Trust in the pharmaceutical sector

Analysis of drug safety controversies by means of drug life cycles

Juan Francisco Hernandez

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Vertrouwen in de farmaceutische sector
levenscycli van geneesmiddelen om controversen rondom geneesmiddelenveiligheid te analyseren
(met een samenvatting in het Nederlands)

Confianza en el sector farmacéutico
análisis de controversias de seguridad de medicamentos por medio de ciclos de vida de medicamentos
(con un resumen en Español)

Proefschrift
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CHAPTER 1

General introduction

Background

Bringing a new medicine to the market is risky business. The odds of getting a drug approved varies from almost 24% (for systemic anti-infective drugs) to less than 10% (for drugs used to treat cardiovascular, gastrointestinal or metabolic disorders) [1]. In other words, almost 8 out of 10 potential drugs are discontinued following a lengthy research and development process of up to 8-9 years (Figure 1) [1]. Bringing a new medicine to the market is also expensive: the costs of developing a drug from the early pre-clinical phase to entering the market are nearly $1 billion US Dollars [1].

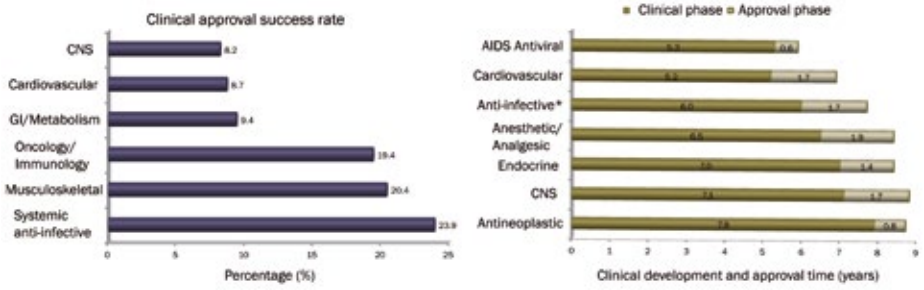

Figure 1. Clinical approval success rates for drugs (purple – percentages) and clinical development and approval times (green – years) indexed by therapeutic area [1].

In the last decades, the pharmaceutical industry has been forced to thrive in this complex paradigm of high risks, high costs and low output. In 2004, the World Health Organization (WHO) published the Priority Medicines for Europe and the World report, wherein the concerns about this complex paradigm are voiced [2]. Since the publication of the Priority Medicines report, several stakeholders from the pharmaceutical industry, governmental agencies, academia, and health care, among other institutions, have collaborated together to remove barriers to drug innovation. They proposed several ways to achieve this including rethinking and implementing regulatory changes; re-conceptualizing businesses; presenting proposals to shorten the drug development and evaluation process; and the institutionalization of public-private partnerships (PPP) to create bridges between stakeholders of the pharmaceutical sector to foster cooperation and nurture innovation [3-5].

In the Netherlands, the 2004 Priority Medicines report led to the institutionalization of the Top Institute Pharma (TIPharma); an institute to support PPPs where government, academia and the pharmaceutical industry joined forces to create, support and fund cross-disciplinary research within the Priority Medicines framework [5]. Within this context, TIPharma created the Escher Project: 16 PhD projects "studying medicine development and the European regulatory system for medicines" [6]. The Escher Project was divided into four themes: 1) evidence generation methods and evidence requirements, 2) scientific dialogue and stakeholder interaction, 3) the decision-making process and benefit-risk assessment, and 4) health technology assessment and evaluating societal impact [6]. Touching upon theme 2 and 4 within Escher, this thesis presents the studies that we have

conducted to analyze and determine the role of different stakeholders (i.e., pharmaceutical companies, regulatory authorities, and doctors) during drug safety controversies and to evaluate the societal impact of drug safety adverse events. For this purpose, we used drug life cycles (DLCs) as a heuristic tool to analyze drug safety controversies, while also the role of (public) trust in these stakeholders during the controversies was analyzed.

Measuring the impact of drug-related safety controversies on public trust

Society has been exposed to several health-related controversies, such as the thalidomide disaster in the late 1950s and early 1960s, where mothers were giving birth to babies with malformations in their extremities due to the use of thalidomide during pregnancy [7]; the Halcion case of 1979 with benzodiazepine-related amnesia, suicide and aggression [8]; the sponsored Mexican flu pandemic in 2010, where scientific advisors from governments and WHO were accused of having shared interests with the industry [9]; the market withdrawal of rosiglitazone in 2010 (in Europe) due to an increased risk of acute myocardial infarction [10]; or the presumed increased suicidality risk associated with the use of antidepressants, in particular the selective serotonin reuptake inhibitors (SSRIs) [11]. In all these instances, a common denominator can be observed: the societal exposure to drug related (health) risks.

Several proposals have been made to either manage or prevent, if possible, the occurrence of drug related risk events and resulting drug safety controversies, such as the need for a culture of transparency, promoting financial incentives for innovative products in high-need/high-risk disease areas, or strengthen the independence of regulatory authorities [3, 4, 12, 13]. However, the exposure of patients or the public to drug-related health risks is part and parcel of the daily practice of prescribing and taking medicines. Hence, new risk events will always pop up and develop into controversies. The challenge is therefore not how to prevent but how to manage the occurrence of drug related adverse events and drug controversies. For this reason, innovative studies on drug safety controversies that make use of a well-structured and common analytical framework are urgently needed to enrich our knowledge about the underlying dynamics of controversies, as well as to shed light on the role of different stakeholders. The knowledge obtained from these studies can be used and will result in improved and evidence-based risk management approaches focused on proactive instead of reactive responses to controversies. Also, the efficacy of regulatory interventions could be assessed with these types of studies.

The interaction between risks and society is complex and hence the governance of risks is a challenging endeavor. This process involves many stakeholders. Governmental institutions, such as regulatory authorities, are expected to provide “good risk governance” to offer guidance and management strategies to other stakeholders in order to properly deal with risks [14]. However, the governance of risks is beset with difficulties – ranging from sudden changes in the public perception of risks to unexpected alterations in prescribing patterns due to the off-label use of medicines. Prompted by the occurrence of

media hypes and public outcries around drug-related adverse events, regulators or other stakeholders may be tempted to execute politically motivated attempts to control the situation that turn out to fuel the controversy instead of calming the debate [14]. Lofstedt et al. mentioned that the inadequate execution of policies resembles a "knee-jerk reaction", which is characteristic during controversies and may contribute to distrust in governmental/regulatory institutions [14].

Many have argued that the consecutive series of drug safety related controversies have damaged (public) trust in the pharmaceutical industry, regulatory authorities, and practitioners [10, 14-16]. But, few have tried to explain this trust undermining process. So far, studies explaining why and how trust is undermined during controversies are anecdotal, not well documented or lacking analytical rigor. For instance, Lofstedt et al. analyzed changes in the nature of communication and regulation of risks in the context of three different controversies [14]. On the basis of this analysis, the authors argued that in Europe the regulation of risks has shifted from a consensual style (i.e., closed door decision-making process) to a model based on transparency, public participation and social and environmental values. According to the authors, the growth of public distrust in governmental/regulatory institutions was the main drive to phase-out this consensual style of regulation [14]. However, Lofstedt's contribution was too limited to clarify the dynamics of drug related (public) trust. In addition, this study did not provide an analytical tool that may be of help to policymakers in government and industry.

Analyses of drug safety controversies have overlooked the life cycle dynamics underlying the public perception and use of drugs. As a result, these analyses have delivered incomplete or inadequate assessments of the historical governance and performance of drugs in a rather volatile market place. Furthermore, clarifications for the synergetic role of stakeholders during drug safety controversies have been done based on qualitative analyses only instead of mixed methods approaches [14]. Therefore, it is important to integrate both aspects of life cycle dynamics (public perception and drug use) in well-structured combinations of qualitative and quantitative analyses and to implement the use of new proxy parameters and forms of visualizations to perform these analyses. These types of analyses may yield new insights which can contribute to a better understanding and governance of drug safety controversies and hence a more sustainable drug development and regulatory system.

Trust issues

In the past few decades, there has been an erosion of trust in pharmaceutical companies, regulatory authorities and healthcare providers [4, 16]. In fact, public polls have reported that positive attitudes towards pharmaceutical companies declined from 79% in 1997 to 44% in 2004 [17]. Still, this lack of trust is not exclusive to the pharmaceutical industry; the same polls have also revealed that health care institutions, such as health insurance companies or managed care companies are even less trusted than pharmaceutical companies [17]. And, trust in the government (including regulatory authorities) has also been reported to be low [14, 18].

Why are we confronted with this erosion of public trust in pharmaceutical companies, regulatory authorities and healthcare providers? There are many possible reasons behind this erosion of trust including insufficient patient safety and innovation, over-regulation, conflicted interests or lack of transparency [4, 9, 19-24]. Remarkably, specialists in the field of risk management, as well as prominent scientific/medical journals have argued that public trust has been eroded in these institutions as a result of regulatory scandals or controversies [14, 16, 25]. However, none of these sources has pre-specified the concept of trust. In other words, it is not clear the meaning of "trust" when referring to the pharmaceutical industry, regulatory authorities and doctors (i.e., pharmaceutical sector). This is an important omission in a global system that is characterized by a rather complex trade-off between benefit and risk of medicines.

To understand the nature, dynamics and characteristics of (public) trust in pharmaceutical companies, regulatory authorities, doctors and other stakeholders, it is necessary to analyze trust in a predetermined context. Therefore, the analysis of trust that is presented in this thesis was conducted in the context of one specific drug safety controversy: the SSRIs and suicidality controversy [16].

The SSRI and suicidality controversy

The SSRI and suicidality controversy has been one of the longest and most remarkable controversies in the past 20 years. In the late 1980s, the SSRIs entered the market as a new pharmacological alternative to treat depression and other psychiatric disorders. They claimed to have fewer side effects, and less risk of overdose, when compared with existing (older) antidepressants, such as tricyclic (TCAs) or monoamine oxidase inhibitors (MAOIs) [26, 27]. However, after their approval, Teicher et al. reported six cases of increased suicidal ideation during fluoxetine (an SSRI) course [28]. These reports stirred safety concerns within the medical sphere. The FDA acted upon these reports and called to a public hearing. In 1991, the FDA concluded that there was no clear evidence for an association between the use of SSRIs and an increased suicidality risk [29]. For more than a decade, the discussion about the safety of SSRIs remained in the background.

As a part of the FDA Modernization Act (FDAMA), GlaxoSmithKline (GSK) submitted extra clinical trial data on children to the FDA in 2002. With these data, GSK aimed to pursue six-month extension for paroxetine (an SSRI) for the treatment of pediatric depression. However, in the same year, the British Broadcasting Corporation (BBC) aired a documentary titled "The Secrets of Seroxat[1]". This documentary reported that the data submitted by GSK had been altered and that negative results—showing an increased suicidality risk with paroxetine—had not been disclosed [30]. The regulatory authorities were familiar with these data because they formed part of the registration dossiers [15]. Nevertheless, in 2004, the attorney-general of New York state sued GSK for "allegedly suppressing negative results" of antidepressant trials [31]. Yet, both the BBC documentary and

1 Seroxat is the brand name for paroxetine, GSK's SSRI.

the lawsuit blew the controversy out of proportions, unleashing an avalanche of negative newspaper articles that brought the safety of SSRIs into dispute. Preliminary regulatory analyses demonstrated that depressive children and adolescents had an increased risk of suicidality while on antidepressants [32]. Prompted by these analyses, in 2003-2004, the European Medicines Agency (EMA), the FDA, and other local regulatory agencies, such as the Medicines Evaluation Board (MEB[2]) in the Netherlands, issued a black box warning to all SSRIs, banning their use in children and adolescents [33-35]. The warning on antidepressants was revised in 2007-2008 and the SSRI ban was extended to young adults (19 to 25-years-old) [11, 35].

Role of stakeholders

Several stakeholders (e.g., doctors, regulators, attorneys, journalists or scientists) have been involved at different stages and intensities during this controversy, voicing their support or opposition on the use of antidepressants through different channels. For instance, David Healy - a British psychiatrist/physicopharmacologist - is an individual stakeholder who has acted as a whistleblower, an expert witness and as an author of several critical scientific articles and books about the efficacy, safety, or other controversial aspects of SSRIs [36, 37]. In similar ways, in the Netherlands, Trudy Dehue – psychologist/philosopher – has played an important catalyzing role during the controversy by publicly discussing topics such as the commercialization of psychiatric research, unethical marketing activities for antidepressants or the questionable standards to diagnose depression and its increasing incidence [38, 39].

What is the objective of this thesis?

The objective of this doctoral thesis is to elucidate the underlying dynamics of drug safety controversies and it aims to provide an analytical framework that is of added value to the governance of drug safety controversies. Also, the role of pharmaceutical companies, regulatory authorities, and doctors during drug safety controversies will be determined. The controversy that was selected as a source of study was the SSRI and suicidality controversy. For this aim, drug life cycles (DLCs) were used as a heuristic tool to analyze this particular controversy. In addition, the role of (public) trust in these stakeholders from the pharmaceutical sector was specifically analyzed as a factor that may influence or alter the effect of measures or actions.

What is the outline of this thesis?

Although many stakeholders within the pharmaceutical sector are continuously talking about trust, a consistent definition of public trust is lacking. This is problematic as it

2 College ter Beoordeling van Geneesmiddelen (Dutch CBG-MEB).

complicates the interpretation of expectations from the public in each of these stakeholders and the comparison between perceptions and results from trust studies in these stakeholders. Therefore, in ***chapter 2,*** we analyze the nature of other definitions of trust and propose a consistent definition of public trust in the pharmaceutical industry, regulatory authorities and doctors. ***Chapter 3*** presents an analysis of the empirical evidence whereon the claims of a lack of (public) trust are based on. For this aim, the methodologies and trust outcomes are analyzed of academic and non-academic empirical studies measuring public trust in 1) pharmaceutical companies, 2) regulatory authorities, and 3) doctors to discern ***what*** has been measured and ***how*** it has been measured.

In the predefined context of the SSRIs and suicidality case, a mixture of measurable parameters (qualitative and quantitative) is selected to build the analytical framework of DLCs. The selection of "measurable parameters" includes variables that may be representative to predict or interpret the nature and dynamics of (public) trust. The parameters that are measured/analyzed in this thesis are publication patterns in scientific journals and in newspapers, sales patterns, prescription patterns, and event-related data.

Based on the premise that media and communications are important vehicles for building and undermining trust [25, 40], we analyze in ***chapter 4*** the long-term dynamics of "good" and "bad" news in British and Dutch newspapers and compare them with publication patterns in scientific journals in the context of the SSRIs and suicidality controversy between 2000 and 2010. Taking into account the influential role of news media on public perceptions and consumption patterns [41-43], in ***chapter 5,*** we analyze trends of SSRI use between 2000 and 2010 in the Netherlands and the United Kingdom (UK) and whether changes in the use of SSRI (trend changes) can be associated with media coverage and regulatory warnings that were issued during the controversy. In ***chapter 6,*** the role of public trust during the SSRI and suicidality controversy is subsequently analyzed using the definition of public trust that is presented in chapter 2 to explain the importance of different components of trust in the relationship between a truster (e.g., public, patients or institutions) and a trustee (e.g., regulatory authorities, industry, governments or doctors). In ***chapter 7,*** we postulate and discuss the application of a multidimensional Drug Life Cycle (DLC) as a heuristic tool to study drug safety controversies.

Finally, in ***chapter 8,*** the findings from the earlier chapters are discussed and placed into the general context of drug safety controversies and current approaches for their management, the role of different stakeholders, and the importance of (public) trust in and between these stakeholders to foster a more sustainable drug innovation and regulatory system.

References

1. Miller G. Is Pharma Running Out of Brainy Ideas? Science. 2010 July 30, 2010;329(5991):502-4.
2. WHO. Priority Medicines for Europe and the World Geneva: WHO; 2004 [cited 2014 August 15]. Available from: http://archives.who.int/prioritymeds/report/index.htm.
3. Ameer B. Novel trial design: a report from the 19th frontiers symposium of ACCP. J Clin Pharmacol. 2008 Jul;48(7):793-8. PubMed PMID: 18499884.
4. Edwards B, Olsen AK, Whalen MD, Gold MJ. Guiding principles of safety as a basis for developing a pharmaceutical safety culture. Curr Drug Saf. 2007 May;2(2):135-9. PubMed PMID: 18690959.
5. Pharma TI. Top Institute Pharma 2014 [cited 2014 August 18]. Available from: http://www.tipharma.com/about-our-institute/our-mission.html.
6. Pharma TI. The Escher Project 2014 [cited 2014 August 18]. Available from: http://escher-projects.org.
7. Kim JH, Scialli AR. Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease. Toxicological Sciences. 2011 July 1, 2011;122(1):1-6.
8. Pieters T, Snelders S. Managing double binds in the pharmaceutical prescription market: the case of Halcion. JP. Gaudillière VH, eds. , editor. London: Palgrave Mac Millan 2012.
9. Bijl D, Schellekens H. The sponsored pandemic of the Mexican flu? The International Journal of Risk and Safety in Medicine. 2011;23(2):73-9.
10. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. New England Journal of Medicine. 2007;356(24):2457-71. PubMed PMID: 17517853.
11. FDA. Antidepressant Use in Children, Adolescents, and Adults Rockville, MD: Department of Health and Human Services; 2007 [cited 2011 7th February 2011]. Available from: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm.
12. Bauchner H FPB. Restoring confidence in the pharmaceutical industry. JAMA. 2013;309(6):607-9.
13. Olsen AK, Whalen MD. Public perceptions of the pharmaceutical industry and drug safety: implications for the pharmacovigilance professional and the culture of safety. Drug Saf. 2009;32(10):805-10. PubMed PMID: 19722724.
14. Lofstedt R, Bouder F, Wardman J, Chakraborty S. The changing nature of communication and regulation of risk in Europe. Journal of Risk Research. 2011;14(4):409-29.
15. Check E. Antidepressants: bitter pills. Nature. 2004 Sep 9;431(7005):122-4. PubMed PMID: 15356601.
16. Lenzer J. Scandals have eroded US public's confidence in drug industry. BMJ. 2004 2004-07-29 00:00:00;329(7460):247.
17. HarrisInteractive. Supermarkets, food companies, airlines, computers and banks top the list of industries doing a good job for their consumers New York, N.Y.: Har-

