		LV monthly
	Vesti Segodnja Pro Zdorovje (Health News today)	Health magazine	RU monthly
Online	Delfi.lv	News portal	LV
	Tvnet.lv	News portal	LV
	Vesti.lv	News portal	RU
	Vesels.lv	Health Information portal	LV
	Medicina.lv	Health Information portal	LV
	azbuka.lv	Health Information portal	RU

TABLE S2. Inclusion criteria: materials selected included one of the four combinations

1	Symptoms or Health issues or Diseases or Conditions	AND	Prescription drug or Drug class
2	Symptoms or Health issues or Diseases or Conditions	AND	Doctor referral or Website referral or Description of a drug's mechanism of action or Treatment suggestion
3	Name or logo of a pharmaceutical company	AND	Reference to a treatment or A problem or A condition or Website referral
4	Disease management programme	AND	Encouragement of addition of one or more drugs to ongoing treatment

TABLE S3. Overlap between relevant provisions within the WHO Ethical Criteria for Medicinal Drug Promotion **and the CGR Guidelines for provision of information on prescription medicines and the relevant sections of the instrument**

Key Criteria	WHO Ethical Criteria	Dutch CGR Guidelines
1.Promotional information	Article 6. Definition of promotion: "all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs." Article 7. "Promotional material should not be designed so as to disguise its real nature." Article 9. "Scientific and educational activities should not be deliberately used for promotional purposes." Article 14b. "Advertisements to the public should not generally be permitted for prescription drugs or to promote drugs for certain serious conditions that can be treated only by qualified health practitioners."	Introduction. Definition of promotion: "all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs." Introduction. "Instances whereby prescription medication or pills are being mentioned without indicating the drug's brand name or company name" are considered indirect reference, for example when naming the active ingredients or the drug's mechanism of action. Article 5. "Information may not encourage irrational use of prescription medicines nor the search for unnecessary treatment." Article 6. "Information may not directly or indirectly lead to the choice of a particular medicine from different available treatments."
2. Misleading or incomplete information	Article 7 . "Advertisements may claim that a drug can cure, prevent, or relieve an ailment only if this can be substantiated. … All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks."	Article 3. "Information may not be misleading. The information provided must comply with the most recent evidence and practice standards. The information must be factually correct and may not contain any misleading elements." Article 17. "No comparison is allowed between relevant treatments and medicines that suggests that the effects of a treatment with a prescription drug are better or equal than those of another relevant treatment or drug." 21.2 b) "No single option for treatment is to be highlighted, for instance by using words, colours or images, different font types, markings or any other elements. " Article 21.2 d) "Treaments should be cathegorised based on acceptable formats. For instance using therapeutic classes or categories, or through therapeutic guidelines. Using expressions such as "most recent, or new is better, most commonly used, is not allowed." Article 23. "Information should be displayed objectively and neutrally and must not contain information which relates directly to a specific treatment. When reference is made to specific

SECTIONS IN THE INSTRUMENT	
Compliant (C)	**Non-compliant (NC)**
NO (in)direct reference to a pharmaceutical intervention, by for example: Naming a therapeutic class or Naming or displaying a specific medicine or Using a picture and/or link suggesting intervention (ex. "stop-now.com") or Naming a treatment in general for which only one drug is available AND/ OR NO reference to a pharmaceutical company is made	(In)direct reference to a pharmaceutical intervention, by for example: Naming a therapeutic class or Displaying a specific medicine or Using a picture and/ or link suggesting intervention (ex. "stop-now.com") or Naming a treatment in general for which only one drug is available IN COMBINATION WITH: A reference to a pharmaceutical company OR Naming a drug by brand name (e.g. company's logo or name mentioned in the text)
The information about pharmaceutical treatment meets national clinical guidelines OR Both a new therapy AND old therapy (in line with national clinical guidelines) are mentioned. (If the new therapy is the only one mentioned and no suggestion is made about its superiority, select N.A)	The treatment presented is off label and / or does not meet national clinical guidelines OR A comparison is made between several pharmaceutical treatments, highlighting the superiority of a given treatment, which does NOT meet clinical guidelines. (Additional information: a treatment is portrayed in a positive light and adjectives such as 'new', 'spectacular' and 'effective' are used)
Claims or statements made about Prevalence or Incidence or Costs or Disease gravity or Disease burden are accompanied by reference(s) to available evidence (e.g. current guidelines and peer-reviewed journals)	NO reference is provided on the sources of the information provided about: Prevalence or Incidence or Costs or Disease gravity or Disease burden

TABLE S3. (continued)

Key Criteria	WHO Ethical Criteria	Dutch CGR Guidelines
		treatment guidelines, the source must be listed…References to scientific literature should also be published…"
3. Use of Fear	Article 14: "While they [advertisements] should take account of people's legitimate desire for information regarding their health, they should not take undue advantage of people's concern for their health." Article 15. "Language which brings about fear or distress should not be used."	Article 4. "Information should not boost or amplify feelings of fear and superstition and should be displayed realistically." Article 5. "Information may not encourage irrational use of prescription medicines nor the search for unnecessary treatment." Article 9."Information should not aim nor encourage the public to seek unnecessary treatment, advice or further examination; nor on the other hand refrain the public from seeking treatment, advice or further examination." Article 20. "The information may not be unjustified, unnecessarily alarming or misleading images of changes to the human body resulting from illness or disease.
4.Inadequate Language	Article 29. "The wording …if prepared specifically for patients, should be in lay language on condition that the medical and scientific content is properly reflected."	Article 7. "Information should be tailored to the average consumer and have understandable language. Medical and scientific terms should be avoided as much as possible, to avoid confusion."
5. Lack of Balance	Article 7. "All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks… Comparison of products should be factual, fair and capable of substantiation".	Article 9."Information should not aim nor encourage the public to seek unnecessary treatment, advice or further examination; nor on the other hand refrain the public from seeking treatment, advice or further examination." Article 17. "No comparison is allowed between relevant treatments and medicines that suggests that the effects of a treatment with a prescription drug are better or equal than those of another relevant treatment or drug." Article 21. "Information should be as balanced and complete as possible. It should reflect the state-of-the-art. When providing information, all relevant factors should be taken into account. All information should be equally displayed both in content and layout, with the same amount of detail." Article 21.2 c) "The positive and negative effects of a treatment are not to be emphasized in such a way that the pros or the cons of a given treatment are highlighted".

SECTIONS IN THE INSTRUMENT	
Compliant (C)	**Non-compliant (NC)**
There is NO reference to fatal events or disability caused by not treating the disease (through a pharmaceutical intervention)	The text and/ or a picture refers fatal events or disability resulting from the non-treatment on the disease
Medical and scientific terminology are correctly described and interpreted	Use of medical and scientific terminology without providing a (correct) explanation or interpretation
Treatment benefits and harms are accurately and proportionally portrayed. (Additional information: Benefits referred can include symptom control or elimination, prevention of recurrence, or eliminating disease. Harms/Risks can include side effects, complications and adverse drug reactions) Sufficient and correct information is provided to clearly distinguish between a condition requiring drug treatment and normal health and/or milder conditions not requiring drug treatment	More emphasis on the benefits of pharmaceutical treatment than on its risks. (Additional information: Benefits referred can include symptom control or elimination, prevention of recurrence, or eliminating disease. Harms/Risks can include side effects, complications and adverse drug reactions) Non-pharmaceutical interventions are erroneously omitted OR Risk factors are portrayed as disease(s) OR Natural ageing processes such as osteoporosis (at 50 +), menopause, arteriosclerosis etc. are portrayed as disease(s)
Symptoms and/or treatment are not emphasized	Symptoms and/ or treatment are accentuated by layout and/ or enumeration

TABLE S3. (continued)

Key Criteria	WHO Ethical Criteria	Dutch CGR Guidelines
		Article 21.2 d) Information about different therapeutic interventions can be provided. In that case, all relevant treatments should be named, including pharmacotherapy and other interventions, such as adjustments to lifestyle, nutrition and habits. Relevant treatments are the standard of care provided, as per treatment guidelines. Completeness ensures that no information is deliberately omitted. When enumerating all the pharmacotherapeutic options for treatment, all the relevant prescription drugs for the specific treatment are to be mentioned."
6. Use of Testimonials	Article 7. "Promotional material should not be designed so as to disguise its real nature." Article 9. "Scientific and educational activities should not be deliberately used for promotional purposes."	Article 18. "Testimonials should portray the opinion or experience of the user truthfully (not that of a professional or any other public figure). They should not include any comparison of the user's situation before and after drug treatment…Before/after testimonials are not allowed because they can lead the public into false expectations regarding the speed of the treatment's effects".
7. Absence of Author/ sponsor	Article 7. "Advertisements may claim that a drug can cure, prevent, or relieve an ailment only if this can be substantiated. … All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks."	Article 22."Each message is to contain the name of the person responsible for the information". Article 23. "Information may refer to scientific studies and results…The source must always be included. The studies and the results that are mentioned must always come from other sources than the medicine's producer and should be verifiable…" "Information should be displayed objectively and neutrally and must not contain information which relates directly to a specific treatment. When reference is made to specific treatment guidelines, the source must be listed…References to scientific literature should also be published…"

SECTIONS IN THE INSTRUMENT	
Compliant (C)	**Non-compliant (NC)**
There is no professional, scientist or public figure supporting the treatment with a specific drug AND/ OR NO before / after treatment comparison involving an individual patient	The opinion or experience of a professional, scientist or a public figure is given in support of treatment with a specific drug AND/ OR A comparison is made of the patient's experience before and after treatment with a specific drug
The author and/or sponsor is /are clearly stated.	The author and/or sponsor is/are not mentioned.