ris Interactive; 2004 [cited 2014 May 16]. Available from: http://www.harrisinteractive.com/vault/Harris-Interactive-Poll-Research-Supermarkets-Food-Companies-Airlines-Computers-and-2004-05.pdf.
18. Edelman. Trust in the pharmaceutical industry 2014 [cited 2014 May 19]. Available from: http://www.edelman.com/post/trust-pharmaceutical-industry/.
19. Fontanarosa Pb RDDCD. Postmarketing surveillance, lack of vigilance, lack of trust. JAMA. 2004;292(21):2647-50.
20. Stegemann S, Baeyens JP, Becker R, Maio M, Bresciani M, Shreeves T, et al. Design of pharmaceutical products to meet future patient needs requires modification of current development paradigms and business models. Z Gerontol Geriat. 2014 2014/04/18:1-3.
21. Hamburg MA. Advancing Regulatory Science. Science. 2011 February 25, 2011;331(6020):987.
22. Schellekens H, Moors E, Leufkens HG. Drug Regulatory Systems Must Foster Innovation. Science. 2011 April 8, 2011;332(6026):174-5.
23. Miller H. Federal Agencies: Waning Integrity, Dwindling Trust: Forbes; 2010 [cited 2012 April 3]. Available from: http://www.forbes.com/2010/07/18/fda-epa-regulation-trust-opinions-columnists-henry-i-miller.html.
24. Brown P, Calnan M. Braving a faceless new world? Conceptualizing trust in the pharmaceutical industry and its products. Health:. 2010 December 15, 2010.
25. Lofstedt R. Risk Management in Post Trust Societies. London: Earthscan; 2005.
26. Adams SM, Miller KE, Zylstra RG. Pharmacologic management of adult depression. American Family Physician. 2008;77(6):785-92+95-96.
27. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. The Journal of clinical psychiatry. 2011 Jul;71(7):839-54. PubMed PMID: 20667290.
28. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. American Journal of Psychiatry. 1990;147(2):207-10.
29. FDA. Psychopharmacological drugs advisory committee Rockville, Maryland: FDA; 1991 [cited 2013 March 15]. Available from: http://www.fda.gov/ohrms/dockets/ac/prozac/2443T1.pdf.
30. BBC. Panorama: The Secrets of Seroxat London: BBC; 2002 [cited 2012 1 February]. Documentary]. Available from: http://news.bbc.co.uk/panorama/hi/front_page/newsid_8425000/8425414.stm.
31. Wadman M. Spitzer sues drug giant for deceiving doctors. Nature. 2004 Jun 10;429(6992):589. PubMed PMID: 15190317.
32. Check E. Analysis highlights suicide risk of antidepressants. Nature. 2004 Aug 26;430(7003):954. PubMed PMID: 15329681.
33. FDA. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications Rockville, MD: Department of Health and Human Services; 2004 [cited 2011 20th January 2011]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm.
34. MHRA. Report of the CSM Expert Working Group on the Safety of Selective Sero-

tonin Reuptake Inhibitor Antidepressants. London: Committee on Safety of Medicines, 2004.
35. EMA. European Medicines Agency finalises review of antidepressants in children and adolescents London: EMA; 2005 [cited 2011 4th February]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/12/news_detail_000882.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1.
36. Healy DI. Conflicting interests in Toronto: anatomy of a controversy at the interface of academia and industry. Perspect Biol Med. 2002 Spring;45(2):250-63. PubMed PMID: 11919383.
37. Healy D. Let them eat Prozac: the unhealthy relationship between the pharmaceutical industry and depression. New York: New York University Press; 2004.
38. Dehue T. De Depressie-Epidemie: Atlas-contact; 2008.
39. TROS. Radar: Gebruik Antidepressiva kan Gevaar Opleveren: TROS; 2010 [cited 2011 7 Februari]. Available from: http://www.trosradar.nl/nieuws/archief/detail/article/gebruik-antidepressiva-kan-gevaar-opleveren/.
40. Goldacre B. Bad Science. Collins H, editor. London: Harper Collins; 2008.
41. Harrabin R, Coote A, Allen J. Health in the News: Risk, Reporting and Media Influence London: King's Fund, 2003.
42. Grilli R, Ramsay C, Minozzi S. Mass media interventions: effects on health services utilisation. Cochrane Database Syst Rev. 2002 (1):CD000389. PubMed PMID: 11869574.
43. David F, Archer M. Medical decisions regarding hormone therapy for menopausal women are significantly influenced by the media. Pharmacoepidemiol Drug Saf. 2007;16(1):28-31.

CHAPTER

2

Understanding trust in pharmaceutical companies, regulatory authorities and doctors

An analysis of the literature

Francisco Hernandez, Ghislaine van Thiel, Aukje Mantel-Teeuwisse, Jan Raaijmakers & Toine Pieters

Manuscript prepared for submission

Abstract

Background - Pharmaceutical companies, regulatory authorities and doctors are major stakeholders of the drug development and evaluating system. Trust among these parties is important for the sustainability of the system. However, the concept of trust has been variably defined. In this paper, we aim to develop a definition of the concept of trust and to illustrate its role in the interaction among major stakeholders in the pharmaceutical sector.

Methods - We performed a meta-narrative review of the literature. We searched for articles on trust through three different databases and through cross-references. Ninety-five articles were included.

Results - In the literature, two components of trust can be distinguished: the vulnerability and competence component. We combined these components in a relational definition of trust in the pharmaceutical sector as: 1) the willingness to assume a position of vulnerability in relation to the provision of care and the management and use of medicines together with 2) the reliance on the competence of pharmaceutical companies, regulatory authorities, and healthcare providers to perform the tasks assigned to them. The two-component definition is used to clarify trust in the context of drug development and use.

Conclusion - In the interactions between stakeholders of the pharmaceutical sector, trust is a critical relational characteristic that contributes to an endurable, collaborative, and sustainable pharmaceutical system. The components of trust in our definition for this context, and the conception of trust as a relational characteristic can be useful in further analyzing the influence of trust.

Introduction

Researchers from a variety of disciplines such as philosophy, sociology, management, economics, and political sciences have examined trust in key institutions including government, business, media, and non-governmental organizations (NGOs). Trust is seen as necessary for stable relationships, social integration, and economic efficiency, among other benefits [1-5]. Trust is also held responsible for collective and voluntary compliance in democratically established regulations and norms for all kinds of human activities [6], whereas distrust destabilizes cooperation, and impedes and distorts communication [5]. Regardless of its perceived importance, trust is defined and measured in disparate ways across studies and disciplines [5, 7-10].

In the pharmaceutical sector, a series of drug safety controversies have appeared to erode public trust [11, 12], according public opinion polls and surveys [13-15]. Furthermore, close ties between science, industry and government, and the resulting conflicts of interest have raised public concern [16-18]. However, no consumer survey or public poll has pre-specified the concept of trust. This is an important omission in a global system that is characterized by a rather complex trade-off between benefit and risk of medicines.

Lofstedt (2005) proposed a definition of trust for regulators and pharmaceutical companies [19]. Although valuable, Lofstedt's definition was mostly directed towards trust in institutions. In our view, a definition of trust should expand its scope to the most important trust relationships in drug development, regulation and drug use. We depicted these relationships in Figure 1. A definition of trust for the pharmaceutical sector is necessary to clarify the nature of trust, enable comparativeness between trust studies to adopt general actions to promote and improve trust. This article presents a conceptual analysis of trust and its relevance to the interaction between the major stakeholders in the pharmaceutical sector.

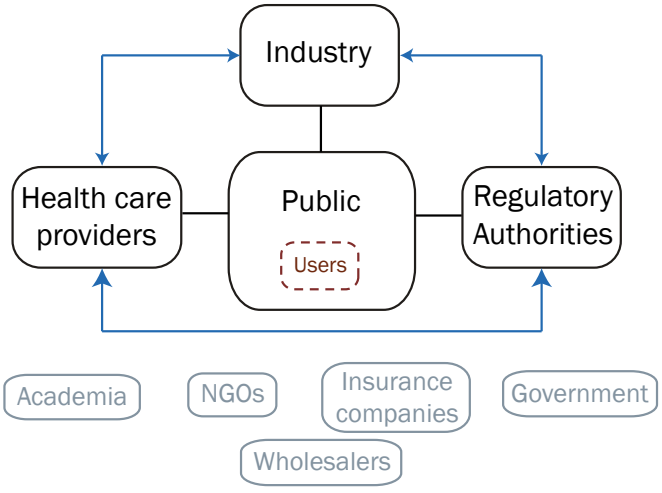

Figure 1. Trust relationships between the most important stakeholders of the drug development, regulation and drug use system. A definition of trust should comprehend and cover the relationships between all these stakeholders and their interactions.

Aim

The aim is to offer a definition of the concept of trust, based on a review of the literature on trust, focusing on pharmaceutical companies, regulatory authorities and doctors. An additional aim is to clarify the dynamics of trust in relationships between the major stakeholders in the pharmaceutical sector.

Methods

We used a "meta-narrative approach" for our review [20]. This is a form of systematic review developed for the synthesis of evidence across multiple disciplinary fields. The search for articles was conducted in three scientific databases to include articles from various disciplines: 1) PubMed, 2) Scopus, and 3) Web of Science.

Trust has been reported to have multi-dimensional traits (i.e., psychological, cognitive and emotional), and can be confused with a multitude of synonyms, such as mutuality, empathy, reciprocity, respect, solidarity, confidence or fraternity that all are in essence different from trust itself [5, 8, 10, 21-29]. To avoid overlap between trust and other terms, we deliberately decided not to use synonyms or truncated modifications of the search keywords. Instead, two combinations of keywords were used, "trust AND concept" and "trust AND definition". Our search was limited to articles only about humans, reviews, systematic reviews, and articles written in English, Spanish or Dutch from January 1, 1980 to June 30, 2013. We used cross-referencing to identify additional articles.

In total, 604 articles were extracted (69 PubMed, 84 Scopus, 185 Web of Science, and 266 cross-references) of which 24 were duplicates. The two criteria for inclusion of articles were: I) the main topic of the article was about trust and II) the article provided a definition or conceptualization of trust. The selection occurred in a three-stage analysis: 1) the content of title, 2) abstract, and/or 3) full-text. The extraction and selection process is portrayed in Figure 2. Two researchers scanned articles independently (FH and TP) and the rate of disagreement was less than 5%.

Results

Definitions of trust

Ninety-five articles were included. From our review of the literature, multiple definitions of trust were identified in the following disciplines: business (n=2), economics (n=12), ethics (n=3), healthcare (n=28) informatics (n=5), law (n=7), management (n=15), marketing (n=2), philosophy (n=4), political sciences (n=7), psychology (n=1), risk management (n=1), and sociology (n=8 articles). The general description of the sample of analyzed articles is listed in Appendix table 1. All definitions were context/discipline dependent and explored the concept of trust in general. We found, however, that most definitions were directly or indirectly characterized by the preponderance of two trust components, namely vulnerability and competence. We will elaborate on this finding in the following paragraphs.

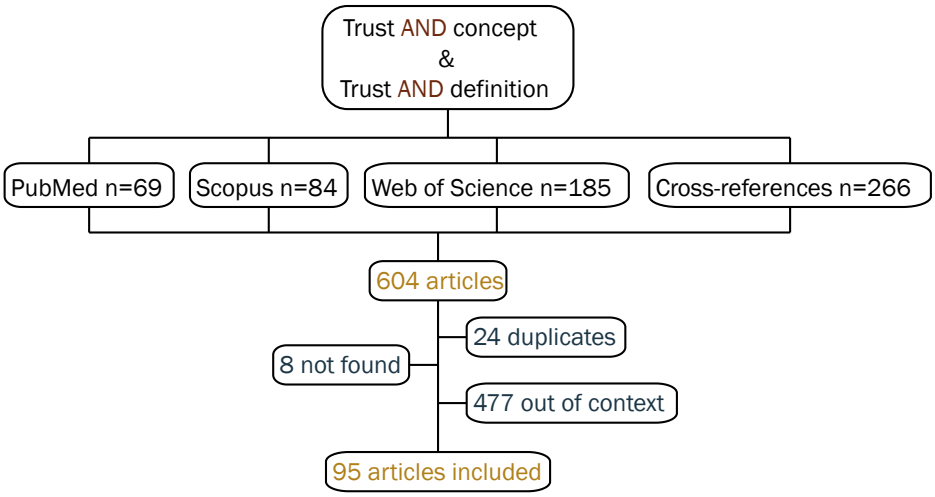

Figure 2. Selection process of the review for inclusion of articles with a definition of trust, according to the PRISMA standards.

The "vulnerability" component

In the literature, we found that trust was often defined as the willingness to assume a position of vulnerability towards an individual, institution, or organization [4-8, 25-57]. Trust is used as a mechanism to cope with vulnerability [40, 58] to compensate for the truster's level of uncertainty or risk by ceding control over the situation, outcome, or possession [9, 40, 59, 60]. In a context of trust, risks are perceived as more acceptable, tolerable, favorable, logical, and less uncertain or dangerous [7, 22, 25, 40, 58-61]. Hall et al. stated that trust is no longer needed in the absence of vulnerability and that trust and vulnerability are inextricable [27]. Others have implied that without risk, trust becomes unnecessary [22, 24, 25, 27, 59-63]. Accepting the possibility to be harmed is a decision based on the assumption that the entrusted party will not exacerbate the initial situation or the condition of the truster before trusting, or will not abuse or exploit his/her vulnerability. Ideally, the trustee will prioritize and aim to protect the truster's interests by honoring the deposited trust. This particular behavior is motivated by the trustee's goodwill to behave in a benevolent, trustworthy, integral, honest, or reliable manner [4-7, 9, 21, 26, 27, 40, 46, 48-53, 55-59, 64-79].

The importance of trust can only be assessed after we realize the value of the object that was entrusted to another person or institution [1, 5, 25, 27, 28, 33, 37, 40, 43, 44, 48, 52, 78, 80-85]. For instance, in a business relationship or an economic transaction, profit or reputation could represent what is at stake in a trust relationship. Similarly, in a healthcare or pharmaceutical setting, the patient's well-being, health or even life may all represent what is at stake, and thus making patients vulnerable when investing their trust.

The "competence" component

Another prominent component of definitions of trust in the literature was the belief, faith, expectation, or reliance in the competence or capability of an individual, institution, or organization to skillfully perform a particular task [1, 8, 22, 30, 31, 33-36, 42, 45, 46, 50, 51, 55-58, 60-66, 69, 74, 77, 79, 80, 82, 84, 86-93]. This is the "competence" component and also includes the trustee's understanding of the truster's needs and the capacity to solve them efficiently [40, 46, 47, 55, 69, 83, 92, 93]. Performing this task, however, is a "voluntarily accepted duty" to act towards the truster in a dependable, secure, reliable, credible, accurate, cooperative, ethical, morally correct, honest, or open manner [1, 8, 22, 56, 60-63, 77, 80, 87-89, 91]. Trust, however, cannot be forced; instead, it should be taught, practiced and nourished freely [94]. The moment this "duty" is deliberately accepted, it is transformed into a responsibility, fiduciary or moral obligation to demonstrate the trustee's concern for the truster's interests [1, 2, 21, 26, 89, 90]. The truster may perceive the competence of the trustee by honoring this "fiduciary" obligation. Trusting a trustee with the performance of a task derives from the trustee's ability or competence to complete this task and the truster's lack of competence to perform it autonomously. A truster is more likely to trust an individual or institution when competence (e.g., professional or technical skills or knowledge) is accompanied by other fundamental (unforced) attributes, such as benevolence, good will, honesty, fidelity, communication, cooperation, and truthfulness [21, 25, 27-29, 56, 78, 83, 84, 91, 92, 94-100]. However, abovementioned attributes, among many others, become less relevant or meaningless if the trustee is incompetent [101].

What does trust mean in the pharmaceutical sector?

Trust is not a dichotomous characteristic as it can be demonstrated in high or low levels [40]. Thus, trust is a dynamic position of acceptance or reliance of a person in relation to another person or institution. The intensity or levels in which the components vulnerability and competence are displayed or perceived are proportionate to the levels of trust is deposited on each of the stakeholders in the pharmaceutical sector. Based on the above, we define trust in pharmaceutical companies, regulatory authorities and doctors as 1) the willingness to accept or assume a position of vulnerability in relation to the provision of care and the management and use of medicines. Trust also means 2) the reliance on or belief in the competence of pharmaceutical companies, regulatory authorities, and healthcare providers to perform the task they are responsible for and expected to do—developing, making and evaluating high quality pharmaceutical products for public use and providing adequate healthcare.

Trust components in interactions between stakeholders

So far, we have focused on a definition of trust in the pharmaceutical sector. To clarify the concept, we now take a look at the trust components in the interaction between the public, pharmaceutical companies, regulatory authorities and doctors.

The pharmaceutical industry

Pharmaceutical companies are responsible for the safety and the efficacy of their marketed products. As in any other business transaction, customers either consciously or unconsciously assume a certain degree of vulnerability when they decide to use a particular product or commodity for a determined purpose [48, 102]. Examples of commodity use are a car for transportation, mobile phones for communication, or medicines for the treatment of a particular illness. In all these situations, customers enter a risk zone. The uncertainties and risks that may be associated with the use of medicines delineate the different levels of vulnerability that patients could be confronted with when using medicines. Drug effects may differ and the public's level of awareness about side effects and adverse events further substantiate drug users' perceptions of their vulnerability and uncertainty, and thereby risks [103]. During pharmaceutical therapy, patients may more easily cope with or manage their vulnerability when trust in the pharmaceutical industry and their products is present [25, 27, 63, 87].

Pharmaceutical companies, as trustees, are responsible for the development, production and distribution of medicines of quality [26, 64, 74, 100, 104]; they have an ethical and moral responsibility towards their product users and society [105]. The past decade, however, a series of drug safety controversies have highlighted unethical industry practices, such as selective publication of trial results or illegal marketing campaigns to promote products [18, 106]. These public issues about the lack of safety or effectiveness of medicines have raised questions about the industry's competence [105, 107, 108]. The levels of competence that the public or patients may perceive from pharmaceutical companies is essential in shaping and giving ground to trust.

Regulatory authorities

Regulatory authorities are independent bodies (institutions) that represent the public and are responsible for: 1) reviewing product safety data during pre- and post-marketing phases and 2) making decisions, based upon that data, whether those products are safe and efficacious enough to grant market approval. Several laws and regulations delineate these responsibilities and decision-making processes [109, 110]. Regulatory authorities, as expert public representatives, are expected to be transparent and communicate their regulatory decision-making process and final decision to the public. Furthermore, they are expected to include and consider comments from the public in their decision-making process before making decisions on market approval or withdrawal [12, 109, 111]. These institutions are expected to function on ethical standards and altruism [3, 26, 112]. From a vulnerability perspective, trust in regulatory authorities is needed to negotiate the uncertainties and risks in the light of possible negative outcomes when using drugs [27, 63, 87].