CHAPTER 5

GENERAL DISCUSSION

INTRODUCTION

Patients and consumers play varied roles in pharmaceutical policy. They represent peers in dedicated platforms hosted by health authorities, provide input on their preferences and experiences in medicines' use, advocate for reimbursement of new therapies, and can also be the target audience of awareness campaigns and pharmaceutical advertising. There are many instances for patient involvement throughout a drug's life cycle which also represent unique opportunities for research from the viewpoint of the public. This thesis presents an analysis of challenging issues in pharmaceutical policy focusing on public and patient involvement and on how the dissemination of information across stakeholders influences the uptake of new pharmaceutical products. In doing so, we have proposed a model for the adoption of innovative drugs across key actors in the health system, where the public (patient and consumers) is a crucial stakeholder. Examples of topics explored in this thesis are: a government-led policy to stimulate innovation, the use of patient reported outcomes to inform drug reimbursement, the corporate sponsorship of patient and consumer groups eligible to work with the European drug regulator, and the exposure to public health campaigns financed by pharmaceutical companies. These studies are a testament of the growing public engagement in pharmaceutical policy and have explored issues which are intrinsically perceived as positive trends. Notwithstanding the ethical and democrative imperative of a growing interface between pharmaceutical policy and patients and consumers, the results of our research do raise important considerations within the scope of public health. We provide below an analysis of our findings per study, in an attempt to extract the key lessons learnt thus far and to further pan out their implications for methodology and future research, as well as policy and practice.

LESSONS LEARNT FROM THE STUDIES IN THIS THESIS

New is not necessarily better

The diffusion of innovation theory explains how and why innovations (new ideas or new technologies) spread. It recognizes that certain factors determine how quickly, and to what extent, an innovation will be adopted and diffused (1). One of such features is the relative advantage of an innovation which shows superiority over whatever it replaces. Another aspect is compatibility, which can best be described as an appropriate fit between the innovation and the intended audience (2).

In **Chapter 2.1.** we assessed the relative advantage of new medicines by studying the level of therapeutic innovation of new approvals in Brazil over a thirteen-year period. This entailed a comparison of added therapeutic value assessments conducted by the Brazilian Chamber for Medicines' Market Regulation (CMED) and the French drug bulletin Prescrire. In addition, we also verified the compatibility of these newly-approved medicines with the Brazilian public health needs by checking their therapeutic indications against the conditions contributing the most to the national burden of disease.

Our results show that few therapeutically innovative drugs entered the Brazilian market from which only a small proportion were approved to be covered by the Brazilian Unified Health System. In contrast, according to the assessments of CMED and Prescrire, the overwhelming majority of the drugs approved between 2004 and 2016 were non-innovative. This indicates that most of newly approved medicines did not exhibit a clinically relevant advantage over existing established therapies, either in terms of better efficacy, safety or patient outcomes. Yet, despite such low therapeutic ratings 11% of non-innovative drugs were adopted in government-funded drug listings. In addition, the majority of new drugs target specific niches, such as oncology and chronic conditions rather than other indications of greater public health relevance for Brazil, such as neglected diseases.

While the findings above showcase a trend that might not be different from higher income countries (3), this situation could be problematic for a country like Brazil, as they suggest not only a divergence between the research and development priorities of pharmaceutical companies and public health needs; but also existing tensions between the theory of adopting a policy to encourage innovation and cost-containment and its actual implementation in practice. One could also question whether the low utility levels of these often extremely costly niche drugs justify the government decision to make them accessible at a wider scale, given the need to allocate resources equitably. Universal access to care remains a challenge for governments and health systems across the world (4). This is also true for Brazil, a complex country with the world's 8th largest economy which is undergoing rapid economic and social changes, but still faces harsh income inequalities and strong regional disparities (5).

Collecting and using data about outcomes that matter for patients

Patterns of use of medicines vary greatly across regions and countries, as they reflect specific political, historical, cultural and socio-economic factors. A particular area where cross-national variations have been identified is within relative effectiveness assessments (6). These assessments are considered by decision-makers when assessing the net benefit of interventions, among which when considering new therapies such as pharmaceutical products. In **Chapter 2.2.** we explored the role played by quality-of-life data in relative effectiveness assessments for Health Technology Assessment (HTA) recommendations of new cancer drugs in six European jurisdictions. National guidelines state that quality of life is a relevant outcome to determine the relative effectiveness of new cancer drugs. However, as our evidence suggests, this is not well-reflected in current assessments, as quality-of-life data were included in just half of all the available reports. In addition, their impact on the recommendations was limited as one-fourth of the recommendations included no information whatsoever on quality-of-life data. We have also observed differences between countries as to the inclusion and extent of use of quality-of-life data, which also shed light on how HTA bodies vary in how they handle and report this type of data. HTA agencies reported concerns about the methodological constraints of collecting quality-of-life data and their subsequent quality and stated unavailability or lack of robustness as motives for non-inclusion of this data in relative effectiveness assessments. Our research is particularly timely as it feeds the current debate on the use of patient reported

outcomes in drug registration and in health technology assessment (7-11). Better collection and reporting of quality-of-life data in clinical trials could be incentivised by establishing more stringent evidence requirements downstream at HTA level, to improve the use of this patient-centred outcome in future reimbursement decisions.

Pharmaceutical promotion under the guise of education

Given the fundamental role of the pharmaceutical industry in the research, development, manufacturing and marketing of new medicines, it comes as no surprise that pharmaceutical companies are also the main provider of information on their new products to health authorities, healthcare professionals and the public, as depicted in our model contained in the Introduction (page 11). This situation generates an asymmetry of information between the pharmaceutical industry and other stakeholders, granting companies the opportunity to select the information to be delivered as well as the timing and the channels for its dissemination.

In **Chapter 3.1** we scoped into the strategies used by the pharmaceutical industry to influence healthcare professionals and the public. Our literature review focused on promotion activities carried out directly by pharmaceutical companies with the aim of enhancing product sales, also analyzing the quality of information provided and the effects thereof.

Our review shows that there is a link between greater reliance on the promotion of pharmaceuticals and less appropriate prescribing. There is ample evidence that promotion affects patterns of prescribing and medicine use, with effects on costs and on appropriateness of medicine use.

Our findings also highlight what appears to be a transition from more traditional promotion techniques aimed at prescribers - such as the use of sales representatives and pharmaceutical advertisements in medical journals - to new forms of promotion fostering the use of scientific research and educational events by key opinion leaders, continuing medical education and disease mongering. The latter seem to be in clear violation of the WHO Ethical Criteria for Medicinal Drug Promotion, which remain the global gold standard for the regulation of drug promotion (12). The WHO Ethical Criteria state clearly that "*promotional material should not be designed as to disguise its real nature*" and that "*scientific and educational activities should not be deliberately used for promotional purposes*".

We have also reviewed initiatives from the pharmaceutical industry, government and governmental organizations aimed at improving the regulation of the promotion of pharmaceuticals. While there are some positive trends, such as rules requiring mandatory disclosure of funding to healthcare professionals and patient groups, more systemic fundamental changes are needed.

Financial ties between pharmaceutical companies and patient groups: convergence or conflict of interests?

Consumer and patient advocacy groups are important participants in the politics of pharmaceuticals as they play powerful roles in health policy, public education, and research (13). Pharmaceutical, biotech and medical device companies sponsor patient organisations in

a variety of ways, ranging from direct financing (donation and grants) to various forms of in-kind sponsorship. Little research has been done to ascertain the nature and extent of the relationship of European patient and consumer organisations. The study contained in **Chapter 3.2** is the first of its kind to provide baseline data on levels of corporate sponsorship among the groups eligible to work with the European Medicines Agency and studies the trends in financial disclosure and transparency between 2007 and 2011. Financial data were retrieved from organisations' and pharmaceutical companies' websites as well as through direct requests.

Our evidence shows that by 2011 the majority (59%) of groups received funding from medicines' manufacturers and/or industry associations. From these, 50% did not publish detailed information on their corporate sponsorship on their websites and another 30% failed to report on financing. This indicates there was low compliance with EMA reporting guidelines during our study period. In addition, the median industry sponsorship increased over time, both in value and in contribution to the organization's annual revenue. Disclosure patterns might have improved in recent years, but additional data collection and analysis would be needed to substantiate that.

The convergence of interests between producers willing to expand markets for their products and patients seeking for a treatment or a cure seems natural and understandable (14), yet the dependence of such groups on pharmaceutical industry funding and their inadequate public disclosure are of concern. The extent of pharmaceutical sponsorship of groups providing advice to the European Medicines Agency and their poor disclosure raises questions about potential conflicts of interest (15) and the co-opting of patient voices. The context in which many of these groups operate at the EMA provides patient representatives with a privileged platform to interact with regulators. Given their growing role and their opportunity to influence decision-making procedures at the European Medicines Agency, the financial practices of such groups demand public scrutiny. Clear, complete and public disclosure of the sponsorship received from the pharmaceutical industry and other corporate donors must be a prerequisite for any interest representative who is interacting with public authorities.

Disease awareness campaigns: blurring the boundaries between information and promotion

The World Health Organization Ethical Criteria for Medicinal Drug Promotion define promotion as "*all informational and persuasive activities of manufacturers and distributors that affect the prescription, supply, purchase and/or use of medicinal drugs*"(12). Direct advertising of prescription medicines to the public, also known as direct-to-consumer advertising (DTCA) is permitted only in the USA and New Zealand. The European Union legislation allows pharmaceutical companies to provide general information on health and diseases, but there cannot be any reference, even indirectly, to a specific medicine (16).

This EU legal provision offers companies the promotional approach also known as disease-awareness or condition-oriented advertisements. This type of unbranded advertising generally involves a broadcast or printed campaign which discusses a set of symptoms or a disease while encouraging consumers to seek further diagnostic and treatment by visiting their doctor.

While much research has been done in other areas of traditional drug promotion (17-19), far less is known about the effects of these unbranded campaigns or on their compliance with the regulatory framework.

This type of unbranded advertising is often part of a broader and integrated marketing campaign that aims to increase sales of prescription-only medicines (20). Existing studies describe a model whereby advertising to the public affects consumers' awareness of and knowledge about a condition. Consumers are exposed to the unbranded advertising and are stimulated to seek further medical care by consulting their doctors and requesting a pharmaceutical treatment. Consumers' requests trigger the prescription for the advertiser's product by the physician, who has previously been subject to targeted branded advertising (21-23). Advocates of disease awareness campaigns claim these can educate the public, make consumers aware of otherwise untreated health problems and help them seek effective care at an earlier stage (24,25). Concerns have been raised about the content and nature of such campaigns and their potential negative effects, such as misleading consumers (26), misinterpreting the evidence about drug benefits and harms (27, 28), as well as encouraging further medical testing. It is pertinent to investigate this specific type of intervention both in terms of the agent carrying out the intervention (pharmaceutical manufacturers or other entities that are funded by pharmaceutical manufacturers) and the link to marketing of health products.

In **Chapter 4.1** a protocol for a systematic review is outlined to assess the effects of unbranded advertising of prescription medicines, conducted by or on behalf of pharmaceutical companies, on consumers' attitudes, knowledge, behaviours, health services use, health outcomes and costs. This review aims to add to a better understanding of the effects of these campaigns by synthetizing existing research evidence and providing a comprehensive overview both of what is known about the outcomes of such campaigns and gaps in research evidence.

In **Chapter 4.2** we assessed the frequency of health and treatment information in printed Dutch media and developed a user-friendly instrument to assess the compliance of disease information campaigns with current regulations. This instrument was based on overlapping criteria from the WHO Ethical Criteria for Medicinal Drug Promotion and the Dutch self-regulation guidelines on the provision of disease and treatment information about prescription-only medicines by pharmaceutical companies to the public. The seven criteria identified were promotional information, misleading or incomplete information, use of fear, inadequate language, lack of balance, use of testimonials and absence of listed author and/or sponsor. Materials referring to health or disease and available treatments published in the most widely circulated newspapers and magazines were collected. From these, disease awareness advertisements were identified and the evaluation tool was used to explore the consistency of the information provided with the WHO and Dutch criteria.

Our results show that there is a focus on disease and treatment information in printed media in the Netherlands, both through news items and disease awareness campaigns. The majority (93%) of disease awareness campaigns identified complied neither with the WHO Ethical Criteria nor with the current Dutch self-regulation guidelines. Although no brand names were mentioned, there were information deficiencies and evidence of information bias. A key concern

is that the context in which the information is provided, mostly through indirect referral, is likely to support treatment with the sponsor's product.

After the publication of the study on disease awareness campaigns in the Netherlands, a group of Latvian researchers expressed interested in applying a similar methodology to measure the frequency of disease awareness campaigns in Latvian media and to assess their compliance with international and European guidelines **(Chapter 4.3)**. In contrast with the Netherlands, significant less resources are devoted to health in Latvia and out-of-pocket payments for health are among the highest when compared to other countries in the Organisation for Economic Cooperation and Development (29). The same instrument was applied as in the Dutch study **(Chapter 4.2)** but the study period was extended to six months and materials were collected from both printed and online media.

Once again, our study confirmed that there is a strong focus on health and treatment information in national media with more than ten items being published every week in Latvia covering health-related news items and disease awareness campaigns. The frequency of disease awareness campaigns was higher than that reported in the Dutch study included in Chapter 4.2. The overwhelming majority of Latvian disease awareness campaigns (94.9%) did not comply with WHO Ethical Criteria nor with the self-regulatory guidelines. The overall compliance results seemed somewhat more positive than those obtained in the Dutch study, but 58.6% of the campaigns included in our Latvian sample failed to comply with two or more Ethical criteria.

Although these campaigns can contain information that is potentially valuable to the public, they also have many features that would make them promotional and are, in some cases, clearly designed to support treatment with the sponsor's product. Yet, they are not subject to the same type of regulatory oversight, as generally, if there is no explicit mention of a product name, these are not considered to be pharmaceutical advertising, even if the sponsor has a product on the market to treat the condition under discussion.

We were unable to identify the author or sponsor in 78% of the Latvian campaigns. This means that the target audience might remain unaware of the promotional intent of the information conveyed and of its commercial source. In addition, the information provided in the campaigns collected in our study was often incomplete or misleading about the presentation of benefits and harms of medicines and lacked balance. Inaccuracies and information imbalance can lead to increased health care costs if new more expensive drugs are used instead of equally effective lower-cost drugs or non-drug interventions.

In both studies, we retrieved examples of indirect references to treatments in association with the name or the logo of a pharmaceutical company. This constitutes unbranded product advertisement and seems to be in contravention of European law. The overall lack of compliance with current guidelines and regulation found in **Chapters 4.2 and 4.3** points to the need for more active monitoring and enforcement.

IMPLICATIONS FOR METHODOLOGY AND FUTURE RESEARCH

In this section we highlight some of the implications of our results for methodology and future research by focusing on three aspects which are relevant to pharmaceutical regulation: the alignment of regulatory and reimbursement evaluations; the importance of access to data and the use of innovative tools in pharmaceutical promotion research.

Measuring patient-reported outcomes: opportunity for future regulatory and health technology assessment alignment

The study on the use and implications of quality-of-life data in relative effectiveness assessments of anticancer medicines (**Chapter 2.2**) sheds light on the need to improve methods to measure and report patient-reported outcomes in oncology clinical trials. The current clinical development of oncology medicines is geared towards meeting requirements of regulatory licensing reviews rather than accommodating the needs of health technology assessment, where data on overall survival and quality-of-life are necessary (30). In some countries, there is a trend towards increasingly aggressive pharmacological treatment of patients with advanced incurable cancer, despite evidence that the treatment may not match patients' subjective expectations or informed preferences and that aggressive chemotherapy is associated with poorer quality of life and death, shorter survival and regret (31).Our results underscore the importance of obtaining an accurate assessment of the extent of treatment benefit by measuring and reporting outcomes that make a difference to patients' lives. In doing so, they might have broader application to future research from the perspective of treatment aims and quality of care. Given the ongoing initiatives across several EU Member States to promote collaboration between drug regulatory agencies and health technology bodies under the auspices of parallel scientific advice to (potential) marketing authorisation holders, our results might also contribute to the future alignment of regulatory and health technology activities, particularly in the field of oncology.

Data access remains piecemeal

The studies contained in this thesis have used both quantitative and qualitative methods to research current gaps in pharmaceutical regulation, or in the implementation thereof, that affect the overall public. The studies included in **Chapter 2** have used data available in the public domain, most available online, from health authorities, drug regulatory agencies, health technology assessment bodies and an independent drug bulletin. Since pharmaceutical promotion is a component of the business activity of pharmaceutical companies, much of the data relevant to its research are not readily available, such as information on spending and on product sales, as is evident from **Chapter 3**. Nevertheless, initiatives across the globe to establish mandatory disclosure portals of pharmaceutical industry payments to healthcare professionals and/or to patient organizations are likely to bring forward the research field. In the USA, because of the Sunshine Act, researchers have been able to link individual administrative prescribing data of thousands of physicians to payments they had received from the pharmaceutical industry

(32,33). This opens possibilities for research methodologies along the lines of dose-response studies, measuring the effects of promotional activities on prescribing behaviour at healthcare professional level (21). Since disease awareness campaigns are often run in tandem with direct promotion to prescribers, one can foresee future studies where the interaction of a specific campaign and payments to physicians are explored, also quantifying effects on prescribing patterns, health use and costs, as well as patient outcomes.