Unfortunately, as expert public representatives, regulatory authorities have occasionally demonstrated limitations and flaws. Abraham (2002) argues that the regulatory authorities' power to control pharmaceutical companies and ensure the public's safety is overruled by the financial and political might of the industry [113]. Cozy relationships between pharmaceutical companies and regulators may have obstructed the objective

evaluation of medicines and their risks [105, 114], rising concerns about the competence of authorities. In addition, regulators' acquaintance with risk communication and the need for more proactive communication strategies are competences where still there is room for improvement [11, 115]. Managing vulnerability and risks is improved when more information is available (open communication), or when the truster is aware of the implications of vulnerability or risk while trusting [12].

The interactions between regulatory authorities and pharmaceutical companies are generally contractual, outlined by legislations and regulations [3, 116]. Although legislation and regulation are contracts of trust (substitutes of trust [49]), scholars have argued that excessive regulation and legislation are detrimental to trust, and excessive general reliance on the law is a symptom of a loss of trust [3, 44, 49, 58, 104, 117]. Instead, balanced law enforcement provides guarantees for the completion of a task or compliance with regulations. Scholars argue that trust, instead of the "regulatory leviathan", is the most important factor in contractual and non-contractual interactions capable of facilitating cooperation and revitalizing the interactions between pharmaceutical companies and regulatory authorities, as well as other stakeholders [2, 26, 44, 118]. Therefore, increasing attention to the role of trust in the interactions between pharmaceutical companies and regulatory authorities is important to avoid unnecessary contracts and regulations.

Doctors and other healthcare providers

How the public interacts with healthcare providers is quite distinct from their interactions with regulatory authorities or pharmaceutical companies. The interactions with healthcare providers include the prescription of medicines, as well as care (other types of interventions/therapies). Usually, patients expose their vulnerability by handing over total or partial control of their situation/illness to a doctor or healthcare provider. It is assumed that trust will arise in situations where vulnerability (uncertainty) is present [27]. In the context of a patient's vulnerability, trust may function as a coping mechanism. Simultaneously, the process of ceding control over an illness includes the expectancy of competence (expertise and knowledge) of healthcare providers [27]. Patients and the public have demonstrated trust in doctors and healthcare providers when they are capable of behaving in a benevolent, caring, empathetic and open manner and have strong communicative skills [10, 46, 83, 84, 119]. Positive outcomes, such as adherence, compliance or recovery, are more likely to occur when trust is in place [27, 83, 120, 121]. However, several behaviors by healthcare providers have been reported to damage instead of enhance their image in the public's eye [18, 122]. For example, Clark argues that in the patient-doctor relationship the principle of caveat emptor is not applicable since patients want to feel secure that extraneous forces do not influence a doctor's prescribing habits or practice [123]. Interactions between doctors and regulatory authorities have not generally been a source of concern to patients or the public. On the contrary, this level of interaction is strongly motivated and accepted, as long as doctors and regulatory authorities improve patient and public safety [3, 103, 124-126].

In contrast to the interactions between regulatory authorities and doctors, public trust may be threatened by doctors' interactions with pharmaceutical companies. The closer or

cozier these interactions are, the greater the public's and patients' lack of trust and wariness becomes [127, 128]. Healthcare providers' integrity and conflict of interests have been questioned, affecting their credibility and reputation in the eyes of the public [122, 127-132]. Citing "malpractice crisis, legalistic atmosphere surrounding treatment, commercialization of medical care, or depersonalization of care", scholars have argued that public trust in the medical profession has decreased over the last years [78, 83, 119, 123].

Discussion

Trust is a multi-dimensional concept with psychological, cognitive and emotional features [49]. According to the literature, the definitions of trust are manifold and context-dependent [5, 7, 8]. So far, the function of public trust in the relationships between and within pharmaceutical companies, regulatory authorities and doctors has not been clarified. Our work extends in this field by providing a literature-based definition of trust as a relational concept with two components: 1) the willingness to assume a position of vulnerability in relation to the provision of care and the management and use of medicines together with 2) the reliance on the competency of pharmaceutical companies, regulatory authorities, and healthcare providers to perform the tasks that they are responsible for and expected to do.

We describe public trust in pharmaceutical companies, regulatory authorities, and doctors. Given the vulnerability that may confront patients or the public in illness situations or when using medicines, and the competency that the public and patients seek from pharmaceutical companies, regulatory agencies, and doctors, both the vulnerability and competence components demonstrate the intertwined and relational nature of trust and the importance of trusting abovementioned stakeholders. However, the importance of trust in pharmaceutical companies and regulatory authorities has been under-researched. We demonstrate the importance of trust by translating the concept of trust to a present context, where the current discourse is focused on increasing safety and lowering risks. In these interactions, trust is a critical relational characteristic that contributes to an endurable, collaborative, and sustainable pharmaceutical system.

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References

1. Fukuyama F. Trust: The social virtues and the creation of prosperity. New York: Free Press; 1995.
2. Putnam R. Making Democracy Work: Civic Traditions in Modern Italy. Princeton: Princeton University Press; 1993.
3. Casadesus-Masanell R. Trust in Agency. Journal of Economics & Management Strategy. 2004;13(3):375-404.
4. Murphy JT. Building trust in economic space. Progress in Human Geography. 2006 Aug;30(4):427-50.
5. Leslie CR. Trust, distrust, and antitrust. Texas Law Review. 2004 Feb;82(3):515-680.
6. Lenard PT. Trust your compatriots, but count your change: The roles of trust, mistrust and distrust in democracy. Political Studies. 2008 Jun;56(2):312-32.
7. Wang YD, Emurian HH. An overview of online trust: Concepts, elements, and implications. Computers in Human Behavior. 2005 Jan;21(1):105-25.
8. Colesca SE. Understanding Trust in e-Government. Inzinerine Ekonomika-Engineering Economics. 2009 2009(3):7-15.
9. Misztal BA. Trust and cooperation: the democratic public sphere. Journal of Sociology. 2001 Dec;37(4):371-86.
10. van der Schee E, Braun B, Calnan M, Schnee M, Groenewegen PP. Public trust in health care: A comparison of Germany, The Netherlands, and England and Wales. Health policy (Amsterdam, Netherlands). 2007;81(1):56-67.
11. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, Belitser SV, Raaijmakers JAM, Pieters T. Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study. BMJ Open. 2011 January 1, 2011;1(2).
12. Dupras C, Williams-Jones B. The Expert and the Lay Public: Reflections on Influenza A (H1N1) and the Risk Society. American Journal of Public Health. 2012 Apr;102(4):591-5.
13. PWC. Recapturing the vision: Restoring trust in the pharmaceutical industry by translating expectations into actions: PriceWaterhouseCoopers; 2007 [cited 2012 27 February]. Available from: http://www.pwc.com/gx/en/pharma-life-sciences/pharmaceutical-industry-thought-leadership.jhtml.
14. Getz KA. Public Confidence and Trust Today - A Review of Public Opinion Polls. Monitor. 2008 September 2008;September 2008:17-21.
15. Olsen AK, Whalen MD. Public perceptions of the pharmaceutical industry and drug safety: implications for the pharmacovigilance professional and the culture of safety. Drug Saf. 2009;32(10):805-10.
16. Bijl D, Schellekens H. The sponsored pandemic of the Mexican flu? The International Journal of Risk and Safety in Medicine. 2011;23(2):73-9.
17. DeLong G. Conflicts of interest in vaccine safety research. Account Res. 2012;19(2):65-88.
18. Take a stand. Nature. 2012 Jul 12;487(7406):139-40.
19. Lofstedt R. Risk Management in Post Trust Societies. London: Earthscan; 2005.

20. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Storylines of research in diffusion of innovation: a meta-narrative approach to systematic review. Social Science & Medicine. 2005;61:417–30.
21. Ide RW, Yarn DH. Public independent fact-finding: A trust-generating institution for an age of corporate illegitimacy and public mistrust. Vanderbilt Law Review. 2003 May;56(4):1113-+.
22. Schoorman FD, Mayer RC, Davis JH. Organizational trust: Philosophical perspectives and conceptual definitions. Academy of Management Review. 1996 Apr;21(2):337-40.
23. Wang H, Schlesinger M, Hsiao WC. The flip-side of social capital: the distinctive influences of trust and mistrust on health in rural China. Soc Sci Med. 2009 Jan;68(1):133-42.
24. Newton K. Trust, social capital, civil society, and democracy. International Political Science Review. 2001 Apr;22(2):201-14.
25. Baier A. TRUST AND ANTITRUST. Ethics. 1986 Jan;96(2):231-60.
26. Blair MM, Stout LA. Trust, trustworthiness, and the behavioral foundations of corporate law. University of Pennsylvania Law Review. 2001 Jun;149(6):1735-810.
27. Hall MA, Dugan E, Zheng BY, Mishra AK. Trust in physicians and medical institutions: What is it, can it be measured, and does it matter? Milbank Quarterly. 2001 2001;79(4):613-+.
28. Jones K. Trust as an affective attitude. Ethics. 1996 Oct;107(1):4-25.
29. Pettit P. The cunning of trust. Philosophy & Public Affairs. 1995 Sum;24(3):202-25.
30. Fisher J, van Heerde J, Tucker A. Does One Trust Judgement Fit All? Linking Theory and Empirics. British Journal of Politics & International Relations. 2010 May;12(2):161-88.
31. Kaffille S, Wirtz G. Engineering Autonomous Trust-Management Requirements for Software Agents: Requirements and Concepts. Sobh T, editor2010. 483-9 p.
32. Lenard PT. Rebuilding Trust in an Era of Widening Wealth Inequality. Journal of Social Philosophy. 2010 Spr;41(1):73-91.
33. Jones J, Barry MM. Developing a scale to measure trust in health promotion partnerships. Health Promot Int. 2011 Dec;26(4):484-91.
34. Mullarkey M, Duffy A, Timmins F. Trust between nursing management and staff in critical care: a literature review. Nurs Crit Care. 2011 Mar-Apr;16(2):85-91.
35. Muller T. Semantics of Trust. In: Degano PESGJ, editor. Formal Aspects of Security and Trust. Lecture Notes in Computer Science. 65612011. p. 141-56.
36. Resnik DB. Scientific research and the public trust. Sci Eng Ethics. 2011 Sep;17(3):399-409.
37. Mouzas S, Henneberg S, Naude P. Trust and reliance in business relationships. European Journal of Marketing. 2007 2007;41(9-10):1016-32.
38. Behnia B. Trust development: A discussion of three approaches and a proposed alternative. British Journal of Social Work. 2008;38(7):1425-41.
39. Hieronymi P. The reasons of trust. Australasian Journal of Philosophy. 2008 Jun;86(2):213-36.
40. Montgomery K, Jordens CFC, Little M. How vulnerability and trust interact during

extreme events - Insights for human service agencies and organizations. Administration & Society. 2008 Oct;40(6):621-44.
41. Brown P, Calnan M, Scrivener A, Szmukler G. Trust in Mental Health Services: A neglected concept. Journal of Mental Health. 2009 Oct;18(5):449-58.
42. Carter MA. Trust, power, and vulnerability: a discourse on helping in nursing. Nurs Clin North Am. 2009 Dec;44(4):393-405.
43. Fetchenhauer D, Dunning D. Do people trust too much or too little? Journal of Economic Psychology. 2009 Jun;30(3):263-76.
44. Maloy JS. Two Concepts of Trust. Journal of Politics. 2009 Apr;71(2):492-505.
45. Verbeke A, Greidanus NS. The end of the opportunism vs trust debate: Bounded reliability as a new envelope concept in research on MNE governance. Journal of International Business Studies. 2009 Dec;40(9):1471-95.
46. Hupcey JE, Miller J. Community dwelling adults' perception of interpersonal trust vs. trust in health care providers. J Clin Nurs. 2006 Sep;15(9):1132-9.
47. Hupcey JE, Penrod J, Morse JM, Mitcham C. An exploration and advancement of the concept of trust. Journal of Advanced Nursing. 2001 Oct;36(2):282-93.
48. Corritore CL, Kracher B, Wiedenbeck S. On-line trust: concepts, evolving themes, a model. International Journal of Human-Computer Studies. 2003 Jun;58(6):737-58.
49. Cross FB. Law and trust. Georgetown Law Journal. 2005 Jun;93(5):1457-545.
50. Goudge J, Gilson L. How can trust be investigated? Drawing lessons from past experience. Soc Sci Med. 2005 Oct;61(7):1439-51.
51. Smith C. Understanding trust and confidence: two paradigms and their significance for health and social care. J Appl Philos. 2005;22(3):299-316.
52. Burke CS, Sims DE, Lazzara EH, Salas E. Trust in leadership: A multi-level review and integration. Leadership Quarterly. 2007 Dec;18(6):606-32.
53. Cvetkovich G, Nakayachi K. Trust in a high-concern risk controversy: A comparison of three concepts. Journal of Risk Research. 2007 2007;10(2):223-37.
54. Welter F. All you need is trust? A critical review of the trust and entrepreneurship literature. International Small Business Journal. 2012 May;30(3):193-212.
55. Christoffersen J. A Review of Antecedents of International Strategic Alliance Performance: Synthesized Evidence and New Directions for Core Constructs. International Journal of Management Reviews. 2013 Jan;15(1):66-85.
56. Eisenman DP, Williams MV, Glik D, Long A, Plough AL, Ong M. The public health disaster trust scale: validation of a brief measure. J Public Health Manag Pract. 2012 Jul-Aug;18(4):E11-8.
57. Valvi AC, Fragkos KC. Critical review of the e-loyalty literature: a purchase-centred framework. Electronic Commerce Research. 2012 Sep;12(3):331-78.
58. Harrison S, Smith C. Trust and moral motivation: redundant resources in health and social care? Policy and Politics. 2004 Jul;32(3):371-86.
59. Das TK, Teng BS. The risk-based view of trust: A conceptual framework. Journal of Business and Psychology. 2004 Fal;19(1):85-116.
60. Mayer RC, Davis JH, Schoorman FD. An Integrative Model of Organizational Trust. The Academy of Management Review. 1995;20(3):709-34.
61. McKnight DH, Chervany NL. What trust means in e-commerce customer relation-

ships: An interdisciplinary conceptual typology. International Journal of Electronic Commerce. 2001 Win;6(2):35-59.
62. McKnight DH, Cummings LL, Chervany NL. Initial trust formation in new organizational relationships. Academy of Management Review. 1998 Jul;23(3):473-90.
63. Goold SD. Trust and the ethics of health care institutions. Hastings Center Report. 2001 Nov-Dec;31(6):26-33.
64. Entwistle V. Trust and shared decision-making: an emerging research agenda. Health Expectations. 2004 Dec;7(4):271-3.
65. Whitley R, McKenzie K. Social capital and psychiatry: Review of the literature. Harvard Review of Psychiatry. 2005 Mar-Apr;13(2):71-84.
66. Connell NA, Mannion R. Conceptualisations of trust in the organisational literature: some indicators from a complementary perspective. J Health Organ Manag. 2006;20(5):417-33.
67. Hoffman AM. A conceptualization of trust in international relations. European Journal of International Relations. 2002 Sep;8(3):375-401.
68. Jones AJI. On the concept of trust. Decision Support Systems. 2002 Jul;33(3):225-32.
69. McCullough LB. Trust, moral responsibility, the self, and well-ordered societies: The importance of basic philosophical concepts for clinical ethics. Journal of Medicine and Philosophy. 2002;27(1):3-9.
70. McKnight DH, Choudhury V, Kacmar C. Developing and validating trust measures for e-commerce: An integrative typology. Information Systems Research. 2002 Sep;13(3):334-59.
71. Shankar V, Urban GL, Sultan F. Online trust: a stakeholder perspective, concepts, implications, and future directions. Journal of Strategic Information Systems. 2002 Dec;11(3-4):325-44.
72. Boyd J. The rhetorical construction of trust online. Communication Theory. 2003 Nov;13(4):392-410.
73. Delhey J, Newton K. Who trusts? The origins of social trust in seven societies. European Societies. 2003 2003;5(2):93-137.
74. Faulkner P. The epistemic role of trust. In: Falcone RBSKLSM, editor. Trust, Reputation, and Security: Theories and Practice. Lecture Notes in Artificial Intelligence. 26312003. p. 30-8.
75. Marsh S, Dibben MR. The role of trust in information science and technology. Annual Review of Information Science and Technology. 2003 2003;37:465-98.
76. Smith C. Trust and confidence: Possibilities for social work in 'high modernity'. British Journal of Social Work. 2001 Apr;31(2):287-305.
77. Goold SD, Klipp G. Managed care members talk about trust. Social Science & Medicine. 2002 Mar;54(6):879-88.
78. Hall MA. Law, medicine, and trust. Stanford Law Review. 2002 Nov;55(2):463-527.
79. Bellaby P. Theme 1: Concepts of trust and methods for investigating it Foreword. Energy Policy. 2010 Jun;38(6):2615-6.
80. Fukuyama F. Social capital, civil society and development. Third World Quarterly. 2001;22(1):7-20.

81. Abbott S, Freeth D. Social capital and health - Starting to make sense of the role of generalized trust and reciprocity. Journal of Health Psychology. 2008 Oct;13(7):874-83.
82. Bhandari H, Yasunobu K. What is Social Capital? A Comprehensive Review of the Concept. Asian Journal of Social Science. 2009;37(3):480-510.
83. Hall MA, Camacho F, Dugan E, Balkrishnan R. Trust in the medical profession: Conceptual and measurement issues. Health Services Research. 2002 Oct;37(5):1419-39.
84. Hall MA, Zheng BY, Dugan E, Camacho F, Kidd KE, Mishra A, et al. Measuring patients' trust in their primary care providers. Medical Care Research and Review. 2002 Sep;59(3):293-318.
85. Powell JL. From "trust society" to the "risk society"? the case of aging and welfare in Europe. Hallym International Journal of Aging. 2009;11(1):65-76.
86. Hosmer LT. TRUST - THE CONNECTING LINK BETWEEN ORGANIZATIONAL THEORY AND PHILOSOPHICAL ETHICS. Academy of Management Review. 1995 Apr;20(2):379-403.
87. Gambetta D. Can We Trust Trust? In: Gambetta D, editor. Trust: Making and Breaking Coopetative Relations. Oxford: University of Oxford; 2000. p. 213-37.
88. Grandison T, Sloman M. A survey of trust in internet applications. Communications Surveys & Tutorials, IEEE. 2000;3(4):2-16.
89. Barber B. The Logic and Limits of Trust. New Brunswick, NJ: Rutgers University Press; 1983.
90. Holton R. FIDUCIARY RELATIONS AND THE NATURE OF TRUST. Boston University Law Review. 2011 May;91(3):991-4.
91. Dy SM, Purnell TS. Key concepts relevant to quality of complex and shared decision-making in health care: A literature review. Social Science & Medicine. 2012 Feb;74(4):582-7.
92. Luzinski C. Trust: a core value of healthy organizations. J Nurs Adm. 2012 Nov;42(11):497-8.
93. Mortensen MH. Understanding attractiveness in business relationships - A complete literature review. Industrial Marketing Management. 2012 Nov;41(8):1206-18.
94. Churchill LR. TRUST, AUTONOMY, AND ADVANCE DIRECTIVES. Journal of Religion & Health. 1989 Fal;28(3):175-83.
95. Michalos AC. THE IMPACT OF TRUST ON BUSINESS, INTERNATIONAL SECURITY AND THE QUALITY OF LIFE. Journal of Business Ethics. 1990 Aug;9(8):619-38.
96. Adler JE. TESTIMONY, TRUST, KNOWING. Journal of Philosophy. 1994 May;91(5):264-75.
97. Holton R. DECIDING TO TRUST, COMING TO BELIEVE. Australasian Journal of Philosophy. 1994 Mar;72(1):63-76.
98. Kass NE, Sugarman J, Faden R, SchochSpana M. Trust - The fragile foundation of contemporary biomedical research. Hastings Center Report. 1996 Sep-Oct;26(5):25-9.
99. Blois KJ. Trust in business to business relationships: An evaluation of its status. Journal of Management Studies. 1999 Mar;36(2):197-215.

100. Hummels H, Roosendaal HE. Trust in scientific publishing. Journal of Business Ethics. 2001 2001;34(2):87-100.
101. Hurley R. The Decision to Trust. Harvard Business Review. 2006:55-62.
102. Korczynski M. The political economy of trust. Journal of Management Studies. 2000 Jan;37(1):1-21.
103. Borg JJ, Aislaitner G, Pirozynski M, Mifsud S. Strengthening and Rationalizing Pharmacovigilance in the EU: Where is Europe Heading to? A Review of the New EU Legislation on Pharmacovigilance. Drug Safety. 2011;34(3):187-97.
104. Tschannen-Moran M, Hoy WK. A multidisciplinary analysis of the nature, meaning, and measurement of trust. Review of Educational Research. 2000 Win;70(4):547-93.
105. Edwards B, Olsen AK, Whalen MD, Gold MJ. Guiding principles of safety as a basis for developing a pharmaceutical safety culture. Curr Drug Saf. 2007 May;2(2):135-9.
106. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008 Jan 17;358(3):252-60.
107. Preserving public confidence. Lancet Oncol. 2008 Jun;9(6):503.
108. Cohen D. New image for the drug industry. BMJ (Clinical research ed). 2011;343.
109. Meghani Z, Kuzma J. The "Revolving Door" between Regulatory Agencies and Industry: A Problem That Requires Reconceptualizing Objectivity. Journal of Agricultural & Environmental Ethics. 2011 Dec;24(6):575-99.
110. Coen D. Business-regulatory relations: Learning to play regulatory games in European utility markets. Governance-an International Journal of Policy Administration and Institutions. 2005 Jul;18(3):375-98.
111. Lumsden MA. The position of the Regulatory Authorities. Climacteric. 2007;10(SUPPL. 2):121-4.
112. Thomas CW. Maintaining and restoring public trust in government agencies and their employees. Administration & Society. 1998 May;30(2):166-93.
113. Abraham J. The pharmaceutical industry as a political player. The Lancet. 2002;360(9344):1498-502.
114. Brown P, Calnan M. Braving a faceless new world? Conceptualizing trust in the pharmaceutical industry and its products. Health (London). 2012 Jan;16(1):57-75.
115. Lofstedt R, Bouder F, Wardman J, Chakraborty S. The changing nature of communication and regulation of risk in Europe. Journal of Risk Research. 2011;14(4):409-29.
116. Cavazos DE, Rutherford MA. Bringing Regulatory Agencies Into Organizational Studies: Broadening the Lens Used to Examine the State. Journal of Management Inquiry. 2012 Jan;21(1):4-12.
117. Alaszewski A. Drugs, risk and society: Government, governance or governmentality? Health Risk & Society. 2011;13(5):389-96.
118. Abraham J. The politics and bio-ethics of regulatory trust: case-studies of pharmaceuticals. Med Health Care Philos. 2008 Dec;11(4):415-26.
119. Skirbekk H, Middelthon A-L, Hjortdahl P, Finset A. Mandates of Trust in the Doctor-Patient Relationship. Qualitative Health Research. 2011 Sep;21(9):1182-90.

120. Straten GF, Friele RD, Groenewegen PP. Public trust in Dutch health care. Social Science & Medicine. 2002 Jul;55(2):227-34.
121. Whetten K, Leserman J, Whetten R, Ostermann J, Thielman N, Swartz M, et al. Exploring Lack of Trust in Care Providers and the Government as a Barrier to Health Service Use. American Journal of Public Health. 2006 2006/04/01;96(4):716-21.
122. Almirall N. The ethics of engagement with the pharmaceutical industry. Mich Med. 2006 Jan-Feb;105(1):10-2.
123. Clark CC. Trust in medicine. J Med Philos. 2002 Feb;27(1):11-29.
124. Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ. 2011 2011-05-10 00:00:00;342.
125. Vladeck DC. The FDA and deference lost: a self-inflicted wound or the product of a wounded agency? A response to Professor O'Reilly. Cornell Law Rev. 2008 Jul;93(5):981-1002.
126. Abraham J, Davis C. Drug evaluation and the permissive principle: continuities and contradictions between standards and practices in antidepressant regulation. Soc Stud Sci. 2009 Aug;39(4):569-98.
127. Moynihan R. Who pays for the pizza? Redefining the relationships between doctors and drug companies. 1: Entanglement. BMJ. 2003 2003-05-29 00:00:00;326(7400):1189-92.
128. Henry D. Doctors and Drug Companies: Still Cozy after All These Years. PLoS Med. 2010;7(11):e1000359.
129. Arkinson J, Holbrook A, Wiercioch W. Public perceptions of physician-pharmaceutical industry interactions: A systematic review. Healthcare Policy. 2010;5(4):69-89.
130. Morin K, Morse LJ. The Ethics of Pharmaceutical Industry Gift-Giving: The Role of a Professional Association. The American Journal of Bioethics. 2003 2003/08/01;3(3):54-5.
131. Brody H. The company we keep: Why physicians should refuse to see pharmaceutical representatives. Annals of Family Medicine. 2005;3(1):82-5.
132. Brody H. Professional medical organizations and commercial conflicts of interest: ethical issues. Ann Fam Med. 2010 Jul-Aug;8(4):354-8.

CHAPTER

3

Measuring trust in pharmaceutical companies, regulatory authorities and doctors

A systematic analysis of the literature

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Abstract

Background - The recurrent discussion about an erosion of trust in pharmaceutical companies, regulatory authorities and doctors has been supported and fueled by drug safety controversies. Nevertheless, we know little about the number, quality and outcome of academic and non-academic empirical studies measuring public trust in these pharmaceutical sector stakeholders.

Objective - To assess the quantity and quality of academic and non-academic studies of public trust in pharmaceutical sector stakeholders.

Methods - A systematic review of the literature up to December 2012 was performed using three databases (i.e., PubMed, Scopus, and Web of Science) for academic studies. Non-academic studies were identified through cross-references and Google. Studies with empirical data measuring trust in pharmaceutical companies, regulatory authorities and doctors were included for analysis. Information regarding the studies' general and methodological characteristics, and their trust outcomes was retrieved using a standardized data extraction form.

Results - Forty-seven academic empirical articles (8 pharmaceutical companies, 3 regulatory authorities, and 36 doctors) and 16 non-academic public polls/surveys were evaluated. Doctors were highly trusted, whereas regulatory authorities and pharmaceutical companies were distrusted. However, considerable methodological drawbacks were observed amongst all studies. The most salient methodological drawbacks were the lack of a definition of trust, the use of various (or no) instruments and scales to measure trust, and inconsistent response rates. Although the quality of trust studies for doctors seemed more rigorous than the other two stakeholders, the lack of standardization was also problematic.

Conclusion - Academic and non-academic empirical studies demonstrated that doctors are trusted by the public, whereas pharmaceutical companies and regulatory authorities are not. However, the current empirical evidence does not substantiate claims of an erosion of trust in these three groups of stakeholders because of serious methodological drawbacks. Methodologically robust measurements of public trust are necessary to further our understanding of the multidimensional nature of trust in these stakeholders.

Introduction

A 2013 editorial in the Journal of the American Medical Association (JAMA) argued that the "lack of trust in pharmaceutical companies threatens the future of biomedical research", since the methodological basis and analyses of industry-funded trials seem to be insufficiently robust in the eyes of scientists and clinicians outside the industry [1]. In 2012, Nature claimed (in the context of pharmaceutical law settlements) that: "the biggest victim of these drug-industry scandals is the public trust that a medicine does what it is claimed to do, and that information on its safety is reliable" [2]. However, neither of these articles provided structured (qualitative/quantitative) evidence supporting their claim of a loss of (public) trust in pharmaceutical companies. In 2011, Lofstedt et al. attributed the lack of public trust in authorities and industry to the growing number of regulatory scandals [3]. To support this claim of an "erosion of trust", Lofstedt presented case vignettes of regulatory scandals, such as the Gardasil vaccination to prevent (pre-) cervical cancers and the relationship between aspartame use and cancer-related concerns [3]. Yet again, no quantitative empirical evidence was presented to support the author's claim of an erosion of trust in pharmaceutical companies or regulatory authorities (those responsible for the evaluation of medicinal products for public use, such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) or national regulatory authorities).

If scholars use empirical data to measure trust, would they succeed in presenting a valid argument about an erosion of trust in pharmaceutical companies, regulatory authorities or doctors (as mediators between abovementioned institutions and patients)? Our first hypothesis is that there is a paucity of empirical studies about public trust in pharmaceutical companies, regulatory authorities and doctors; and that the available empirical evidence lacks the methodological rigor to support a claim of an erosion of trust that would surpass trend-watching approaches. Given the important role that pharmaceutical companies, regulatory authorities and doctors play within the drug life cycle (in development, evaluation, authorization, and responsible, respectively), their influence on patients and public health, and the possibility that they have been under-researched, we decided to focus on empirical public trust studies in the abovementioned stakeholders and combine them in one study. These three stakeholders represent different stages during the life cycle of drugs worldwide. The role and importance of other stakeholders (e.g., insurance companies) may differ per country or region, which are bound to the health care system structure, and therefore were not included in our analysis.

Independent (non-academic) institutions have conducted attitudinal consumer surveys and public polls to measure trust [4-7]. Few scholars have cited the results of these non-academic studies to argue that there is an erosion of trust in pharmaceutical companies, regulatory authorities or doctors [8-10]. Our second hypothesis is that these public polls and surveys' results reflect changes in public perceptions instead of structured measurements concerning the very essence of trust as a multi-dimensional and relational characteristic.

Scholars from different disciplines have studied the epistemology of trust, have defined trust as a concept, and have concluded that trust is essentially not the same

as reliance, mutuality, trustworthiness, confidence, reciprocity or other possible "synonyms" of trust [11-21]. Taking into account the conceptual and epistemic differences between trust and other possible "synonyms", we deliberately decided to solely focus on trust instead of including other concepts, such as confidence, reliance or trustworthiness; these concepts may relate to trust but may also have a slight different definition. Understanding the complexities and flaws of measuring trust may contribute to improving the quality of trust studies and ultimately supporting efforts to restore trust in abovementioned stakeholders.

Aim

The purpose of the present study is to analyze the methodologies and trust outcomes of academic and non-academic empirical studies measuring public trust in 1) pharmaceutical companies, 2) regulatory authorities, and 3) doctors to discern ***what*** has been measured and ***how*** it has been measured. A systematic review of the scientific literature was performed to identify empirical studies that measured trust. In addition, a review of non-academic public polls and surveys was also conducted.

This study is the first methodological assessment of empirical studies on public trust and their outcomes that demonstrates the quantity and quality of available empirical data to either support or reject the recurrent claims of an erosion of trust in pharmaceutical companies, regulatory authorities and doctors.

Methods

Empirical studies from the scientific literature

We systematically searched for articles in three databases: PubMed, Web of Science, and Scopus. To search for articles pertaining to the pharmaceutical industry, we used various combinations of the terms: "trust OR public opinion AND drug industry(ies) OR pharmaceutical industry(ies) OR pharmaceutical company(ies)". Articles concerning regulatory authorities were searched using combinations of the terms: "trust OR public opinion AND regulatory agency(ies) OR regulatory authority(ies)". Empirical articles about doctors were searched with combinations of the keywords: "trust OR public opinion AND physician(s) OR doctor(s)".

As trust has been reported to have multidimensional characteristics (i.e., psychological, cognitive, and emotional), it could be confused with a multitude of "synonyms, equivalents or derivatives" that are all in essence different from trust itself [11-16]. Scholars have already clarified conceptual and epistemic differences between trust and trustworthiness, confidence, or reliance among many other possible "synonyms" [17, 18, 20-22]. Hence, we formulated our keyword search queries without using truncation variations or other "synonyms or equivalents" of trust to specifically and solely identify articles measuring public trust in the abovementioned stakeholders. The inclusion in our analysis of terms similar to trust or "synonyms or equivalents" of trust, which are not the same as trust,

would introduce a conceptual and epistemic bias to our results, thereby weakening our analyses by scattering our research scope.

The screening process of articles comprehended two main conditions prior to be classified as included: (1) the article should be about public trust in pharmaceutical companies, regulatory authorities or doctors, and (2) the articles should provide empirical data on measuring trust (e.g., questionnaires, interviews, polls, surveys or internet forms/commentaries). Articles without empirical data or data relating to another sector were classified as "out of context". The search queries were limited to articles about humans, no time span (until December 2012), and were written in English, Dutch, or Spanish.

Public polls and surveys from independent institutions

To find public polls and surveys from independent (non-academic) institutions using Google, combinations of the following terms were used: "public", "poll(s)", "survey(s)", "pharmaceutical company(ies) or industry(ies)", "regulatory authority(ies) or agency(ies), and "doctors". In addition, we searched for additional polls or surveys through cross-referencing.

In-depth appraisal of studies

All articles were obtained in full-text and screened by the first author. From the selected academic articles and non-academic public polls and surveys, we extracted and indexed information into three main categories:

A. General information: author, year of publication, type of study (interview, survey, etc.), method (questionnaire, internet, telephone, or face-to-face), participants' characteristics (public/patients, type of patients, demographics, or age group) and number, topic, multicultural sample, oversampling minorities, and region.

B. Methodological information: representativeness, instrument used to measure trust, rating of answers/scales, use of a pre-specified definition of trust, and response/participation rate.

C. Trust outcome: the levels of trust as outcome that were reported per study were extracted in this category without being modified or reported in a new or different trust scale.

Data analysis and data presentation

Information regarding the studies' general and methodological characteristics, and their trust outcomes was retrieved using a standardized data extraction form. Academic and non-academic empirical studies were appraised in terms of methodological robustness and state of trust in each of the abovementioned stakeholders. The number of items presented under the methodological information category per article determined the methodological robustness: weak (1 or 2 items), moderate (at least 3 items), moderate/strong (4 items) or strong (all 5 items). The trust outcome (state of trust) was indexed as low, medium/low, medium, medium/high and high trust according to the articles' reported outcomes. Two researchers scanned articles independently (FH and TP) and the rate of disagreement was less than 5%.

Results

We identified 435 studies about public trust in pharmaceutical companies, 156 for regulatory authorities, and 512 for doctors. After eliminating duplicates and articles classified as out of context, eight articles for pharmaceutical companies [23-30], three for regulatory authorities [31-33], and 36 for doctors [34-69] (of which five were reviews [47-49, 58, 62]) remained for analysis (Figure 1).

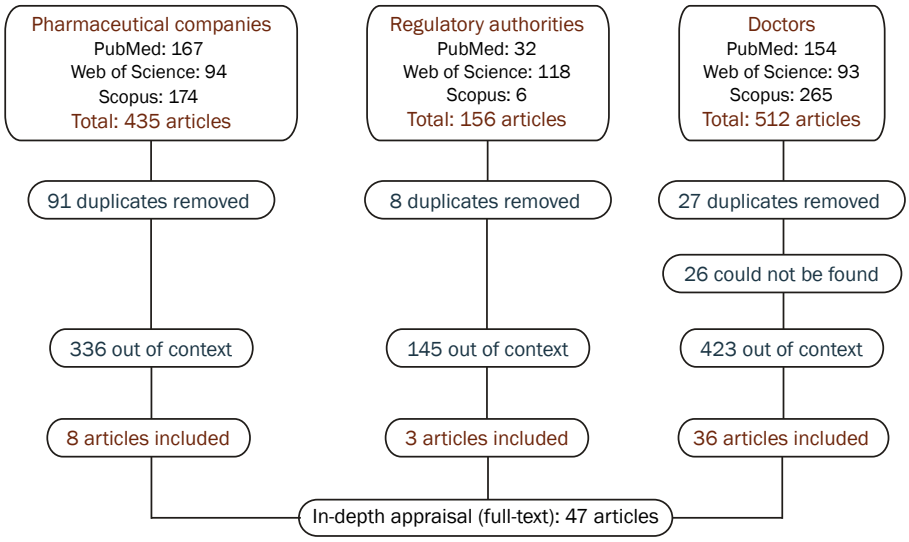

Figure 1. Prisma flowchart of inclusion procedure for in-depth appraisal of empirical articles.

General information for academic studies

A summary of the study characteristics is presented in Table 1 and a detailed description of the studies (including detailed study outcomes) appears in Appendix 1. The majority of the empirical studies were conducted in the United States (n=28) with single exceptions from other countries, such as the Netherlands, Australia, New Zealand, Norway, or Taiwan, among others. The empirical studies captured the opinion of 262,152 participants (median: 6241.3 participants per study with a range of 17 to 149,688). The majority of the studies surveyed trust in adults (18 years and older); only one study surveyed children and young people (<24 years old). Two studies did not report the age of the participants. Most studies (n=40) collected participants' demographic, socioeconomic, educational, behavioral or lifestyle characteristics to analyze their influence on trust. Participants from various cultures were included in 53% of the studies (n=25) and eight studies of the total 47 articles oversampled minorities. Twenty-four articles surveyed participants from the general public, 20 surveyed patients, two surveyed patients' relatives, and one article did not report the type of participants. The variation in patient type was wide, including outpatients or users of healthcare systems to chronic patients (e.g., asthma, depression, diabetes, rheumatoid arthritis, hypertension) and patients with serious illnesses (i.e., with cancer or HIV) (see Appendix 1). The oldest identified article was from 1991, followed by an upward trend in quantity per year that peaked in 2011 (n=9, Figure 2).