Similarly, recent initiatives promoting the disclosure of payments to patient organizations in European countries could also play a role in fuelling future research on the patient and consumer voice. While there is ample evidence of the association between industry funding and bias in research, education and practice, there are limited data on the possibility of similar associations between industry funding and advocacy group positioning (14). Given the ever expanding role of civil society groups in advocating for changes in health policy, future research studying the effect of financial sponsorship on patient and consumer groups' perspectives on health policies or changes to the regulatory and legislative framework would be highly informative. It would also be relevant to ascertain if such results could be extrapolated to a wider population of patient and consumer organisations. Other variables may also inform organisations' policy positions, such as the type of condition the organisation represents. Patients with diseases for which few treatments exist have different needs than patients with more common chronic conditions and might have differing perspectives on certain policy proposals. We would recommend that a larger study is executed studying possible associations between organisational perspectives on certain policies, the kind of condition or health issue around which they are mobilised and corporate sponsorship by the pharmaceutical industry.

Another important aspect is the fact that much of the evidence available and reported in our review on pharmaceutical promotion and its regulation (**Chapter 3.1**) comes from industrialized countries. The little evidence gathered from low and middle income countries showed a potentially greater impact on health care: dissemination of misleading promotional information to physicians with little or no information on safety aspects and frequent lack of compliance with international regulations. In resource-constrained settings where independent medicines information might be either scarce or inexistent, this can be highly problematic. This paucity of studies on pharmaceutical promotion could be caused by several factors, among which insufficient research due to lack of funding, an overstretched health workforce or an inadequate logistic infrastructure enabling data collection, linkage and analysis.

Innovative aspects in the regulation of pharmaceutical promotion

The *WHO Ethical Criteria for Medicinal Drug Promotion*, published in 1988, remain the global standard for the regulation of pharmaceutical promotion with an explicit aim to support the rational use of medicines (12). While the WHO Ethical criteria provide a set of guiding principles on which national regulations and codes can be based, they are not binding and thus their enactment into the legislation of UN Member States is not mandatory. Vacca's analysis of advertising and promotion of pharmaceutical regulation in seven Latin American countries

showed that the Ethical Criteria acted as a reference in norm-setting, but reported several shortcomings: exclusion of key concepts necessary to prevent harm and protect health; room for interpretation; use of vague wording to define promotion, advertising and medical information and little information on enforcement and sanctions (34).

As the implementation of the WHO Ethical Criteria remains incomplete across the world, researchers have called for an update, claiming that many new marketing strategies are not adequately covered by the 1988 document (35). New targets for promotional activities have also emerged such as patient groups as well as new means for dissemination which go beyond national borders, such as the Internet and social media. The ever-increasing scope and complexity of digital advertising and its span across various media outlets poses a challenge to authorities which are faced with regulatory frameworks that have not kept abreast with these developments. One of the points highlighted by researchers is the need to expand the document to include a broader range of ethical values, providing also details on how to interpret and act upon them (35). These recommendations offer one of several possible solutions to bridging the gap between the Ethical Criteria and practical application of regulatory standards. Our innovative methodology, presented in **Chapters 4.2 and 4.3**, offers another approach, showing that the existing principles can be interpreted and applied into a practical tool enabling further scrutiny of materials, distinguishing legitimate awareness campaigns from covert unbranded advertising. Our studies demonstrate that the empirical application of the criteria using an instrument is possible. Its application in the Netherlands and Latvia also adds an international scope as it allows a comparison of results across two European countries. We can foresee that similar adaptations could take place in other settings which take into account local self-regulation guidelines. The conversion of ethical principles into a functioning tool might also have implications for other research examining how normative standards are or not implemented in practice.

IMPLICATIONS FOR POLICY AND PRACTICE

Pharmaceutical policy that responds to public needs: added therapeutic value as a criterion for drug approval

In considering the results of this body of research, one question comes to light: to what extent is current pharmaceutical policy responding to public needs? An underlying component of public-driven pharmaceutical policy is clinical research. Ioannidis has advocated a reorientation of clinical research, recommending that it should be undertaken if there is a realistic prospect of making a difference to health and disease outcomes. He defends that many of the features that make clinical research useful can be identified and highlights, among others, two keys principles which are also very pertinent to our findings: patient centeredness and transparency (36).

Core to the concept of patient centeredness is the need for clinical research to respond to existing pressing health problems and unmet medical needs. This resonates also with our results. Our study in Brazil (**Chapter 2.1**) shows but a partial overlap between approved indications

for recently approved drugs in Brazil and the national disease burden. One could presume that the available therapeutic arsenal is already sufficient to treat the conditions contributing the most to the burden of disease. However, our findings indicate a focus on specific therapeutic classes such as antineoplastics and immunossupressants. The mismatch observed between real needs and new medicines is not uncommon, even though addressing problems with higher disease burdens is of greater utility in clinical research and ultimately to society (36). The review (**Chapter 3.1**) and the studies in the Netherlands and Latvia (**Chapters 4.2 and 4.3**) represent another aspect of a mismatch between patient needs and medicine promotion and use. They contain several examples of disease mongering (37) a practice which consists of widening diagnostic boundaries of illnesses and aggressively promoting their public awareness to expand the markets for treatment.

The need to centre research around patients' priorities by encouraging the development of real therapeutic innovation emerges from the studies included in Chapter 2. Ideally, such an overhaul would encompass eliciting patient needs prior to research onset, as well as designing clinical studies that explore outcomes relevant to patients and respond to questions which are valid from a societal perspective (38). In addition, placing public interests at the core means aligning clinical research with public priorities, understanding the weight patients and consumers assign to different problems and outcomes as well as their willingness to accept an intervention (36, 39). This also entails measuring and collecting data objectively as to ensure its robustness to enable appropriate analysis and comparison.

When researching and later disseminating information about new medicines, many manufacturers opt for a strategy focusing on one or more features which could be perceived as positive to help paint their new product in a better light (40). Yet quite frequently such attributes do not translate into better health outcomes for patients in real life. Oncology is a therapeutic domain where this tendency is strikingly visible (41-43). A systematic evaluation of oncology approvals by the European Medicines Agency between 2009 and 2013 has shown that most drugs entered the market without evidence of benefit on survival or quality of life. At a minimum of 3.3 years after market entry, there was still no conclusive evidence that these drugs either extended or improved life for most cancer indications (44). The accompanying editorial by Cohen stated clearly that *"the findings raise serious questions about why the current regulatory environment supports the approval of cancer drugs that may leave patients at risk of experiencing toxicity and reduced quality of life without deriving meaningful benefit"*. Adding up to this equation are also the high prices of anticancer drugs which are leaving patients without access to other treatments that could save their lives (45). How can this paradox be solved?

The clinical advantage of a new medicine can be assessed by comparing its incremental therapeutic value to that of the best available treatment options already on the market. This can be translated into positive patient-relevant endpoints and appropriate levels of effectiveness, efficacy and safety (46). Only 10% of drugs approved between 1999 and 2005 by the EMA were superior to already available drugs, showing a statistically significant difference in primary clinical endpoints (47). Similar rates for therapeutic added value have also been reported by

different researchers and independent drug bulletins (48,49). Our findings from the Brazil study (**Chapter 2.1**) also corroborate this trend.

The current drug approval procedure in the European Union consists of a benefit-risk assessment, balancing desirable and undesirable effects of the new medical product. This evaluation is based on three criteria: pharmaceutical quality, safety and efficacy. Market authorization is granted when there is a positive benefit-risk ratio, but the procedure does not demand a demonstration of superiority of the new medicine over already existing standard therapies. The European marketing authorization procedure does not entail a systematic assessment of added therapeutic value nor are manufacturers legally required to provide any comparisons (50). In fact, only 48% of all new medicines approved in the EU between 1999 and 2005 were compared with existing drugs at the time of marketing authorization (51). Most assessments of added therapeutic value in Europe are conducted by national authorities responsible for deciding the pricing and reimbursement status of new medicines.

The French independent bulletin *Prescrire,* assessed the therapeutic value of new drugs entering the market in France between 2008 and 2017 in terms of efficacy, safety or convenience (52). It concluded that 47% of the 943 new medicines or new indications were nothing new. While the product might have been a new substance it was considered superfluous as it did not add to the clinical possibilities offered by other medicines that were already available. Having a wider range of therapeutic options might be useful to tailor patient therapy or to stimulate price competition, but one can question whether it is judicious to provide a marketing authorization and its coupled patent protection to so many medicines that are "me-toos", i.e. copies of other medicines within the same therapeutic class which do not show an established treatment advantage. Many defend that to foster real innovation the current criteria for drug approval should be expanded to include a fourth requirement, that of a clear demonstration of added therapeutic value (43, 48, 53-55). By introducing comparative requirements at the time of market approval, manufacturers would be encouraged to focus on therapeutic areas with limited treatment options, thus addressing more pressing health problems and meeting societal needs.