Table 1. Characteristics and outcome about public trust in each of the stakeholders of the pharmaceutical sector from the in-deep analyzed academic empirical studies (summary-outcome).

First author, year, and region	Representative	Sample (#)	Trust definition	Type of intervention	Method	Measurements	Methodological robustness	Trust outcome
Pharmaceutical companies								
Allen, J. D. et al., 2010. USA	Yes (national)	451	No	Survey	Internet	4-point scale	Moderate	High
Bunniran, S. et al., 2009. USA	180 participants would provide a power of 80% (45 per group)	248	Yes	Survey	Internet	5-point-Likert scale	Moderate	Low
Edwards, D., 2009. Australia	Not reported	134	No	Survey	Internet	5-point-Likert scale and open-ended answers	Weak	Low
Freeman, B. D. et al., 2006. USA	Not reported	117	No	Interview	Face-to-face	5-point-Likert scale	Moderate	Low
Gale, N. K. et al., 2011. UK	Not reported	17	No	Interview	Face-to-face	Not reported	Weak	Low
Goff, S. L. et al., 2008. USA	Not reported	50	No	Interview	Telephone	Not reported	Weak	Low
Henrich, N. et al., 2011. Canada	Not reported	1796 (thread)	No	Analysis of comments in news pages	Internet	Analysis of comments in news pages	Weak	Low
Lukoschek, P., 2003. USA	Not reported	42	No	Interview	Face-to-face	Not reported	Weak	Low
Regulatory authorities								
Himmelstein, M. et al., 2011. UK	Not reported	941	No	Survey	Internet	5-point-Likert scale	Weak	Medium/ Low
Krska, J. et al., 2011. UK	Yes	436	No	Interview	Face-to-face	5-point-Likert scale	Weak	Low
Snyder, P. J. et al., 2009. USA, UK, Australia, Ireland, and Canada	Not reported	676	No	Survey	Internet	Not reported	Weak	Low
Doctors								
Alexander, J. A. et al., 2011. USA	Yes (national)	8140	No	Survey	Telephone	3-point scale	Weak	High
Bachinger, S. M. et al., 2009. Netherlands	Not reported	201	Yes	Survey	Question-naire (mail or at site)	5-point-Likert scale	Moderate	High

First author, year, and region	Representative	Sample (#)	Trust definition	Type of intervention	Method	Measurements	Methodological robustness	Trust outcome
Benkert, R. et al., 2008. USA	Not reported	145	Yes (instrument)	Interview	Face-to-face	5-point-Likert scale	Moderate	High
Berrios-Rivera, J. P. et al., 2006. USA	Not reported	102	Yes (instrument)	Survey	Question-naire (phone or at site)	5-point-Likert scale	Moderate	High
Blackstock, O. J. et al., 2012. USA	177 participants would provide a power of 80%	175	Yes (instrument)	Interview	Face-to-face	5-point-Likert scale	Moderate/Strong	High
Blendon, R. J. et al., 2001. USA	Not reported	500 to 2000	No	Review of public polls	Pre-1985, face-to-face, post-1985 by phone	Not reported	Weak	High
Brodsky, S. L. et al., 1991. USA	Not reported	301	No	Interview	Telephone	5-point-Likert scale	Weak	High
Calnan, M. et al., 2005. UK	Not reported	1187	Yes (instrument)	Survey	Post	5-point-Likert and 10-point scale	Weak	High
Calnan, M. et al., 2004. UK	Not reported	1187	Yes	Survey	Post	10-point scale	Moderate	Medium/ High
Chu-Weininger, M. Y. et al., 2006. USA	Not reported	564	Yes (instrument)	Survey	Telephone	Not reported	Moderate	High
Copeland, V. C. et al., 2003. USA	Not reported	50	No	Interview	Face-to-face	Open questions	Weak	Medium/ High
Dugan, E. et al., 2005. USA	Not reported	2109	Yes (instrument)	Interview	Telephone	5-point-Likert scale	Moderate	High
Franks, P. et al., 2005. USA	Not reported	4746	Yes (instrument)	Survey	Face-to-face	5-point-Likert scale	Moderate	High
Graham, J. L. et al., 2010	Not reported	Review of the literature	-	-	-	-	Strong	Medium/ Low
Hargreaves, D. S. et al., 2012. UK	Not reported	Review of surveys from the NHS	No ("had confi-dence and trust in doctors")	Survey	-	5-point-Likert scale	Strong	Medium/ Low
Hillen, M. A. et al., 2011	-	Review of the literature	Yes	-	-	-	Strong	Medium/ High

First author, year, and region	Representative	Sample (#)	Trust definition	Type of intervention	Method	Measurements	Methodological robustness	Trust outcome
Hunt, K. A. et al., 2005. USA	Not reported	38005	Yes (instrument)	Survey	Telephone	5-point-Likert scale	Strong	Medium/ High
Johansen, M. A. et al., 2009. Norway	Yes (national)	1000	No	Interview	Telephone	5-point-Likert scale	Weak	Medium/ High
Keating, N. L. et al., 2004. USA	Not reported	417	No	Interview	Telephone	3-point scale	Weak	High
Kerse, N. et al., 2004. New Zealand	Not reported	370	No	Survey	Face-to-face	5-point-Likert scale	Moderate	High
Krupat, E. et al., 2004. USA	Not reported	1766	No	Survey	Post	6-point-Likert scale	Weak	High
Lee, Y. Y. et al., 2007. Singapore	Not reported	361	Yes	Survey	Face-to-face	5-point-Likert scale	Moderate	Medium/ High
Lim, J. Y. et al., 2011. Korea	Not reported	Not reported	Yes	Survey	Not reported	5-point-Likert scale	Weak	High
Mainous Iii, A. G. et al., 2004. USA	Not reported	119	Yes (instrument)	Interview	Face-to-face	5-point-Likert scale	Moderate	High
McKinstry, B. et al., 2006. USA	Not reported	Review of the literature (2916 participants)	Yes	Randomized controlled trials (RCTs) or other studies where trust was assessed as a primary or secondary outcome.	-	-	Strong	High
Minamisawa, A. et al., 2011. Japan	Not reported	504	Yes (instrument)	Survey	Not reported	5-point-Likert scale	Moderate/Strong	High
Moseley, K. L. et al., 2006. USA	Not reported	526	Yes (instrument)	Survey	Not reported	5-point-Likert scale	Moderate/Strong	High
Pagan, J. A. et al., 2007. USA	Yes (national)	25637	No ("had confidence and trust in doctors")	Survey	Telephone	5-point-Likert scale	Weak	Medium/ High

First author, year, and region	Representative	Sample (#)	Trust definition	Type of intervention	Method	Measurements	Methodological robustness	Trust outcome
Pedersen, V. H. et al., 2012. 31 out of 33 in USA	Not reported	Review of the literature (603 participants) - 33 articles included	No	Survey	-	-	Strong	Medium/ Low
Pescosolido, B. A. et al., 2001. USA	Yes (national)	3870 and 2832 respondents (AMCUS and GSS)	No	Survey	Face-to-face	5-point-Likert scale	Moderate/Strong	High
Rawaf, M. M. et al., 2007. USA	Not reported	793	Yes	Survey	Face-to-face	5-point-Likert scale	Strong	High
Sloan, F. A. et al., 2005. USA	Yes (national)	149688	No	Survey	Not reported	5-point-Likert scale	Moderate/Strong	High
Tarrant, C. et al., 2003. UK	Not reported	1078	No ("had confidence and trust in doctors")	Survey	Question-naire (site)	10-point scale	Weak	High
Torke, A. M. et al., 2004. USA	Not reported	25	No ("had confidence and trust in doctors")	Interview	Face-to-face	Open questions	Weak	High
Weng, H. C., 2008. Taiwan	Not reported	983	Yes (instrument)	Interview	Face-to-face	5-point-Likert scale	Moderate/Strong	High
Weng, H. C. et al., 2011. Taiwan	Not reported	5344	Yes (instrument)	Interview	Face-to-face	5-point-Likert scale	Moderate/Strong	High

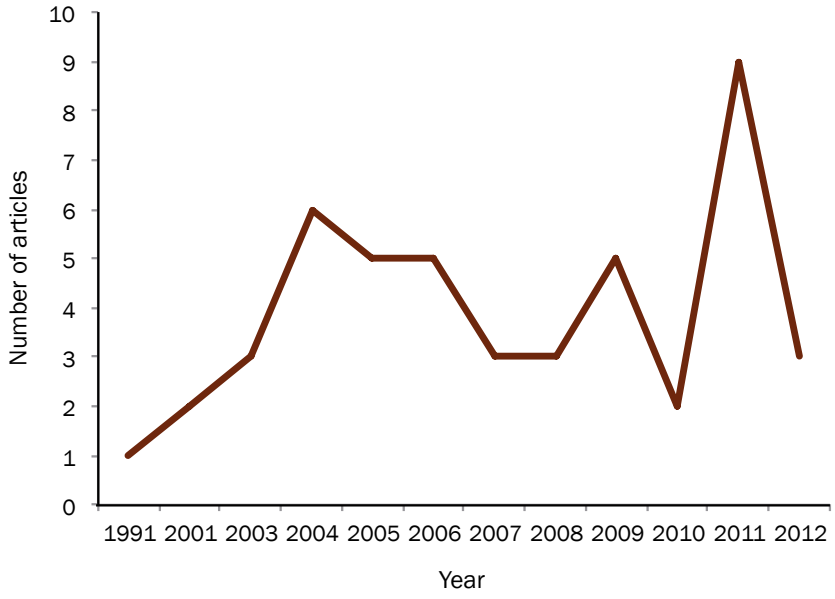

Figure 2. Number of academic studies analyzing trust per year.

Methodological information in academic studies

The methodology to measure trust varied considerably among academic empirical articles. Eight articles reported that their study was representative (national), whereas most of the studies did not report (n=37) this characteristic at all, and two studies reported low representativeness. Only eight articles defined trust in the text as substantiated by scientific literature, and the definitions were manifold (Table 1, Appendix 1). The majority of articles (n=26) did not provide a pre-specified definition of trust, whereas 13 articles attempted to circumvent the lack of a definition by referring to the instrument used to measure trust (although this was not always stated in the text). Surveys (n=26) were most often used to assess participants' trust followed by interviews (n=16). These studies were mainly conducted face-to-face (n=16), by telephone (n=9), or on the Internet (n=6). The instruments used to measure trust (if used) were also diverse; the most frequent were the Trust in Physician Scale (TPS, n=7), open-ended questions (n=7), Wake Forrest/Hall's Trust in Physician Scale (n=6), and the Public Trust in Dutch Healthcare Questionnaire (n=2). Twelve articles did not report the use of an instrument (Appendix 1). Nearly 60% of all articles (n=28) used a 5-point Likert scale to rate the answers from the instruments that measured public trust (totally agree=1 to totally disagree=5). Ten articles, however, did not report the use of a scale or other method to quantify the participants' answers (Table 1). Concerning the methodological robustness of the academic studies (total 47), most articles (n=20) were weak, 13 were moderate, seven were moderate/strong, and seven studies (including all five reviews) were qualitatively strong (Table 2, Figure 3).

Table 2. Academic articles per stakeholder indexed into their trust outcome and methodological robustness.

State of trust & Methodology robustness/ Stakeholder	High trust				Medium/high trust			Medium/low trust		Low trust		Grand Total
	Strong	Moderate/ Strong	Moderate	Weak	Strong	Moderate	Weak	Strong	Weak	Moderate	Weak	
Pharmaceutical companies	-	-	1	-	-	-	-	-	-	2	5	8
Regulatory authorities	-	-	-	-	-	-	-	-	1	-	2	3
Doctors	2	7	8	9	2	2	3	3	-	-	-	36
Grand Total	**2**	**7**	**9**	**9**	**2**	**2**	**3**	**3**	**1**	**2**	**7**	**47**

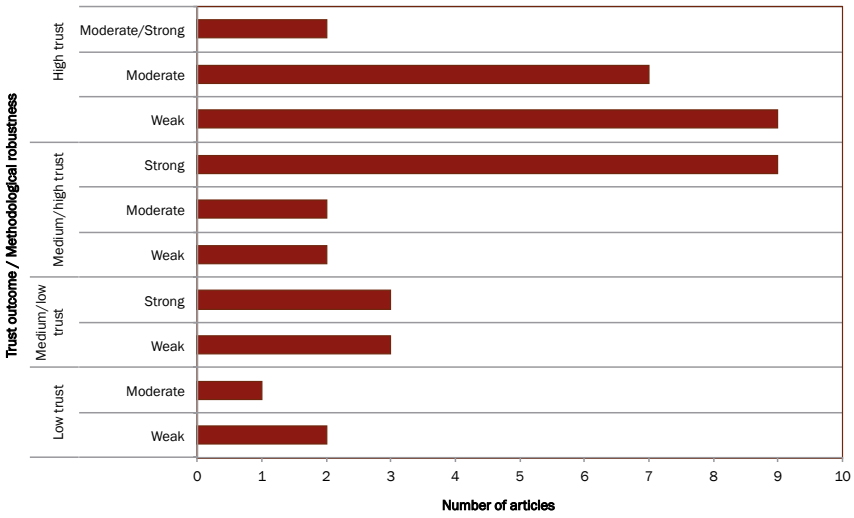

Figure 3. Number of academic articles indexed under trust outcome and their methodological robustness.

General information for non-academic public polls/surveys

We found 16 non-academic public polls/surveys from independent institutions (Table 3, Appendix 2). Three institutions were responsible for these studies: Gallup (n=8), Harris interactive (n=5), and The Henry J. Kaiser Family Foundation (n=3); all were conducted in the United States. The majority of these studies (n=13) were representative (national). The 16 polls/surveys captured the opinion of 18,292 participants (median: 1407.07 participants per study with a range of 992 to 2371) (Table 3). Most of the studies (n=13) surveyed adults (18 years and older); however, three did not report the participants' age (Appendix 2). None of the 16 polls/surveys reported the participants' characteristics, or the response rate, whether the sample was multicultural or if minorities were oversampled. Three polls did not report the type of participants, whereas the other 13 surveyed random samples of the general public—apparently not patients (Appendix 2).

Table 3. Characteristics and outcome about public trust in each of the stakeholders of the pharmaceutical sector from the public polls and surveys from non-academic independent institutions (summary-outcome).

Institute, year, region	Representative	Sample (#)	Trust definition	Type of intervention	Method	Measurements	Trust outcome
KFF, 2000, USA	Not reported	Not reported	No	Poll	Not reported	Not reported	High (doctors and regulatory authorities), low (pharmaceutical companies)
Gallup, 2002, USA	Yes	1007	No	Survey	Telephone interviews	3-answer type (positive, neutral and negative)	Low (doctors and pharmaceutical companies)
Gallup, 2004, USA	Yes	1017 /1015	No	Survey	Telephone interviews	3-answer type (positive, neutral and negative)	Low (doctors and health care), high (regulatory authorities)
Gallup, 2005, USA	Yes	1001	No	Survey	Telephone interviews	5-answer type (Very somewhat neutral somewhat very)	Low (doctors, health care and pharmaceutical companies)
KFF, 2005, USA	Not reported	Not reported	No	Poll	Not reported	5-answer type (Very somewhat neutral somewhat very)	Low (doctors, health care, regulatory authorities and pharmaceutical companies)
Harris, 2006, USA	Yes	1726	No	Survey	Online interview	5-answer type (Very somewhat neutral somewhat very)	High (doctors and regulatory authorities), low (pharmaceutical companies)
Harris, 2006, USA	Yes	2371	No	Poll	Online interview	Not reported	High (doctors), low (regulatory authorities and pharmaceutical companies)
Gallup, 2007, USA	Yes	1019	No	Survey	Telephone interviews	5-answer type (Very somewhat neutral somewhat very)	Low (regulatory authorities)
Harris, 2007, USA	Yes	1726	No	Survey	Online interview	5-answer type (Very somewhat neutral somewhat very)	Low (doctors, health care, regulatory authorities and pharmaceutical companies)
KFF, 2008, USA	Not reported	Not reported	No	Poll	Not reported	Not reported	Moderate (pharmaceutical companies)
Gallup, 2009, USA	Yes	1009	No	Survey	Telephone interviews	Not reported	Low (regulatory authorities and pharmaceutical companies)
Gallup, 2010, USA	Yes	1021	No	Poll	Telephone interviews	Not reported	High (doctors), low (pharmaceutical companies)
Gallup, 2010, USA	Yes	992	No	Survey	Telephone interviews	Not reported	High (doctors), moderate (pharmaceutical companies)
Harris, 2010, USA	Yes	2151	No	Survey	Online interview	Not reported	High (doctors), low (pharmaceutical companies)
Harris, 2012, USA	Yes	2237	No	Survey	Online interview	Not reported	Low (pharmaceutical companies)

Methodological information in non-academic public polls/surveys

The methodological structure of the public polls/surveys was either underreported or poorly conducted. None of these studies stated a definition of the concept of trust either in the text or with the questions (Table 3). Surveys (n=11) were the most often used method to assess participants' trust, followed by polls (n=5). These studies were generally conducted by telephone (n=8) or in Internet interviews (n=5). Structured instruments to measure public trust were not reported; all 16 studies used open questions (Appendix 2). Half of these studies (n=8) did not report the use of a tool to rate the participants' answers. Five studies reported the use of a five-answer type scale, two used a three-answer type, and one used a four-answer type scale (Table 3).

State of trust

Pharmaceutical companies

Academic studies

Most articles did not primarily measure public trust in pharmaceutical companies. In the eight studies about the pharmaceutical industry, only one article reported medium/high levels of public trust since companies were seen as capable of producing good quality vaccines and thus increasing the chance of vaccination [23]. The other seven studies reported low levels of trust, citing undesired and unethical advertisement, high financial gain, or lack of transparency [24-30]. One study peripherally reported medium levels of trust in regulatory authorities; however, it was unclear whether this was the main research topic [24]. Five studies had weak methodological robustness and three had moderate (Table 2).

Non-academic public polls/surveys

Thirteen non-academic studies analyzed public trust in pharmaceutical companies [70-82]. Of these, one reported medium levels of trust, whereas the other 12 studies demonstrated low levels of trust in pharmaceutical companies (Table 3). Public arguments substantiating the medium levels of trust included the belief that pharmaceutical companies are good at serving their customers, confidence in the companies' skills to produce medical products of high quality, and their scientific contribution to public health. On the other hand, the public distrusted companies because of the high prices of medicines, the companies' lack of honesty, transparency, and trustworthiness, and their influence at a governmental level and high profits (Appendix 2).

Regulatory authorities

Academic studies

All three empirical studies on regulatory authorities reported low to medium levels of trust [31-33]. Two studies demonstrated that most of the public/patients were not familiar with regulatory authorities—in this case the British Medicines and Healthcare products Regulatory Agency (MHRA)—and this might have explained the low levels of trust [31, 32].

One study also peripherally reported low public trust levels in pharmaceutical companies [33]. All studies had weak methodologies (Table 2).

Non-academic public polls/surveys

Six non-academic public polls/surveys studied public trust in regulatory authorities [70, 72, 74, 75, 77, 83]. The results were mixed. While public trust in regulatory authorities was medium to fairly high (Table 3), the public also distrusted the regulatory authorities since they were seen as slow, bureaucratic and politically influenced institutions that were not entirely capable of ensuring the safety and efficacy of prescription drugs (Appendix 2).

Doctors

Academic studies

Public trust in doctors was the primary research question in most of the empirical academic studies. The majority of these studies (n=33) reported high levels of trust in doctors [34-46, 49-61, 63-69]. The high levels of trust correlated with doctors' characteristics, such as prioritizing patients' needs, being caring, honest, sympathetic, communicative with patients and listening, as well as knowledge and technical skills, ability to diagnose, availability, and being respectful and patient. Other correlates for high trust in doctors were having a good/better health status, not having had disputes with doctors, long patient-doctor relationships, low education levels, and age (elderly). Three articles reported low levels of trust in doctors, whereby race and an ethnic background that differed from the doctor were correlated with distrust in doctors (African American and Hispanics distrusted doctors the most) [47, 48, 62]. Young people and more highly educated participants had less trust in doctors (Table 1, Appendix 1). Seven studies (including the five reviews) showed strong methodological robustness, while the rest (n=29) showed a moderate to weak methodology. There was no visible correlation between empirical studies with a structured methodology and higher or lower levels of trust (Figure 3).

Six academic empirical studies about doctors demonstrated that high levels of trust positively influenced therapeutic outcomes (i.e., compliance, adherence, diagnosing and discussing treatment options on time) [35, 38, 46, 53, 57, 62]. Patients who distrusted doctors were less likely to follow a doctor's advice, comply or be adherent to taking medications.

Non-academic public polls/surveys

Ten out of the 16 non-academic polls/surveys that analyzed public trust in doctors reported generally high levels of trust (Table 3) [70-76, 78-80]. High trust in doctors was grounded in the public's perception that doctors will do the right thing for their patients and prioritize their needs (Appendix 2). In contrast, the health care system, which is mainly serviced by doctors, received significantly less public trust than the doctors did [71-73, 78]. Reasons for this low trust were the high prices that the public pays for health care and medications, the soaring profits health care institutions are making and their poor performance (Appendix 2). Peripherally, one poll demonstrated that nearly half of the public distrusted the safety of medicines [84].

Discussion

In the present article, we present a systematic review of academic and non-academic empirical studies measuring public trust in pharmaceutical companies, regulatory authorities, and doctors. We found that the amount of academic empirical data measuring public trust in pharmaceutical companies and regulatory authorities is scarce. The number of articles surveyed in the present study is therefore insufficient to outline strong tendencies and limited findings. However, the present study is the first systematic review about empirical (academic and non-academic) public trust studies in pharmaceutical companies and regulatory authorities. Public trust was not the main topic of research or outcome in most of the identified academic empirical articles, and their methodological structure and robustness was rather poor. In contrast to the studies that examined public trust in pharmaceutical companies and regulatory authorities, the academic empirical studies that measured public trust in doctors used more structured methodologies and the number of articles surveyed was larger than those concerning pharmaceutical companies and regulatory authorities. However, the present review comprehended a much greater number of articles surveyed when compared with earlier reviews about trust in doctors. Although studies with better structured methodologies showed higher levels of trust, there was no correlation since studies reporting higher levels of trust were about doctors and only coincidentally showed better-structured methodologies. The methodologies that were used to measure trust in doctors varied considerably among empirical articles, thereby lacking standardization, which also hampered the comparability of the results. The methodological robustness of non-academic public polls/surveys was also quite poor. Academic and non-academic empirical studies demonstrated low levels of public trust in pharmaceutical companies and regulatory authorities, whereas doctors were highly trusted. The scarce amount of empirical public trust studies in pharmaceutical companies and regulatory authorities that we have found may indicate that public trust in these institutions have been severely overlooked, underestimated and under-researched.

The present systematic review has limitations. We solely focused on studies that measured public trust. We therefore limited our keyword sets to trust only. Studies that measured other "synonyms, derivatives or equivalents" of trust or proxies for low trust levels, such as conspiracy theories, were excluded from our analysis as they structurally and conceptually differ from our main research objective. Moreover, the indexing methodologies of the databases that we used may vary according to the criteria and (research) policies applied amongst databases. The keywords that are assigned to studies (to be identifiable throughout scientific databases) depend on the authors' and/or the databases' choices. Assigning therefore the most appropriate keywords to cover the topic of a particular study and the subjects of study in the most accurate way is a decisive step for the identification of valid studies (according to the inclusion criteria) through databases. This is a factor that may limit our retrieval capacity and we might therefore have missed some relevant articles. This is always the Achilles heel of systematic reviews or meta-analyses. Of course, we realize that there are far more articles available that could have been found if we would have broadened our search, though less specific concerning the object and subject of study.

For instance, in the context of influenza pandemics and vaccines safety issues, studies on public trust in several institutions have been published which we did not identify based on our keyword sets [85-88]. Here, it was observed that public trust in pharmaceutical companies was relatively high in line with trust in authorities or the government, but this trust decreased after the pandemic alert and media attention [85-87]. However, in a similar fashion as in our dataset, we could not discern whether an explicit a priori definition of trust was given to the participants, as it was not reported in the articles. Nevertheless, given the number and quality of retrieved articles and the use of different databases to complement our search in different disciplines, we are confident that we included and analyzed a substantial part of the academic and non-academic literature that specifically focused on measuring public trust in pharmaceutical companies, regulatory authorities and doctors. Yet, based on the limited amount of articles found concerning pharmaceutical companies and regulatory authorities, strong tendencies or inferences may not preferably be outlined. Caution ought to be taken when interpreting the results.

Methodological issues in academic and non-academic studies

This review found several methodological drawbacks characterized by more differences than similarities. The disappointingly low quality of the public measurements of trust was attributed to both a lack of a definition of trust and methodological standardization between and within academic and non-academic studies, as well as varying and sometimes very low response rates/participation rates. These methodological disadvantages also hampered a thorough analysis of the trust outcomes of the studies, such as a meta-analysis.

Only one academic empirical study of pharmaceutical companies clearly defined trust, while no studies defined trust for regulatory authorities. Even academic studies that measured trust in doctors, which had better methodological structure, varied significantly with regard to defining trust a priori to the participants. The lack of a definition of trust in non-academic public polls/surveys was also consistent. The absence of a pre-specified definition of trust in academic and non-academic empirical studies is a notable methodological disadvantage. Since the concept of trust has been reported to have multi-dimensional traits (i.e., psychological, cognitive and emotional) and trust definitions are manifold [11-15, 89], it is most important to provide a clear definition of trust in empirical studies to participants a priori [16]. Trust can be confused with a multitude of synonyms, such as mutuality, empathy, reciprocity, respect, solidarity, confidence or fraternity, and behavior can reflect trust [16]. Therefore, a conceptual clarification of the meaning of trust is desirable for empirical precision, methodological robustness, and to discern between the participants' objective/subjective responses in relation to attitudes about trust [22]. If the participants or researchers do not know what trust is, then how can it be measured?

Another methodological concern of academic and non-academic empirical studies was the use of various instruments to measure trust, or the use of open-ended questions to circumvent the lack of an instrument. Using open-ended questions to measure trust has been questioned since this method allows for personal interpretations (answers) that can vary significantly depending on the type of participant (e.g., public or patient), personal needs, age, cultural background, or feelings [90]. It is important to note that the situation

or patient's vulnerability (and need for trust) is completely different than that of the public. A personal interpretation of trust raises the possibility of bias in trust measurements by introducing the patient's subjectivity thus affecting the validity of the results [90].

A few academic trust studies of doctors in our sample used measurement instruments like the Trust in Physician Scale (TPS) and the Wake Forrest/Hall's Trust in Physician Scale. These instruments (i.e., structured questionnaires with answer scales) measure important components of the doctor-patient trust relationship, such as vulnerability, fidelity, honesty, competence or professional skills, instead of measuring trust directly [22, 91, 92]. The use of a structured/validated instrument corrects and avoids subjectivity, helps to distinguish between trustworthiness and trust (or between satisfaction and trust), and clarifies the multidimensional nature of trust [92]. Furthermore, pre-specified instruments can assist in the participants' decision process by helping them to differentiate from real situations or consequences instead of hypothetical ones [93].

What's the state of trust?

Most academic and non-academic studies demonstrated low public trust in pharmaceutical companies and regulatory authorities, although some showed medium trust in these stakeholders. While these results may seem contradictory, they also illustrate the complexity and multi-dimensional nature of trust. Yet again, there was too much variation in measurements and the robustness of the methodologies was rather poor. This bipolar (trust/distrust) public attitude may be explained by looking to the definition of public trust for the pharmaceutical sector. We define public trust in the pharmaceutical sector as "the willingness to assume a position of vulnerability in relation to the provision of care and the management and use of medicines", and as "having confidence in the competences of pharmaceutical companies, regulatory authorities, and health care providers to perform the tasks they are responsible for and expected to do". Pharmaceutical companies and regulatory authorities may not be entirely trusted when it comes to the public/patients' vulnerability concerning their perceived prioritized position, integrity, honesty, transparent behavior, or increasing costs, as reflected in the empirical studies. For instance, the public attributed the lack of trust in pharmaceutical companies to the rising costs of health care and medicines, as well as excessive advertisement expenditure. A 2007 Pricewaterhouse-Coopers' report demonstrated that the public generally believed that drug consumption accounts for 40% - 80% of the total health care budget. In fact, the true drug consumption accounts for only 5% - 15% of the total health care costs in the United States. In addition, more than 70% of the public estimates that drug development costs are not higher than US$500 million, whereas the actual costs, in 2005, reached US$1 billion [7]. The public could benefit from explicit information regarding health care, pharmaceutical companies' practices, expenditures and costs to increase awareness and avoid misconceptions that may be damaging trust. Nonetheless, according to the empirical studies reviewed, pharmaceutical companies and regulatory authorities contrarily seem to be trusted since they are still seen as competent enough to develop, manufacture and oversee drugs.

Most academic and non-academic studies were conducted in the United States. Fukuyama argued that the United States is a "high-trust" society in transition towards

less "high-trust" levels [94, 95]. Our study indicated that there are critical public views of pharmaceutical companies and regulatory authorities, since participants cited excessive regulation and a possible political agenda as a reason for distrust, confirming Fukuyama's assertions. The organizational literature claimed that excessive regulation and reliance on the law to obey regulations are "symptoms of a loss of trust" and drown voluntary trust by undermining cooperation, good will, decency or sympathy [96, 97]. Therefore, these institutions should focus their strengths on the creation of (more) cooperative environments and agreements motivated by plain trust rather than increasing the number of regulations, which may increase the costs of drugs. Studies demonstrated that regulations are not always cost-effective [98] and may hamper innovation.

Regulatory authorities, in particular at a European level, seemed to be less trusted since they were not entirely recognized in society. As representatives of the public, regulatory authorities should work to increase public communication and recognition through various channels and inform and educate the public about their societal role. Enabling bilateral communication processes between the public and regulators could avoid or limit the occurrence of "information vacuums" or media interventions. It has been demonstrated that "information vacuums" and unbalanced media interventions may distort the communication process and damage trust [99-101].

Most academic and non-academic studies demonstrated high levels of public trust in doctors. Physicians who prioritize their patients' needs, are honest, patient, respectful, caring, good at communicating, and technically skilled were highly trusted [42-44, 47, 49, 52, 54, 55, 63, 67]. Hall et al. denoted trust in physicians by the inherent presence of vulnerability while trusting, which arises and becomes more tangible during illness [22]. Patients can manage this vulnerability when they recognize abovementioned characteristics in their doctors and trust them. On the other hand, academic and non-academic studies reporting high to medium/medium/low levels of trust in doctors demonstrated the consequences of doctor's misbehaviors, such as being judgmental, discriminatory, condescending, dishonest, or impatient [36, 43, 44, 47, 61, 67]. Low trust in doctors seemed to be correlated with participants having a racial/ethnic background that differed from their doctor, being non-Caucasian, young, uninsured, highly educated, and less healthy [45, 47-50, 52, 58, 61, 62, 64-66, 69].

Academic studies demonstrate that having relationships with pharmaceutical companies seemed to damage public trust in doctors [25, 42, 102], whereas non-academic studies demonstrated that patients consider this as irrelevant as long as patients receive better treatments [74, 77]. Interpersonal relationships, characterized by face-to-face contacts (patient-doctor relationship) seem to evoke and profit higher levels of public trust than trust in organizations [22, 92, 103-105]. This may also explain the various levels of public trust found among pharmaceutical companies, regulatory authorities and doctors. More importantly, doctors, as gatekeepers of the health care system, seem to mediate public trust in health care institutions [105]. A sample of our studies demonstrated that having high levels of trust in doctors was beneficial for patients in term of diagnoses, therapies, adherence and outcomes [35, 38, 46, 53, 57, 62]. Trust flourishes and functions best

based on personal experiences and individual relationships, as seen in doctors, compared to legal or regulatory environments in which trust is assumed to exist between the public/patients and institutions or within organizations.

A better understanding of how public trust in pharmaceutical companies, regulatory authorities and doctors is mediated is necessary to create a more cooperative and innovative drug development and evaluation system. There is an urgent need for methodologically robust and standardized measurements of public trust to achieve this understanding and work on restoring trust. Patients can benefit from high trust levels in terms of treatment and outcomes, regulatory authorities can enjoy more public support when deciding about issues of public interests, and pharmaceutical companies can benefit in terms of public recognition, support, social coherence, and economic reward. Understanding and creating a culture of trust between the pharmaceutical companies and regulatory authorities is essential for innovation, collaboration, drug safety, and can help to lower the burden of excessive regulations that have a direct impact on health care costs.

Conclusion

Scientific articles and news media claim that there is an erosion of trust in pharmaceutical companies, regulatory authorities and doctors. We conclude that such a statement cannot be fully substantiated with the academic and non-academic empirical data that are currently available. Based on the scarce amount of public trust studies in pharmaceutical companies and regulatory authorities, strong inferences could not be outlined. Although the claims of an erosion of trust are understandable, based on single events or media portrayals, the quality of the academic and non-academic studies that examine trust is relatively low. There is an overall lack of standardization, comparability, and representativeness among studies, and no consensus or definition of trust.

The present systematic review underlines the need for more and better-structured (methodologically robust) studies on public trust in abovementioned stakeholders. Methodologically robust assessments, where trust components are measured (i.e., vulnerability or competences) instead of trust in general, would clarify the multidimensional nature of trust and indicate reliable and objective public trust levels in pharmaceutical companies, regulatory authorities and doctors.

References

1. Bauchner H FPB. Restoring confidence in the pharmaceutical industry. JAMA. 2013;309(6):607-9.
2. Take a stand. Nature. 2012 Jul 12;487(7406):139-40.
3. Lofstedt R, Bouder F, Wardman J, Chakraborty S. The changing nature of communication and regulation of risk in Europe. Journal of Risk Research. 2011;14(4):409-29.
4. Gallup. Gallup - Home: Gallup; 2013 [cited 2013 January 28]. Available from: http://www.gallup.com/home.aspx.
5. HarrisInteractive. HarrisInteractive. 2012;2012(27 April).
6. KFF. Kaiser Family Foundation. Kaiser Family Foundation. 2012;2012(27 April).
7. PWC. Recapturing the vision: Restoring trust in the pharmaceutical industry by translating expectations into actions: PriceWaterhouseCoopers; 2007 [cited 2012 27 February]. Available from: http://www.pwc.com/gx/en/pharma-life-sciences/pharmaceutical-industry-thought-leadership.jhtml.
8. Edwards B, Olsen AK, Whalen MD, Gold MJ. Guiding principles of safety as a basis for developing a pharmaceutical safety culture. Curr Drug Saf. 2007 May;2(2):135-9.
9. Getz KA. Public Confidence and Trust Today - A Review of Public Opinion Polls. Monitor. 2008 September 2008;September 2008:17-21.
10. Olsen AK, Whalen MD. Public perceptions of the pharmaceutical industry and drug safety: implications for the pharmacovigilance professional and the culture of safety. Drug Saf. 2009;32(10):805-10.
11. Leslie CR. Trust, distrust, and antitrust. Texas Law Review. 2004 Feb;82(3):515-680.
12. Colesca SE. Understanding Trust in e-Government. Inzinerine Ekonomika-Engineering Economics. 2009 2009(3):7-15.
13. van der Schee E, Braun B, Calnan M, Schnee M, Groenewegen PP. Public trust in health care: A comparison of Germany, The Netherlands, and England and Wales. Health policy (Amsterdam, Netherlands). 2007;81(1):56-67.
14. Ide RW, Yarn DH. Public independent fact-finding: A trust-generating institution for an age of corporate illegitimacy and public mistrust. Vanderbilt Law Review. 2003 May;56(4):1113-+.
15. Wang H, Schlesinger M, Hsiao WC. The flip-side of social capital: the distinctive influences of trust and mistrust on health in rural China. Soc Sci Med. 2009 Jan;68(1):133-42.
16. Newton K. Trust, social capital, civil society, and democracy. International Political Science Review. 2001 Apr;22(2):201-14.
17. McLeod C. Trust. In: Zalta EN, editor. Stanford Encyclopedia of Philosophy. Spring 2011 ed: Metaphysics research lab, CSLI, Stanford University; 2011.
18. Baier A. TRUST AND ANTITRUST. Ethics. 1986 Jan;96(2):231-60.
19. Blair MM, Stout LA. Trust, trustworthiness, and the behavioral foundations of corporate law. University of Pennsylvania Law Review. 2001 Jun;149(6):1735-810.
20. Jones AJI. On the concept of trust. Decision Support Systems. 2002 Jul;33(3):225-32.
21. Jones K. Trust as an affective attitude. Ethics. 1996 Oct;107(1):4-25.