Opening the black box: transparency as a means to an end

In today's health policy arena, the relationships between patient groups and pharmaceutical companies have been converted into important business tools. Patient advocacy groups are political actors and can help raise awareness about new medicines at an earlier stage, provide credible product endorsement, argue for fewer controls on drug licensing and pricing and increased support for medical research (13) (56). In doing so, they represent opportunities for pharmaceutical companies for direct interaction with the final user, either bypassing or adding pressure on more traditional intermediaries such as prescribers, regulatory agencies and payers. Another advantage is that patient groups are commonly perceived as being more trustworthy than other actors with obvious vested interests (13).

One of the objectives of the World Health Organization Good Governance for Medicines Programme is to increase transparency and accountability in medicine regulatory systems. A key component of that is promoting individual and institutional integrity (57). Article 63

of the European regulation governing procedures for the authorization and supervision of medicines establishes that "*members of the Scientific Committees and experts shall not have financial and other interests in the pharmaceutical industry that could affect their impartiality*"(58). Bearing this in mind, the European Medicines Agency has developed a policy on conflicts of interest (59). Each expert – scientific or patient - is invited to fill in a form and declare eventual conflicts of interest on an annual basis. The EMA policy considers any funding from a pharmaceutical company to an institution or an organization to be an indirect conflict of interest. Experts with indirect conflicts of interests are attributed the lowest risk level, which means that ample participation in activities and roles is allowed. An individual representing an organization that receives funds from pharmaceutical companies can be invited to participate in a committee meeting or other fora as an expert. While the completed competing interest forms are available to EMA officials and for consultation online, participants at the same event might remain unaware of the financial ties binding the expert's organization and marketing authorization holders.

The rationale behind the attribution of an indirect conflict of interest could be that experts working at large institutions receiving sponsorship from the pharmaceutical industry may not be directly involved in the sponsored activities and thus they are not representing the institution, but rather their own expertise. It seems somewhat unlikely that this would be justifiable for patient representatives who are involved in activities as active members or employees of the organisation. We would therefore be inclined to suggest an amendment to the EMA Policy on Conflicts of Interest. Nonetheless, the agency's efforts to improve transparency of eligible groups in recent years must be noted, as the criteria to be met by eligible organisations have been updated and clearer requirements for sponsorship thresholds and disclosure to the EMA have been introduced (60).

As outlined in **Chapter 1** the need for health authorities to engage in dialogue with patients and consumers is unquestionable. However, as shown in the article on patient and consumer groups (**Chapter 3.2**) the nature and extent of the ties between groups representing patients and the pharmaceutical industry do raise questions about whether the interaction with sponsored patient groups could come at a cost for health authorities - that of the erosion of public trust. The same public trust that these agencies were trying to build when they first encouraged exchanges with the public and civil society. After all, enabling discussions with groups that have financial ties with the same marketing authorization holders you are mandated to regulate could be perceived publicly as opening the door to undue commercial interests.

The widespread industry support of patient advocacy organizations eligible to work with the European Medicines Agency and the limitations of the disclosure practices of such organizations provide strong reasons in favour of creating a "sunshine" law to cover pharmaceutical industry payments to patient-advocacy organizations at European level. Similar initiatives have also been called for in the USA (56, 61) and drug regulatory authorities in France, the Netherlands and Portugal have started to systematically collect and publish online funding information about patient and consumer organizations (62-64). The disclosure of all sponsorship sources, the intended purpose of the funding (65), its value and the proportion

of organisational revenue it represents, is important as it provides a qualitative and quantitative evidence base from which to assess potential conflicts of interest. This could be a first step to help disentangle the complexity of the relationship between patient groups and corporate sponsors.

The lack of adequate transparency provisions concerning funding of patient and consumer organisations is one example of a failing in the current approach to transparency. There have been policy developments in Europe which have unveiled the financial links between the pharmaceutical industry and healthcare professionals. Fabbri et al. conducted a descriptive content analysis of the transparency provisions implemented by February 2017 in nine European Union (EU) countries concerning payments by pharmaceutical manufacturers to health professionals (66). They concluded that significant gaps remain in disclosure requirements and their implementation. The situation differed substantially from country to country and the most striking differences were between governmental and self-regulatory approaches, especially as to the comprehensiveness of the disclosed data. The authors called for minimum standards for disclosures to be implemented across Europe by establishing a transparency portal including all payments to healthcare professionals and organizations by health-related industries in a format that would enable further analysis.

Another unprecedented move to implement greater transparency, this time at health authority level, was adopted by the European Medicines Agency (EMA) in 2014 with the establishment of its policy on the publication clinical data (67). Since October 2016, the EMA has been sharing clinical data submitted by pharmaceutical companies during their marketing authorization applications under the centralized procedure. Public access to full clinical data is particularly important to protect public health as it allows independent analysis, enhances knowledge about the effects of medicines and prevents publication bias (68). This unparalleled policy at world-level aims to avoid duplication of clinical trials and to foster the development of new medicines, while building public confidence in EMA's scientific and decision-making processes (69).

Strategies which increase the access to clinical, regulatory, health technology assessment and pricing information are key to advance pharmaceutical research and policy. Not only do they encourage further analysis of decisions affecting health but they also provide a platform for institutional accountability and information sharing. Some of the initiatives outlined above are in their infancy so any evaluation is premature. Considering the commercial interests at hand within the pharmaceutical policy arena, initiatives to promote and encourage the transparency of all stakeholders as well as the nature and extent of their relationships are to be applauded and sustained. Yet ultimately, one should bear in mind that while transparency is a means to uphold public scrutiny, it is not a substitute for independence.

Covert pharmaceutical promotion practices underline regulatory gaps

Pharmaceutical industry marketing has been frequently cited as an important driving force of pharmaceuticalization which has been defined as "*the translation of transformation of human conditions, capabilities, and capacities into opportunities for pharmaceutical intervention*" (65). Several studies in this thesis confirm the existence of covert promotional activities, under

the guise of education, such as the use of key opinion leaders when disseminating information on new products to peer physicians, or broadcast condition-oriented campaigns to the public. Pipon has characterised direct to consumer information campaigns (70) as an effective means of drug familiarization (71) i.e. making the population acquainted with a particular and one-sided view of a condition, in terms of severity, incidence and treatment. The goal is then to expand the market of people to treat, including those who are unlikely to benefit by using a marketing technique known as disease branding which entails fostering the creation of a condition and aligning it with a product (72). This message is then disseminated to consumers, physicians and other stakeholders under the guise of an informational campaign which either redefines the importance of an existing condition or develops a whole new condition to build recognition for an unmet market need. If individuals believe that a new treatment can accomplish more than has been clinically demonstrated, they may make decisions based on an inaccurate understanding of the drug's harms and potential benefits (73).

The stages of the pharmaceutical production and distribution chain are under complex control. Within the realm of pharmaceutical promotion, the preferred mode of achieving public policy objectives is through co- and self-regulation (13). There is a longstanding debate on the merits and shortcomings of self-regulation with respect to its ability to ensure compliance with marketing rules (74). A 2007 study on the effectiveness of codes of conduct on pharmaceutical marketing noted a growing body of academic and non-academic literature from around the world that highlighted public concern over the pharmaceutical industries marketing practices and the industry's self-regulation of these practices (75). The ability of the self-regulatory codes in Sweden and the United Kingdom to adequately monitor and control promotion was called into question in an examination of code complaints, complainants and rulings for the period 2004-2012. According to the authors, the prevalence and severity of breaches testifies to a discrepancy between the ethical standard codified in industry codes and the actual conduct of the industry (76). There have also been suggestions of a partial regulatory failure (74).

Not all promotion necessarily leads to inappropriate medicine use. However, there is a tension between the competitive pressures that manufacturers face to expand product sales, and support for judicious use of the most cost-effective of available alternatives (77). The behaviour of multinational companies which are accountable to their shareholders does not necessarily mirror or respond to public health priorities (78).

To realize the full potential health benefits of medicines both access to accurate information from the industry as well as independent information are needed, with a clearer distinction between commercial activities and health-care provision and use. The focus on product-specific information by regulators creates a leeway for other non-classical promotional practices. The results of our studies on disease awareness campaigns indicate that condition-oriented unbranded advertising can also be highly misleading with the aims of promoting a treatment and encouraging product sales.

In order to better manage medicine use so as to maximize health benefits and cost-effectiveness, national governments need to adopt two complementary approaches within

a broader national medicines policy. First, the regulation of the promotion of pharmaceuticals needs to be improved to address current voids in their response to new developments. This is a necessary precondition to the promotion of rational medicine use. Secondly, publicly-financed, independent information needs to be integrated into health service provision. Even the best-regulated promotion of pharmaceuticals aims, by definition, to sell a product, and cannot replace non-commercial, unbiased comparative information sources.

FINAL CONCLUSION

This thesis presented an analysis of challenging issues in pharmaceutical policy from a patient perspective, untangling how the dissemination of information across stakeholders influences the uptake of new pharmaceutical products. Within the realm of pharmaceutical policy, we have explored initiatives or practices which are intrinsically perceived as positive developments but that, after thorough examination, demand further monitoring and action. These span a range of policy arenas including patient-relevant outcomes as backbone for regulatory and reimbursement decisions, public participation in regulatory decision-making, as well as transparency and information access.