22. Hall MA, Dugan E, Zheng BY, Mishra AK. Trust in physicians and medical institutions: What is it, can it be measured, and does it matter? Milbank Quarterly. 2001 2001;79(4):613-+.
23. Allen JD, Othus MKD, Shelton RC, Li Y, Norman N, Tom L, et al. Parental Decision Making about the HPV Vaccine. Cancer Epidemiology Biomarkers & Prevention. 2010 Sep;19(9):2187-98.
24. Bunniran S, McCaffrey Iii DJ, Bentley JP, Bouldin AS. Pharmaceutical product withdrawal: Attributions of blame and its impact on trust. Research in Social and Administrative Pharmacy. 2009;5(3):262-73.
25. Edwards D, Ballantyne A. Patient awareness and concern regarding pharmaceutical manufacturer interactions with doctors. Intern Med J. 2009 Mar;39(3):191-6.
26. Freeman BD, Kennedy CR, Coopersmith CM, Zehnbauer BA, Buchman TG. Genetic research and testing in critical care: Surrogates' perspective. Critical Care Medicine. 2006 Apr;34(4):986-94.
27. Gale NK, Greenfield S, Gill P, Gutridge K, Marshall T. Patient and general practitioner attitudes to taking medication to prevent cardiovascular disease after receiving detailed information on risks and benefits of treatment: a qualitative study. Bmc Family Practice. 2011 Jun;12.
28. Goff SL, Mazor KM, Meterko V, Dodd K, Sabin J. Patients' beliefs and preferences regarding doctors' medication recommendations. Journal of General Internal Medicine. 2008 Mar;23(3):236-41.
29. Henrich N, Holmes B. What the Public Was Saying about the H1N1 Vaccine: Perceptions and Issues Discussed in On-Line Comments during the 2009 H1N1 Pandemic. Plos One. 2011 Apr;6(4).
30. Lukoschek P. African Americans' beliefs and attitudes regarding hypertension and its treatment - A qualitative study. Journal of Health Care for the Poor and Underserved. 2003 Nov;14(4):566-87.
31. Himmelstein M, Miron-Shatz T, Hanoch Y, Gummerum M. Over-the-counter cough and cold medicines for children: A comparison of UK and US parents' parental usage, perception and trust in governmental health organisation. Health Risk & Society. 2011;13(5):451-68.
32. Krska J, Jones L, McKinney J, Wilson C. Medicine safety: experiences and perceptions of the general public in Liverpool. Pharmacoepidemiol Drug Saf. 2011 Oct;20(10):1098-103.
33. Snyder PJ, Papp KV, Bartkowiak J, Jackson CE, Doody RS. Commentary on "a roadmap for the prevention of dementia II. Leon Thal Symposium 2008." Recruitment of participants for Alzheimer's disease clinical trials: the role of trust in caregivers, clinical researchers, regulatory authorities, and industry sponsors. Alzheimers Dement. 2009 Mar;5(2):122-4.
34. Alexander JA, Hearld LR, Hasnain-Wynia R, Christianson JB, Martsolf GR. Consumer trust in sources of physician quality information. Med Care Res Rev. 2011 Aug;68(4):421-40.
35. Bachinger SM, Kolk AM, Smets EM. Patients' trust in their physician--psychometric properties of the Dutch version of the "Wake Forest Physician Trust Scale". Patient

Educ Couns. 2009 Jul;76(1):126-31.
36. Benkert R, Peters R, Tate N, Dinardo E. Trust of nurse practitioners and physicians among African Americans with hypertension. J Am Acad Nurse Pract. 2008 May;20(5):273-80.
37. Berrios-Rivera JP, Street RL, Jr., Garcia Popa-Lisseanu MG, Kallen MA, Richardson MN, Janssen NM, et al. Trust in physicians and elements of the medical interaction in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Rheum. 2006 Jun 15;55(3):385-93.
38. Blackstock OJ, Addison DN, Brennan JS, Alao OA. Trust in primary care providers and antiretroviral adherence in an urban HIV clinic. J Health Care Poor Underserved. 2012 Feb;23(1):88-98.
39. Blendon RJ, Benson JM. Americans' views on health policy: A fifty-year historical perspective. Health Affairs. 2001 Mar-Apr;20(2):33-46.
40. Brodsky SL, Knowles RI, Cotter PR, Herring GH. Jury selection in malpractice suits: an investigation of community attitudes toward malpractice and physicians. Int J Law Psychiatry. 1991;14(3):215-22.
41. Calnan M, Montaner D, Horne R. How acceptable are innovative health-care technologies? A survey of public beliefs and attitudes in England and Wales. Social Science and Medicine. 2005;60(9):1937-48.
42. Calnan MW, Sanford E. Public trust in health care: the system or the doctor? Qual Saf Health Care. 2004 Apr;13(2):92-7.
43. Chu-Weininger MY, Balkrishnan R. Consumer satisfaction with primary care provider choice and associated trust. BMC Health Serv Res. 2006;6:139.
44. Copeland VC, Scholle SH, Binko JA. Patient Satisfaction: African American Women's Views of the Patient-Doctor Relationship. Journal of Health and Social Policy. 2003;17(2):35-48.
45. Dugan E, Trachtenberg F, Hall MA. Development of abbreviated measures to assess patient trust in a physician, a health insurer, and the medical profession. BMC Health Serv Res. 2005;5:64.
46. Franks P, Fiscella K, Shields CG, Meldrum SC, Duberstein P, Jerant AF, et al. Are patients' ratings of their physicians related to health outcomes? Annals of Family Medicine. 2005;3(3):229-34.
47. Graham JL, Giordano TP, Grimes RM, Slomka J, Ross M, Hwang LY. Influence of trust on HIV diagnosis and care practices: A literature review. Journal of the International Association of Physicians in AIDS Care. 2010;9(6):346-52.
48. Hargreaves DS, Viner RM. Children's and young people's experience of the National Health Service in England: A review of national surveys 2001-2011. Archives of Disease in Childhood. 2012;97(7):661-6.
49. Hillen MA, de Haes H, Smets EMA. Cancer patients' trust in their physician-a review. Psycho-Oncology. 2011 Mar;20(3):227-41.
50. Hunt KA, Gaba A, Lavizzo-Mourey R. Racial and ethnic disparities and perceptions of health care: Does health plan type matter? Health Services Research. 2005;40(2):551-76.
51. Johansen MA, Johnsen JA, Hartvigsen G, Ellingsen G, Bellika JG. Bridging the gap

between patients' expectations and general practitioners' knowledge through disease surveillance. Stud Health Technol Inform. 2009;150:423-7.

52. Keating NL, Gandhi TK, Orav EJ, Bates DW, Ayanian JZ. Patient Characteristics and Experiences Associated with Trust in Specialist Physicians. Archives of Internal Medicine. 2004;164(9):1015-20.
53. Kerse N, Buetow S, Mainous Iii AG, Young G, Coster G, Arroll B. Physician-patient relationship and medication compliance: A primary care investigation. Annals of Family Medicine. 2004;2(5):455-61.
54. Krupat E, Hsu J, Irish J, Schmittdiel JA, Selby J. Matching patients and practitioners based on beliefs about care: Results of a randomized controlled trial. American Journal of Managed Care. 2004;10(11 I):814-22.
55. Lee YY, Ng CT, Siti Aishah MG, Ngiam JZ, Tai BC, Lim MK, et al. Public trust in primary care doctors, the medical profession and the healthcare system among Redhill residents in Singapore. Ann Acad Med Singapore. 2007 Aug;36(8):655-61.
56. Lim JY, Lee HH, Hwang YH. Trust on doctor, social capital and medical care use of the elderly. Eur J Health Econ. 2011 Apr;12(2):175-88.
57. Mainous Iii AG, Kern D, Hainer B, Kneuper-Hall R, Stephens J, Geesey ME. The Relationship between Continuity of Care and Trust with Stage of Cancer at Diagnosis. Family Medicine. 2004;36(1):35-9.
58. McKinstry B, Ashcroft RE, Car J, Freeman GK, Sheikh A. Interventions for improving patients' trust in doctors and groups of doctors. Cochrane Database of Systematic Reviews. 2006 (3).
59. Minamisawa A, Suzuki T, Watanabe K, Imasaka Y, Kimura Y, Takeuchi H, et al. Patient's trust in their psychiatrist: A cross-sectional survey. European Archives of Psychiatry and Clinical Neuroscience. 2011;261(8):603-8.
60. Moseley KL, Clark SJ, Gebremariam A, Sternthal MJ, Kemper AR. Parents' trust in their child's physician: using an adapted Trust in Physician Scale. Ambul Pediatr. 2006 Jan-Feb;6(1):58-61.
61. Pagan JA, Balasubramanian L, Pauly MV. Physicians' career satisfaction, quality of care and patients' trust: the role of community uninsurance. Health Econ Policy Law. 2007 Oct;2(Pt 4):347-62.
62. Pedersen VH, Armes J, Ream E. Perceptions of prostate cancer in Black African and Black Caribbean men: A systematic review of the literature. Psycho-Oncology. 2012;21(5):457-68.
63. Pescosolido BA, Tuch SA, Martin JK. The profession of medicine and the public: examining Americans' changing confidence in physician authority from the beginning of the 'health care crisis' to the era of health care reform. J Health Soc Behav. 2001 Mar;42(1):1-16.
64. Rawaf MM, Kressin NR. Exploring racial and sociodemographic trends in physician behavior, physician trust and their association with blood pressure control. J Natl Med Assoc. 2007 Nov;99(11):1248-54.
65. Sloan FA, Rattliff JR, Hall MA. Impacts of managed care patient protection laws on health services utilization and patient satisfaction with care. Health Services Research. 2005;40(3):647-67.

66. Tarrant C, Stokes T, Baker R. Factors associated with patients' trust in their general practitioner: a cross-sectional survey. Br J Gen Pract. 2003 Oct;53(495):798-800.
67. Torke AM, Corbie-Smith GM, Branch Jr WT. African American Patients' Perspectives on Medical Decision Making. Archives of Internal Medicine. 2004;164(5):525-30.
68. Weng HC. Does the physician's emotional intelligence matter? Impacts of the physician's emotional intelligence on the trust, patient-physician relationship, and satisfaction. Health Care Manage Rev. 2008 Oct-Dec;33(4):280-8.
69. Weng HC, Chen YS, Lin CS, Tu YK, Lin HH, Yu SW. Specialty differences in the association between health care climate and patient trust. Med Educ. 2011 Sep;45(9):905-12.
70. KFF. THE PUBLIC AND PRESCRIPTION DRUGS: Kaiser Family Foundation; 2000 [cited 2012 March 7]. Available from: http://www.kff.org/rxdrugs/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=13541.
71. Gallup. Health Care, Lawyers, Energy and Accounting Suffer in Public's Eye Princeton, N.J.: Gallup; 2002 [cited 2013 January 18]. Available from: http://www.gallup.com/poll/6616/Health-Care-Lawyers-Energy-Accounting-Suffer-Publics-Eye.aspx.
72. Gallup. Vioxx Recall Hits a Low-Rated Industry Princeton, N.J.: Gallup; 2004 [cited 2013 January 18]. Available from: http://www.gallup.com/poll/14212/Vioxx-Recall-Hits-LowRated-Industry.aspx.
73. Gallup. Restaurants Highest-Rated Industry; Oil and Gas Lowest Princeton, N.J.: Gallup; 2005 [cited 2013 January 18]. Available from: http://www.gallup.com/poll/18037/Restaurants-HighestRated-Industry-Oil-Gas-Lowest.aspx.
74. KFF. Views On Prescription Drugs And The Pharmaceutical Industry: Kaiser Family Foundation; 2005 [cited 2012 March 21]. Available from: http://www.kff.org/healthpollreport/feb_2005/upload/full_report.pdf.
75. HarrisInteractive. Large Numbers of People Do Not Trust the Institutions They Identify as Most Responsible for Drug Safety Rochester, N.Y.: Harris Interactive; 2006 [cited 2013 January 21]. Available from: http://www.harrisinteractive.com/news/allnewsbydate.asp?newsid=1216.
76. Gallup. Annual Update: Americans Rate Business and Industry Sectors Princeton, N.J.: Gallup; 2007 [cited 2013 January 18]. Available from: http://www.gallup.com/poll/28615/Annual-Update-Americans-Rate-Business-Industry-Sectors.aspx - 1.
77. KFF. Views on Prescription Drugs and the Pharmaceutical Industry (Spotlight): Kaiser Family Foundation; 2008 [cited 2013 January 21]. Available from: http://www.kff.org/spotlight/rxdrugs/upload/rx_drugs.pdf.
78. Gallup. On Healthcare, Americans Trust Physicians Over Politicians Princeton, N.J. : Gallup; 2009 [cited 2013 January 18]. Available from: http://www.gallup.com/poll/120890/Healthcare-Americans-Trust-Physicians-Politicians.aspx.
79. Gallup. In U.S., More Than 8 in 10 Rate Nurses, Doctors Highly Washington, D.C.: Gallup; 2010 [cited 2013 January 18]. Available from: http://www.gallup.com/poll/145214/Rate-Nurses-Doctors-Highly.aspx.
80. Gallup. Obama Retains More Trust Than Congress on Healthcare Princeton, N.J.: Gallup; 2010 [cited 2013 January 18]. Available from: http://www.gallup.com/poll/126338/Obama-Retains-Trust-Congress-Healthcare.aspx.

81. HarrisInteractive. Oil, Pharmaceutical, Health Insurance, and Tobacco Top The List Of Industries That People Think Should Be More Regulated New York, N.Y.: Harris Interactive; 2010 [cited 2012 March 7]. Available from: http://www.harrisinteractive.com/vault/HI-Harris-Poll-Industry-Regulation-2010-12-02.pdf.
82. HarrisInteractive. American Red Cross, Nature Conservancy, Consumers Union and AARP are Organizations Inside the Beltway Most Trusted by Public New York, N.Y.: Harris Interactive; 2012 [cited 2012 March 7]. Available from: http://www.harrisinteractive.com/NewsRoom/HarrisPolls/tabid/447/ctl/ReadCustom Default/mid/1508/ArticleId/942/Default.aspx.
83. HarrisInteractive. The FDA's Reputation with the General Public is Under Assault New York, N.Y.: Harris Interactive; 2006 [cited 2012 April 3]. Available from: http://www.harrisinteractive.com/news/allnewsbydate.asp?newsID=1060.
84. HarrisInteractive. Large Numbers of People Are Not Very Confident in their Own Knowledge and the Safety of Prescription Medications and this Often Leads to Non-Adherence Rochester, N.Y.: Harris Interactive; 2007 [cited 2013 January 21]. Available from: http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=1206.
85. Bangerter A, Krings F, Mouton A, Gilles I, Green EGT, Cl√©mence A. Longitudinal Investigation of Public Trust in Institutions Relative to the 2009 H1N1 Pandemic in Switzerland. Plos One. 2012;7(11):e49806.
86. Gilles I, Bangerter A, Cl√©mence A, Green ET, Krings F, Staerkl√© C, et al. Trust in medical organizations predicts pandemic (H1N1) 2009 vaccination behavior and perceived efficacy of protection measures in the Swiss public. Eur J Epidemiol. 2011 2011/03/01;26(3):203-10.
87. Wagner-Egger P, Bangerter A, Gilles I, Green E, Rigaud D, Krings F, et al. Lay perceptions of collectives at the outbreak of the H1N1 epidemic: heroes, villains and victims. Public Understanding of Science. 2011 July 1, 2011;20(4):461-76.
88. Wilson CB, Marcuse EK. Vaccine safety--vaccine benefits: science and the public's perception. Nat Rev Immunol. 2001 Nov;1(2):160-5.
89. Schoorman FD, Mayer RC, Davis JH. Organizational trust: Philosophical perspectives and conceptual definitions. Academy of Management Review. 1996 Apr;21(2):337-40.
90. Whitley R, McKenzie K. Social capital and psychiatry: Review of the literature. Harvard Review of Psychiatry. 2005 Mar-Apr;13(2):71-84.
91. Anderson LA, Dedrick RF. DEVELOPMENT OF THE TRUST IN PHYSICIAN SCALE: A MEASURE TO ASSESS INTERPERSONAL TRUST INPATIENT-PHYSICIAN RELATIONSHIPS. Psychological Reports. 1990 1990/12/01;67(3f):1091-100.
92. Hall MA, Camacho F, Dugan E, Balkrishnan R. Trust in the medical profession: Conceptual and measurement issues. Health Services Research. 2002 Oct;37(5):1419-39.
93. Fetchenhauer D, Dunning D. Do people trust too much or too little? Journal of Economic Psychology. 2009 Jun;30(3):263-76.
94. Koehn D. Should we trust in trust? American Business Law Journal. 1996 Win;34(2):183-&.
95. Fukuyama F. The end of history and the last man. New York, N.Y.: The Free Press; 1992.
96. Cross FB. Law and trust. Georgetown Law Journal. 2005 Jun;93(5):1457-545.

97. Putnam D. RELATIONAL ETHICS AND VIRTUE THEORY. Metaphilosophy. 1991 Jul;22(3):231-8.
98. Bouvy JC, Koopmanschap MA, Shah RR, Schellekens H. The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. Clin Pharmacol Ther. 2012 Feb;91(2):281-8.
99. Bouder F. Benefit/risk communication by the European Medicines Agency: a study of influential stakeholders' expectations and attitudes London: EMA; 2011 [cited 2013 15 February]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/05/WC500106865.pdf.
100. Lofstedt R. Risk Management in Post-Trust Societies. London: Pelgrave Macmillan; 2005.
101. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, Belitser SV, Raaijmakers JAM, Pieters T. Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study. BMJ Open. 2011 January 1, 2011;1(2).
102. Arkinson J, Holbrook A, Wiercioch W. Public perceptions of physician-pharmaceutical industry interactions: A systematic review. Healthcare Policy. 2010;5(4):69-89.
103. Goold SD. Trust and the ethics of health care institutions. Hastings Center Report. 2001 Nov-Dec;31(6):26-33.
104. Mechanic D, Meyer S. Concepts of trust among patients with serious illness. Social Science & Medicine. 2000 Sep;51(5):657-68.
105. Brown P, Calnan M. Braving a faceless new world? Conceptualizing trust in the pharmaceutical industry and its products. Health:. 2010 December 15, 2010.