Three key points stand out. First, the importance of applying rigorous standards for drug approval and reimbursement as a corner stone for appropriate medicine use. Placing public interests at the core means aligning clinical research with public priorities, designing clinical studies that explore outcomes relevant to patients and respond to questions which are valid from a societal perspective. The introduction of comparative requirements at the time of market approval could encourage manufacturers to go beyond incremental innovation and to focus on therapeutic areas with limited treatment options, thus addressing more pressing health problems and meeting societal needs.

Second, the need to ensure proper representation in regulatory and pharmaceutical policy debates. Bearing in mind that the formation of pharmaceutical policy at the EU level relies on a multi-stakeholder approach, it is imperative that all sponsorship sources be publicly disclosed, as well as the intended purpose of the funding, its value and the proportion of organisational revenue it represents. There are strong reasons in favour of creating a "sunshine" law to cover pharmaceutical industry payments to patient-advocacy organizations at European level. This could be a first step to help disentangle the complexity of the relationship between patient groups and corporate sponsors.

Third, there are gaps in regulation of pharmaceutical promotion, especially in addressing new forms of promotion disguised as educational activities, such as the use of key opinion leaders and disease awareness campaigns. While there are some overall positive trends in some countries more systemic fundamental changes are needed to address current gaps. These require either an improvement or a better enforcement of current regulations.

Finally, the focus of pharmaceutical policies has been changing over the last years from product-driven procedures to patient-driven decisions. This transition did not come naturally for many stakeholders who traditionally did not see patients as their peers. A pivotal example

where the need for patient engagement is vital is the current debate on regulatory reform, flexibilities and data disclosure. These are discussions which touch the core of pharmaceutical policies and which can be of great consequence to overall health outcomes (79).

This thesis aimed to unfold challenging developments in pharmaceutical policy while providing guidance for the future, recognizing medicines as social goods which are instrumental to public health and embedding values such as transparency and public health driven policy. Sitting patients at the table must be more than a window-dressing exercise or the ticking of a box. Real inclusion of patients and consumers in health policy entails a commitment to apply democratic principles ensuring that those more directly affected and concerned by decisions are heard and actively engaged in the processes leading to those choices, be it in research, policy-making or practice.

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CHAPTER 6

SUMMARY

CHAPTER 6.1

SUMMARY

Today's patients are more vocal, informed and eager to participate in processes which affect them. This also applies to the pharmaceutical policy arena – and to debates around the research and development of new drugs, their access and use. Patients and consumers play varied roles in pharmaceutical policy. They represent peers in dedicated platforms hosted by health authorities, provide input on their preferences and experiences in medicines' use, advocate for reimbursement of new therapies, and can also be the target audience of awareness campaigns and pharmaceutical advertising. There are many instances for patient involvement throughout a drug's life cycle which also represent unique opportunities for research.

This thesis presents an analysis of challenging issues in pharmaceutical policy from a patient perspective untangling how the dissemination of information across stakeholders influences the uptake of new pharmaceutical products. In doing so, we have put forward a model for the adoption of innovative drugs across key actors in the health system. Within the realm of pharmaceutical policy, we have explored initiatives or practices which are intrinsically perceived as positive developments but that, after thorough examination, demand further monitoring and action. These span a range of policy arenas including patient-relevant outcomes as backbone for regulatory and reimbursement decisions, public participation in regulatory decision-making, as well as transparency and information access.

In **Chapter 2.1.** we assessed the relative advantage of new medicines by studying the level of therapeutic innovation of new approvals in Brazil over a thirteen-year period. Our results show that most of newly approved medicines did not exhibit a clinically relevant advantage over existing established therapies, either in terms of better efficacy, safety or patient outcomes. In addition, the majority of new drugs target specific niches, such as oncology and chronic conditions rather than other indications of greater public health relevance for Brazil, such as neglected diseases.

In **Chapter 2.2.** we explored the role played by quality-of-life data in relative effectiveness assessments for Health Technology Assessment (HTA) recommendations of new cancer drugs in six European jurisdictions. Our evidence suggests that quality-of-life data were included in just half of all the available reports. In addition, their impact on the recommendations was limited as one-fourth of the recommendations included no information whatsoever on quality-of-life data.

In **Chapter 3.1** we scoped into the strategies used by the pharmaceutical industry to influence healthcare professionals and the public. Our literature review focused on promotion activities taken directly by pharmaceutical companies with the aim of enhancing product sales, also analyzing the quality of information provided and the effects thereof. There review shows that there is ample evidence that promotion affects patterns of prescribing and medicine use, with effects on costs and on appropriateness of medicine use.

The study contained in **Chapter 3.2** is the first of its kind to provide baseline data on levels of corporate sponsorship among the groups eligible to work with the European Medicines Agency and studies the trends in financial disclosure and transparency between 2007 and 2011. Our evidence shows that by 2011 the majority (59%) of groups received funding from medicines'

manufacturers and/or industry associations and that there was low compliance with EMA reporting guidelines during our study period.

In **Chapter 4.1** a protocol for a systematic review is outlined to assess the effects of unbranded advertising of prescription medicines, conducted by or on behalf of pharmaceutical companies, on consumers' attitudes, knowledge, behaviours, health services use, health outcomes and costs.

In **Chapter 4.2** we assessed the frequency of health and treatment information in printed Dutch media and developed a user-friendly instrument to assess the compliance of disease information campaigns with current regulations. Our results show that there is a focus on disease and treatment information in printed media in the Netherlands and that the majority (93%) of disease awareness campaigns identified complied neither with the WHO Ethical Criteria nor with the current Dutch self-regulation guidelines. In **Chapter 4.3** The same instrument was applied in another country - Latvia - where we found a greater frequency of disease awareness campaigns. Similarly, the overwhelming majority of Latvian disease awareness campaigns (94.9%) did not comply with the WHO Ethical Criteria nor with the self-regulatory guidelines. In both studies, we retrieved examples of direct and indirect references to treatments in association with the name or the logo of a pharmaceutical company which seem to be in contravention of European law.

Three key points stand out. First, the importance of applying rigorous standards for drug approval and reimbursement as a corner stone for appropriate medicine use. Placing public interests at the core means aligning clinical research with public priorities, designing clinical studies that explore outcomes relevant to patients and respond to questions which are valid from a societal perspective. The introduction of comparative requirements at the time of market approval could encourage manufacturers to go beyond incremental innovation and to focus on therapeutic areas with limited treatment options, thus addressing more pressing health problems and meeting societal needs.

Second, the need to ensure proper representation in regulatory and pharmaceutical policy debates. Bearing in mind that the formation of pharmaceutical policy at the EU level relies on a multi-stakeholder approach, it is imperative that all sponsorship sources be publicly disclosed, as well as the intended purpose of the funding, its value and the proportion of organisational revenue it represents. There are strong reasons in favour of creating a "*sunshine*" law to cover pharmaceutical industry payments to patient-advocacy organizations at European level. This could be a first step to help disentangle the complexity of the relationship between patient groups and corporate sponsors.

Third, there are gaps in regulation of pharmaceutical promotion, especially in addressing new forms of promotion disguised as educational activities, such as the use of key opinion leaders and disease awareness campaigns. While there are some overall positive trends in some countries more systemic fundamental changes are needed to address current gaps. These require either an improvement or a better enforcement of current regulations.

Finally, the focus of pharmaceutical policies has been changing over the last years from product-driven procedures to patient-driven decisions. This transition did not come naturally for many stakeholders who traditionally did not see patients as their peers. This thesis aimed

to unfold challenging developments in pharmaceutical policy while providing guidance for the future, recognizing medicines as social goods which are instrumental to public health and embedding values such as transparency and public health driven policy. Sitting patients at the table must be more than a window-dressing exercise or the ticking of a box. Real inclusion of patients and consumers in health policy entails a commitment to apply democratic principles ensuring that those more directly affected and concerned by decisions are heard and actively engaged in the processes leading to those choices, be it in research, policy-making or practice.

CHAPTER 6.2

SAMENVATTING

Patiënten vandaag de dag zijn meer mondig, geïnformeerd en graag bereid deel te nemen in zaken die op hen betrekking hebben. Dit is ook van toepassing op het gebied van geneesmiddelenbeleid – en rond discussies rond het onderzoek en de ontwikkeling van nieuwegeneesmiddelen, alsmede het gebruik, toegang tot en toepassing van deze nieuwe geneesmiddelen.

Patiënten en consumenten spelen verschillende rollen in het geneesmiddelenbeleid.

Zij zijn vertegenwoordigd in specifieke fora die door gezondheidsinstanties zijn ingesteld, leveren input met betrekking tot hun voorkeuren en ervaringen in gebruik van geneesmiddelen, bepleiten vergoeding van nieuwe behandelingen, en kunnen ook een doelgroep zijn voor bewustwordingscampagnes en geneesmiddelenpromotie. Er zijn vele stadia van de betrokkenheid van patiënten gedurende de levenscyclus van een geneesmiddel, die ook unieke onderzoeksmogelijkheden bieden.

Dit proefschrift geeft een analyse van uitdagingen in geneesmiddelenbeleid vanuit het perspectief van patiënten en laat zien hoe de verspreiding van informatie tussen belanghebbenden de acceptatie van nieuwe farmaceutische producten beïnvloedt.

In het proefschrift wordt een model voorgesteld van of en hoe innovatieve geneesmiddelen door sleutelpartijen in het gezondheidssysteem worden geaccepteerd. Binnen het terrein van het geneesmiddelenbeleid hebben we initiatieven of toepassingen onderzocht die weliswaar als positieve ontwikkelingen kunnen worden beschouwd, maar die, na zorgvuldige analyse, toch nadere beschouwing en actie vereisen. Deze omvatten een scala van beleidsterreinen, waaronder uitkomsten die van belang zijn voor patiënten als een uitgangspunt voor regelgeving en besluiten rond vergoeding, publieke participatie in besluitvorming inzake regulering, alsmede transparantie en toegang tot informatie.

In **Hoofdstuk 2.1** onderzochten wij het relatieve voordeel van nieuwe geneesmiddelen door het niveau van therapeutische innovaties te bestuderen van recent goedgekeurde geneesmiddelen in Brazilië over een tijdsspanne van dertien jaar. Onze resultaten tonen aan dat de meeste nieuwe goedgekeurde geneesmiddel geen of maar een beperkt klinisch relevant voordeel hadden boven bestaande therapieën, zowel wat betreft werkzaamheid, veiligheid of patiënt-relevante uitkomsten. Daarbij richt het merendeel van nieuwe geneesmiddelen zich eerder op specifieke therapeutische niches, zoals oncologie en bepaalde chronische ziekten, dan op andere zaken van groter belang voor de volksgezondheid in Brazilië, zoals verwaarloosde ziekten.

In **Hoofdstuk 2.2** keken wij naar de rol die gegevens over kwaliteit-van-leven in relatieve effectiviteitsevaluaties van gezondheidstechnologie spelen bij aanbevelingen over nieuwe kankermiddelen in zes Europese landen. Ons onderzoek laat zien dat de gegevens over kwaliteit-van-leven in slechts de helft van de beschikbare evaluaties waren opgenomen. Daarbij was de invloed op de aanbevelingen beperkt, aangezien in een kwart van de evaluaties geen enkele informatie over de kwaliteit-van-leven stond.

In **Hoofdstuk 3.1.** onderzochten wij de strategieën die door de farmaceutische industrie worden gebruikt om zorgverleners en het algemene publiek te beïnvloeden. Ons literatuuroverzicht gaat nader in op de directe promotieactiviteiten van farmaceutische bedrijven met het doel de verkoop te vergroten, waarbij we ook keken naar de kwaliteit van

de beschikbare informatie en de effecten daarvan. Het onderzoek laat zien dat er veel bewijs is dat de geneesmiddelenpromotie patronen van voorschrijven en gebruik van geneesmiddelen beïnvloedt, met effecten op de kosten en de selectie van geneesmiddelen.

De studie in **Hoofdstuk 3.2** is een eerste in zijn soort die inzicht biedt over het niveau van industriesponsoring van groepen die samenwerken met het European Medicines Agency en die de trends over financiële openbaarheid en transparatie in de periode 2007-2011 zichtbaar maakt. Het onderzoek laat zien dat rond 2011 de meerderheid (59%) van deze partijen fondsen van fabricanten van geneesmiddelen en/of branchevereinigingen ontving en dat organisaties zich in deze periode weinig aantrokken van de EMA richtlijnen.

In **Hoofdstuk 4.1** staat een protocol voor het uitvoeren van een systematische review naar de effecten van het promoten door of in opdracht van farmaceutische bedrijven van receptplichtige geneesmiddelen, zonder het noemen van de merknaam , op het de houding, kennis en gedrag van consumenten, het gebruik van degezondheidszorg, de effecten op de gezondheid en de kosten.

In **Hoofdstuk 4.2** keken wij naar de frequentie van het aanbieden van informatie over gezondheid en behandeling van ziektes in de gedrukte pers in Nederland. Daarbij ontwikkelden wij een gebruiksvriendelijk instrument om de naleving van gangbare richtlijnen bij informatiecampagnes over ziektes vast te stellen. Ons onderzoek toont aan dat informatie over gezondheid en de behandeling van ziektes in gedrukte media in Nederland veel voorkomt. Bovendien dat de meerderheid (93%) van deze bewustmakingscampagnes niet conform de WHO etische criteria en de vingerende richtlijnen rond zelfregulering in Nederland waren.

In **Hoofdstuk 4.3** werd hetzelfde instrument toegepast in een ander land – Letland- waar wij een grotere frequentie aan informatiecampagnes van ziekten aantroffen. Vergelijkbaar, de overgrote meerderheid van informatiecampagnes van ziekten in Letland (94,9%) was niet conform de WHO etische criteria noch met de eigen gangbare richtlijnen rond zelfregulering. In beide studies vonden wij voorbeelden van direkte en indirekte verwijizngen naar behandeling met de naam of het logo van een farmaceutisch bedrijf, hetgeen niet conform Europese wetgeving is.

In het proefschrift komen drie hoofdpunten duidelijk naar voren. Ten eerste, het belang van de toepassing van hoge standaarden voor de goedkeuring en vergoeding van geneesmiddelen als basis voor het juiste gebruik. Door het publieke belang centraal te stellen zal klinisch onderzoek, zowel wat betreft vraagstelling als ontwerp, zich meer kunnen richten op prioriteiten die vanuit een maatschappelijk en patiëntenperspectief relevant zijn. Daarnaast kan meer nadruk op vergelijkende therapeutische meerwaarde producenten stimuleren zich meer te richten op therapeutische indicaties met beperkte behandelingsmogelijkheden om zo meer tegemoet te kunnen komen aan maatschappelijke behoeftes.

Ten tweede, de noodzaak voor een juiste vertegenwoordiging van belanghebbenden in debatten rond regelgeving en farmaceutisch beleid. Gegeven het feit dat geneesmiddelenbeleid op Europese niveau een multi-stakeholder aangelegenheid is, is het noodzakelijk dat alle bronnen van sponsoring publiekelijk bekend zijn, als ook het beoogde doel van de sponsoring, de hoogte van het bedrag en het percentage van de inkomsten voor de betreffende organisatie. Er zijn

belangrijke argumenten voor een *'Sunshine'* wet om de betalingen vanuit de farmaceutische industrie aan patientenorganisaties op Europees niveau te regelen. Dit zou een eerste stap kunnen zijn om de complexiteit in de relatie tussen patientenorganisaties en de industrie te ontwarren.

Ten derde, er zijn nog steeds lacunes in de regelgeving van de promotie van farmaceutische producten, vooral in het adresseren van nieuwe vormen van promotie verpakt als educatieve activiteiten, zoals het inzetten van belangrijke opiniemakers en bewustmakingscampagnes. Hoewel er een aantal positieve trends in sommige landen te zien is, zijn er meer systematische en fundamentele veranderingen nodig om de huidige lacunes te vullen. Deze vereisen hetzij een verbetering, dan wel een strictere handhaving van de huidige regels.

Tenslotte, de focus van farmaceutisch beleid is de laatste jaren verschoven van product gedreven procedures naar meer patiënt gedreven besluitvorming. Deze verschuiving is voor vele stakeholders die patiënten niet als gelijken beschouwden niet vanzelfsprekend. Dit proefschrift had als doel een aantal uitdagingen in het geneesmiddelenbeleid te analyseren, met ook een duidelijk knipoog naar de toekomst, met als uitgangspunt dat geneesmiddelen grote maatschappelijke betekenis hebben en dat waarden als transparantie en publieke orientatie daarbij een duidelijk plaats moeten hebben. Met patiënten rond de tafel zitten dient niet alleen 'voor de bühne' te zijn of het afvinken van een vakje. Het daadwerkelijk betrekken van patiënten en consumenten in gezondheidsbeleid vergt commitment tot het toepassen van democratische principes die garanderen dat direct betrokkenen gehoord worden en actief deel kunnen nemen aan het maken van keuzes, zowel in onderzoek, het maken van beleid of het vormgeven van de praktijk.

CHAPTER 6.3

RESUMO

Os doentes de hoje são mais vocais, informados e interessados em participar nos processos que os afectam. Isto também se aplica à temática da política farmacêutica, nomeadamente às discussões sobre a pesquisa e desenvolvimento de novos fármacos bem como ao acesso e utilização de medicamentos. Doentes e consumidores desempenham funções várias na política farmacêutica. Representam os seus pares em plataformas estabelecidas pelas autoridades da saúde, partilham as suas preferências e experiências quanto ao uso de medicamentos, defendem a comparticipação de novas terapias e podem também ser o alvo de campanhas de consciencialização pública e de publicidade farmacêutica. Ao longo do ciclo de vida de um medicamento existem numerosas ocasiões para a participação do doente que representam também oportunidades privilegiadas para pesquisa.

Esta tese apresenta uma análise de temas desafiantes na política farmacêutica sob o prisma do doente analisando de que forma a divulgação da informação através dos vários actores da cadeia influencia a utilização de novos produtos farmacêuticos. Assim sendo, sugerimos um modelo para a adopção de novos medicamentos pelos actores-chave do sistema de saúde. No âmbito da política farmacêutica, exploramos iniciativas ou práticas que são intrinsecamente identificadas como sendo positivas, mas que, depois de um exame atento, requerem monitorização e resposta adequadas. Estes desenvolvimentos cobrem uma área vasta de políticas, desde a implementação de desfechos clínicos relevantes para os doentes como requisito base para as decisões de regulamentação e reembolso de medicamentos, à partipação do público nas tomadas de decisões regulamentares, e ainda à transparência e acesso à informação.

No **Capítulo 2.1** avaliamos a vantagem relativa de novos medicamentos, analisando o nível de inovação terapêutica de novos fármacos aprovados no Brasil durante um período de treze anos. Os nossos resultados mostram que a grande maioria dos novos medicamentos não representa um avanço clínico significativo em relação a terapias já existentes, quer em termos de eficácia, quer em termos de segurança ou de desfechos relevantes para os doentes. Além disso, muitos dos novos medicamentos estão indicados para tratar nichos terapêuticos específicos, como a oncologia ou doenças crónicas, em detrimento de outras indicações de maior relevância para a saúde pública no Brasil, como as doenças negligenciadas.

No **Capítulo 2.2** exploramos o papel desempenhado pelos dados de qualidade de vida nas avaliações relativas de eficiência de novos medicamentos contra o cancro em seis jurisdições europeias, no contexto da avaliação das tecnologias de saúde. Os nossos resultados sugerem que os dados sobre a qualidade de vida só constam em metade dos relatórios disponíveis e que têm um impacto limitado, já que um quarto das recomendações finais não incluía qualquer informação sobre os dados de qualidade de vida.

No **Capítulo 3.1**, elencamos as estratégias usadas pela indústria farmacêutica para influenciar os profissionais de saúde e o público. Esta revisão da literatura visou as atividades promocionais levadas a cabo por empresas farmacêuticas com o objetivo de aumentar as vendas de produtos e analisou também a qualidade das informações prestadas e os seus efeitos. É vasta a evidência de que a publicidade afecta os padrões de prescrição e o uso de medicamentos, com efeitos tanto ao nível dos custos como da selecção de medicamentos.

O estudo contido no **Capítulo 3.2** é o primeiro deste tipo a fornecer dados de base sobre os níveis de patrocínio recebido pelas organizações de doentes e consumidores elegíveis para trabalhar com a Agência Europeia de Medicamentos (EMA) e estuda as tendências de apoio financeiro e transparência entre 2007 e 2011. Os nossos resultados mostram que em 2011 a maioria (59%) dos grupos de doentes e consumidores recebeu apoio financeiro de laboratórios farmacêuticos ou associações industriais, e que houve uma baixa conformidade com os requisitos de divulgação da EMA durante o período de estudo.

No **Capítulo 4.1** foi delineado um protocolo para uma revisão sistemática que avalia os efeitos da publicidade de medicamentos sujeitos a receita médica que não menciona o nome de marca, conduzida por ou em nome de empresas farmacêuticas, nas atitudes, conhecimentos e comportamentos dos consumidores, no uso de serviços de saúde, nos resultados para a saúde e nos custos.

No **Capítulo 4.2** estudamos a frequência de informação sobre saúde e tratamento disseminada na imprensa escrita nos Países Baixos e desenvolvemos um instrumento de fácil utilização para analisar a conformidade das campanhas de consciencialização de doenças com as regulamentações actuais. Os nossos resultados mostram que há um foco da informação dedicado às doenças e ao tratamento e que a maioria (93%) das campanhas de consciencialização não estão de acordo com os critérios éticos da Organização Mundial de Saúde (OMS) nem com as directrizes holandesas de autorregulação. No **Capítulo 4.3**, o mesmo instrumento foi aplicado noutro país europeu - a Letónia - onde encontramos uma maior frequência de campanhas de consciencialização de doenças. Da mesma forma, na Letónia a esmagadora maioria das campanhas (94,9%) não cumpriu os Critérios Éticos da OMS nem as diretrizes de autorregulação. Em ambos os estudos, identificamos exemplos de referência directa e indirecta a tratamentos específicos associados ao nome ou ao logotipo de uma empresa farmacêutica, o que nos parece estar em contravenção com a lei europeia.

Sobressaem três pontos fundamentais. Em primeiro lugar, a importância de aplicar padrões rigorosos durante a autorização de introdução no mercado e durante o reembolso ou comparticipação, como pedra de toque para a promoção de um uso responsável do medicamento. Colocar os interesses públicos no centro da questão significa alinhar a pesquisa clínica com as prioridades públicas, desenhando estudos clínicos que exploram desfechos relevantes para os doentes e que respondem a questões que são válidas para a sociedade. A aplicação de requisitos comparativos aquando da autorização de introdução no mercado poderá encorajar os laboratórios farmacêuticos a ir além da inovação incremental e provocar um enfoque em áreas terapêuticas com poucas opções terapêuticas, respondendo assim a problemas de saúde mais prementes e às reais necessidades públicas.

Em segundo lugar, a necessidade de assegurar uma representação adequada nas discussões regulamentares e nos debates relativos à política do medicamento. Tendo em conta que o processo de elaboração da política do medicamento a nível europeu consiste numa abordagem por vários intervenientes, é imperativo assegurar que todas as fontes de apoio são divulgadas publicamente, bem como o intuito desse apoio, o seu valor e a proporção que ocupa nos rendimentos da organização financiada. Existem fortes motivos para propor a criação

de uma lei de transparência a nível europeu que institua a publicação obrigatória de todos os pagamentos feitos pela indústria farmacêutica a associações de doentes. Este poderia ser o primeiro passo para ajudar a desenredar os laços complexos que unem os grupos de doentes às empresas patrocinadoras.

Em terceiro lugar, existem lacunas na regulamentação da publicidade aos medicamentos, particularmente no que toca a novas formas de promoção sob o véu de actividades educativas, como o uso de líderes de opinião e de campanhas de consciencialização pública. Ainda que existam alguns avanços positivos, mudanças mais sistémicas são necessárias para colmatar estas lacunas. Estas alterações implicam uma nova abordagem legislativa ou uma melhor aplicação da regulamentação em vigor.

Finalmente, o foco da política farmacêutica alterou-se ao longo dos últimos anos, passando de processos centrados no producto para decisões centradas no doente. Esta foi uma transição pouco natural para os intervenientes, que tradicionalmente não reconheciam os doentes enquanto pares. Esta tese procurou levantar o véu de alguns desafios da política farmacêutica, facultando uma orientação futura imbuída nos valores da transparência e do interesse público, e reconhecendo que os medicamentos são bens sociais instrumentais para a saúde pública. Promover a interacção com os doentes deve ser mais do que um exercício de fachada. A inclusão real dos doentes e dos consumidores nas políticas de saúde exige a aplicação dos princípios democráticos para assegurar que aqueles mais directamente afectados pelas decisões sejam ouvidos e estejam activamente envolvidos nos processos que levam a essas escolhas, quer na pesquisa, na política e na prática.

CHAPTER 7

APPENDIX

CHAPTER 7.1

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CHAPTER 7.2

SCIENTIFIC PUBLICATIONS INCLUDED IN THIS THESIS

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Compliance of disease awareness campaigns in printed and online media in Latvia with national and international regulatory guidelines
Submitted for publication

CHAPTER 7.3

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CHAPTER 7.4

ABOUT THE AUTHOR

Teresa was born and raised in Porto, Portugal, where she studied Pharmaceutical Sciences at the Faculty of Pharmacy. In 2005 she obtained a Masters in Public Health from the Netherlands Institute of Health Sciences (Erasmus University, Rotterdam).

Teresa has more than fifteen years' experience in the coordination and public relations of not-for-profit organizations in the field of pharmaceutical policy, having worked for the International Pharmaceutical Federation, Health Action International and the independent bulletin Prescrire in a variety of positions covering project management, communications and policy advocacy.

Her career placements have always been connected to international pharmacy and public health, and as a result, she became particularly interested in topics related to equitable access to essential medicines, medicines safety and rational use. She has developed invaluable knowledge of key stakeholders in European pharmaceutical policy as well as evidence-based advocacy skills. This has required expertise in identifying and maintaining contacts with NGO networks, policy-makers, academia and health authorities. She has also gained extensive experience as a fundraiser, public speaker, event organizer and editor. Between 2012 and 2017 Teresa worked part-time to pursue her PhD studies at Utrecht University, which resulted in the present thesis.

In 2018 Teresa moved from the NGO to the public sector. She is currently working as a Researcher for the Health Protection Unit of the National Institute for Public Health and the Environment (RIVM) in Bilthoven, the Netherlands.