Appendixes

Appendix 1. Characteristics and outcome about public trust in each of the stakeholders of the pharmaceutical sector from the in-depth analyzed academic empirical studies (complete-outcome)

First author, year, and region	Type of participants (public or patients)	Instrument	Topic	Outcome about trust
Pharmaceutical companies				
Allen, J. D. et al., 2010. USA	Public	Integrative model of behavioral prediction	Parent's decision making relating HPV vaccine	Parents who trusted pharmaceutical companies were almost 4.5 times more likely to vaccinate their daughters, 2.09 fold intended to vaccinate, and 2.04 undecided
Bunniran, S. et al., 2009. USA	Public	Unidimensional summated scale	Consumer reactions to drug withdrawal	Pharmaceutical companies (37.1%) received the lowest trust scores with insurance companies (27%). The public sees pharmaceutical companies as responsible for drug withdrawals (mean 6.00 of 7 possible) and the FDA (mean 5.06). The FDA (49.3%) and doctors (45.15%) in general were in the middle (0-100% scale, where 100% is high trust). *Not clear if trust in the FDA and doctors was also the main research topic.
Edwards, D., 2009. Australia	Public	-	Trustworthiness of pharmaceutical advertisement and the industry	Trustworthiness of advertisement was low, 59% of respondents think that pharmaceutical companies influenced doctors' prescriptions (5 or 6). Suspicious participants about advertisement were more informed about these activities. Participants prefer doctors who do not receive promotional visits.
Freeman, B. D. et al., 2006. USA	Relatives of patients (Surrogate Decision-Makers SDM)	Public attitudes towards pharmacogenomics	Surrogate decision makers' attitude towards genetic testing	Surrogate decision makers distrust pharmaceutical companies to conduct genetic research (39.3%) more than the federal government (64.1%). Respondents fear that results would remain confidential. *Results about pharma were not main research topic - secondary
Gale, N. K. et al., 2011. UK	High coronary risk patients	Open questions/ transcripts from audio recordings	Attitude of patients and GPs towards prevention drugs of CVD	Trust in drug industries was low. Lack of trust was associated with negative health outcomes and mistrust in research findings.
Goff, S. L. et al., 2008. USA	Public	Open questions/ transcripts from audio recordings	Patients' beliefs about doctor's medication recommendations	Some participants considered pharmaceutical detailing as positive, while the majority of the participants viewed pharmaceutical detailing as negative, citing the influence on doctor's decision making, possible financial or social gain, and possible biased information from pharmaceutical representatives.
Henrich, N. et al., 2011. Canada	Public	Analysis of comments in news pages	Public perceptions towards the H1N1 pandemic in Canada	Pharmaceutical companies were not trusted. The public reported reasons, such as financial gain caused by the pandemic (i.e., a public health crisis), the millions of vaccine doses sold to the government, and that adequate clinical trials were lacking before selling these vaccines. *Results about pharma were not main research topic - secondary

First author, year, and region	Type of participants (public or patients)	Instrument	Topic	Outcome about trust
Lukoschek, P., 2003. USA	Hypertension patients	Open questions/ transcripts from audio recordings	Patient attitudes regarding hypertension treatment	Lack of trust in pharmaceutical companies caused patients to believe that some medication was harmful and non-effective. African American patients distrusted pharmaceutical companies and some doctors, as they believed they were used as guinea pigs to test medications. Distrust was associated with non-adherence.
Regulatory authorities				
Himmelstein, M. et al., 2011. UK	Public	Open-ended and multiple questions	Parents' trust on regulatory institutions	54.4% of the public mistrusted the MHRA recommendations. One-third of the sample remained unaware of the recommendations, despite widespread publicity.
Krska, J. et al., 2011. UK	Public	Open-ended and multiple questions	Public perceptions of drug safety	The UK regulatory agency (MHRA) was unknown to most of the participants (78.4%), which partially explained the low level of trust, and for this reason trust was not directly measured. Only 6.2% of the participants were aware that the public could report suspected ADRs directly to the regulator. MHRA functions to ensure medicine safety were not known/clear for most of the public.
Snyder, P. J. et al., 2009. USA, UK, Australia, Ireland, and Canada	Public	-	Public perception of trust in health care delivery and research	Very little trust was placed in governmental groups such as the FDA. 57% trusted the FDA ''somewhat,'' and 29% of respondents did not trust them ''at all'' with their physical or psychological well-being. *41% did not trust pharmaceutical companies at all, and 51% trusted them ''somewhat'' with their physical or psychological well-being.
Doctors				
Alexander, J. A. et al., 2011. USA	Chronic patients (asthma, heart disease, depression, diabetes, and hypertension)	Framework consumer marketing (market segment adaptive)	Trust in physician's quality of information	83.4% of the participants trusted physicians' information a lot (14.3% a little, 1.6% not at all, 0.7% don't know). In contrast, trust in regulatory authorities' information was 24.5% a lot, 53.7% a little, 19.8% not at all, 2.0% don't know.
Bachinger, S. M. et al., 2009. Netherlands	Outpatients	Hall's Trust in Physicians Scale	Patient's trust in their physician	Participants indicated high levels of trust in doctors (mean 4.3, max 5). Trust in physicians was associated with satisfaction and willingness to recommend their physicians. Longer experiences with physicians reflected high levels of trust. However, men in particular need more time to trust their physician or are more inclined to stay with their physician once trust has been build. The older the patient, the more trusting in their physicians.
Benkert, R. et al., 2008. USA	Hypertension patients	Trust in Physician Scale (TPS) AND Cultural Mistrust Inventory (CMI)	Levels of trust in physicians and nurses in African Americans and low incomers	75% of patients reported high levels of trust in doctors (mean 3.9, max 5). Cultural (mis)trust was neutral. Trust was associated with satisfaction with care. Both satisfaction and cultural mistrust were found to be significant correlates of trust in the provider. Nurses received higher levels of trust than doctors (p=0.011). Low-income African American patients experienced unequal and discriminatory treatment, which can result in mistrust.

First author, year, and region	Type of participants (public or patients)	Instrument	Topic	Outcome about trust
Berrios-Rivera, J. P. et al., 2006. USA	Chronic patients (Rheumatoid Arthritis RA and Systemic Lupus Erythematous SLE)	Hall's Trust in Physicians Scale	Identify elements of the relationship between patients and doctors associated with trust	Trust in Physician Scale was 7.1 +/- 1.6, reflecting fairly high levels of trust. English speakers rated their physicians as more patient-centered than either Spanish speakers or bilingual speakers (P<0.05).
Blackstock, O. J. et al., 2012. USA	HIV patients using ARV therapy	Hall's Trust in Physicians Scale	Trust in physician and adherence to ARV therapy (HIV)	The mean trust score was high (45.5+/- 6.0) among participants. Trust in doctors and ARV adherence was significantly associated. Adherent patients (77.3%) reported a high level of trust compared to 46.4% of non-adherent participants who reported high trust (p<.001)
Blendon, R. J. et al., 2001. USA	Public	-	Public views on health policy (trends)	Although trust in leaders of medicine has declined over the last 30 years, this has not affected Americans' high level of trust for practicing physicians, who have consistently been among the highest ranked professionals. Americans' assessment of the honesty and ethical standards of physicians remain unchanged over the last 25 years. Since 1997, public trust in pharmaceutical companies has decreased in 20% points.
Brodsky, S. L. et al., 1991. USA	Public	Attitudes Towards Physicians	Community attitudes towards physicians and malpractice	High levels of trust towards health care, doctors, obstetricians, hospitals, and nurses were found. The range of trust was from 65% up to 92% of the subjects rating doctors as good or excellent.
Calnan, M. et al., 2005. UK	Public	Public Trust in Dutch health care questionnaire	Public attitudes to innovative health care technologies	Confidence in health care was positively correlated with attitudes towards technology. Levels of trust and confidence in health care and general practitioners were immensely high, more than hospital doctors but less than hospital nurses.
Calnan, M. et al., 2004. UK	Public	Public Trust in Dutch health care questionnaire	Public trust in health care and doctors, determinants	The mean level of confidence (trust) in healthcare system was 6.0 out of a score of 10. This declined to 5.6 when asked about their confidence in the future of healthcare. 89% respondents reported at least a fair amount of confidence in general practitioners, 87% in hospital doctors, and 89% in nurses. However, only 17% of the participants trusted in the quality of education of doctors in UK. Low trust was determined by factors such as "being taken seriously" and "getting enough attention".
Chu-Weininger, M. Y. et al., 2006. USA	Public	Hall's Trust in Physicians Scale	Satisfaction and trust in the health care provider	Consumers trusted doctors based on satisfaction issues such as years with the same doctor, capability to diagnose, to listen and concern. Trust was reinforced when the doctor was reachable for a talk outside of the office (4.28 times higher trust and satisfaction). Long waiting times demonstrated 65% less chances of being satisfied and damaged trust. Disputes with a doctor lowered the levels of trust (1.75 times less odds to trust their doctors).
Copeland, V. C. et al., 2003. USA	Public	Open questions/ transcripts from audio recordings	African American women views about health care and doctors	Women trusted more doctors that appeared sympathetic, caring, and communicative (taking time to talk). Women who trusted their doctors complied more with their therapeutic regimen. Trust was damaged as doctors treated women without respect, showed less patience, and were judgmental, insensitive, patronizing, and condescending. Doctors that avoid personal interaction with patients, prescribe too fast, or refer to another doctor present a picture of low professionalism and competencies.

First author, year, and region	Type of participants (public or patients)	Instrument	Topic	Outcome about trust
Dugan, E. et al., 2005. USA	Public	Hall's Trust in Physicians Scale	Develop 3 abbreviated instruments to measure trust in doctors, health care providers and institutions	Participants had high levels of trust in physicians. This trust was correlated with satisfaction with the physician and health care, would recommend to friends and family, no desire to switch to another doctor, number of years with the same physician, and the number of visits. Trust was also associated with having enough choice in selecting a physician, not having had a dispute, and not having sought a second opinion due to concerns about care. Trust decreased with poorer (physical and mental) health.
Franks, P. et al., 2005. USA	Outpatients	Health Care Climate Questionnaire AND Primary Care Assessment Survey	Patients' ratings of their physicians and reported changes of health status	Most of the patients trusted their doctors. Patients with high trust in doctors had better outcomes and better health in general. Patients who express negative affect also tend to report worse health and health care.
Graham, J. L. et al., 2010	-	-	Impact of trust on medical care outcomes for HIV patients	Less Black participants (43%) trusted their physicians compared to whites (80%, P<.01), and had higher distrust than whites (3.1 vs 1.8, P < .01). Blacks believe their physicians would expose them more often to unnecessary risks than whites (45.5% vs 34.8%, P < .01). Race remained a strongly significant factor on the distrust score (OR, 4.7; 95% CI, 2.9-7.7), as well as education level (more trust within less educated). Trust was positively influenced by patient-doctor relational factors such as continuity, effective communication, demonstration of care, and perceived competence of the provider. Nurses were more trusted than physicians.
Hargreaves, D. S. et al., 2012. UK	Users of the health care system	Liberating the NHS. Transparency in outcomes – a framework for the NHS'	Representation of children in national NHS surveys (2001-2011)	The 2004 survey showed that children and young people were significantly less likely than adults to feel confidence and trust in their doctors or that they were treated with respect and dignity. In 2008, young participants (16–24 years old) had significantly poorer trust in doctors than participants above 25 years old. No differences in gender were observed. The 2009/2010 survey demonstrated less trust in doctors amongst young participants (18–24 year old) than older patients.
Hillen, M. A. et al., 2011	-	-	Cancer patients' trust in their physicians	Eleven studies reported patients' trust levels. Patients reported high levels of trust in their oncologists, and surgeons. Moderate-to-high trust scores were reported in two other studies. Lower trust was reported in three studies: patients using complementary medicine, women who underwent breast-conserving therapy, and patients in end-of-life care. Higher trust levels were observed amongst women, elderly, and education level (sometimes). African Americans showed less trust than Caucasians. Amongst Europeans, Germans had more trust in doctors. Doctor's competences, communicative skills, concern, and honesty showed to generate and reinforce trust.

First author, year, and region	Type of participants (public or patients)	Instrument	Topic	Outcome about trust
Hunt, K. A. et al., 2005. USA	Public	Community Tracking Study	Does race and ethnic disparities influence trust in doctors?	The general population showed high levels of trust towards physicians, and thereby satisfaction. People tend to respond to trust questions with a high rating (e.g., last visit to a doctor as very good or excellent). Responding any lower is not the ''norm''. African Americans, Latinos, and others are less trusting and less satisfied with their physicians than whites.
Johansen, M. A. et al., 2009. Norway	Public	"To what degree do you trust your regular doctor to be fully informed about the prevalence of infectious diseases in your neighborhood".	Patients' trust in doctors' awareness about infectious diseases in the area.	Nearly half the respondents trusted their regular doctor to be more or less "fully informed" about the prevalence of infectious diseases in their neighborhood, while around one quarter had less trust in their GP. Women (18.2%) had higher confidence than men (10.8%; $p < .05$). Also, respondents from villages and rural areas (mean 3.36) had higher confidence than those from urban areas (mean 3.10), $t = -3.16$, $df = 886$, $p < .01$.
Keating, N. L. et al., 2004. USA	Patients of cardiologists, neurologists, nephrologists, gastroenterologists, or rheumatologists	Picker-Commonwealth Survey of Patient-Centered Ambulatory Care	Patients' trust in their specialists	Most patients (79%) trusted their specialist. Black and Hispanic patients were less trusting than white patients (P=.005). Patients with excellent or very good health status trusted more their doctors than those with fair, or poor health. Women were less trusting than men. Good communication with doctors was associated with greater trust, and also enough consultation time, sufficient information, and being involved in the doctor's decision.
Kerse, N. et al., 2004. New Zealand	Outpatients	Trust in Physician Scale (TPS)	Physician-patient relationship and medication compliance	Most of the patients had great levels of trust in doctors (mean:44.57; SD:6.25). High trust was associated with medication compliance, and influenced by continuity of care.
Krupat, E. et al., 2004. USA	Outpatients	Patient-Practitioner Orientation Scale (PPOS)	Influence of patient guidance on trust in their doctors	Patients who were guided by their doctors (Guided Choice) showed higher levels of trust compared with Informed Choice and Usual Care patients. Patient-centered doctors generated higher ratings of trust than other doctors who were less caring for their patients. Guiding patients in taking decisions and providing them different choices has a direct impact on the trust patients have in doctors.
Lee, Y. Y. et al., 2007. Singapore	Public	Trust in Physician Scale (TPS)	Public trust in doctors in Singapore	Reasonable levels of trust were measured for doctors (59.7), the medical profession (61.8) and the healthcare system (61.5). Proportions with neutral trust are quite large for doctors (40.4%), healthcare system (40.0%) and the medical profession (33.7%). Healthcare providers' expertise has the highest trust (mean 64.5%), followed by quality of care (63.8%), patient focus (60.1%), communication skills (59.2%), and quality of cooperation (56.7%), while policies of the healthcare system had the lower trust (46.5%).
Lim, J. Y. et al., 2011. Korea	Public	Modified Picker Survey	Influence of social capital on trust in doctors	Personnel and community levels of social capital have a significant positive effect on the trust levels of elderly patients. Participants living in a high social capital community had higher levels of trust in doctors than otherwise because of the greater quality of care in these areas (competent doctors with better communicative skills and information). The wealthier the elderly patient could be, the greater trust in doctors is perceived.

First author, year, and region	Type of participants (public or patients)	Instrument	Topic	Outcome about trust
Mainous Iii, A. G. et al., 2004. USA	Colorectal and breast cancer patients	Trust in Physician Scale (TPS)	Relationship between continuity of care and trust in physicians	Patients who had a regular doctor had a high degree of trust in that doctor. 64% of the patients discussed the importance of early cancer detection with their doctors, prior diagnosis. Cancer stage (at diagnosis) was associated with the levels of trust in doctors. Higher trust in doctors was associated with earlier detection.
McKinstry, B. et al., 2006. USA	Public	-	Effects of interventions intended to improve patient's trust in their doctors or group of doctors.	All studies measured patient trust in their physician, although each study used different measures of trust. In general, all studies demonstrated high levels of trust in doctors. Trust was influenced by race, educational level, age and gender in less intensity.
Minamisawa, A. et al., 2011. Japan	Outpatients	Trust in Physician Scale (TPS)	Investigate trust in psychiatrists of patients with several types of mental disorders	The overall score was 42.9 ± 7.2, meaning high levels of trust in psychiatrists (max score 55). Shorter duration of treatments and a less experience was associated with lower levels of trust in psychiatrists. Patients with neurotic disorders seem to have a lesser trust in their psychiatrists, compared to those with mood disorders.
Moseley, K. L. et al., 2006. USA	Parents of outpatients	Trust in Physician Scale (TPS)	Investigate parents' trust in physicians (pediatricians)	Parents of patients showed high level of trust in pediatricians (mean score was 45.4 out of max score 55). Fathers had lower trust compared to mothers. Older parents showed lower levels of trust towards pediatricians than younger parents. Trust in pediatricians was also influenced by private insurance status, parent education greater than high school, and not having a child age >3 years. African American or "other" race parents had significantly lower trust in their pediatrician than Caucasian parents.
Pagan, J. A. et al., 2007. USA	Public	4 statements: (a) 'I trust my doctor to prioritize my medical problems'; (b) 'My doctor is influenced by health insurance rules'; (c) 'My doctor might perform unnecessary procedures'; and (d) 'My doctor may not refer me to a specialist when needed.'	The influence of un-insurance status on the level of trust in doctors	69% of the respondents trusted that their doctors would prioritize their interests and medical needs. Only 21% distrusted doctors in a way that doctors could be strongly influenced by health insurance companies when making medical care decisions; and 5.1% distrusted their doctors as doctors might perform unnecessary tests and procedures. Uninsured had lower trust in doctors.
Pedersen, V. H. et al., 2012. 31 out of 33 in USA	Public	-	Perceptions of Black men about prostate cancer and doctors	High levels of mistrust in the health-care system, limited access to health care and in relationships with health professionals were prominent. Nearly 40% of respondents distrusted the US health-care system because of less help to Black men. 45% believed that they received poor quality health care because of their race. Black men who trusted their physician were more likely to have regular prostate examinations and had lower risk of being diagnosed symptomatically.

First author, year, and region	Type of participants (public or patients)	Instrument	Topic	Outcome about trust
Pescosolido, B. A. et al., 2001. USA	Public	2 surveys: Access to Medical Care in the United States (AMCUS 1975-76) and Survey and the 1998 General Social Survey (GSS).	American's changing confidence in doctors over a 20-year period	Public confidence in physician authority has become less positive over the years. Still, trust in physicians remains relatively high. 67% of the respondents trust physicians to treat patients with respect and prioritize their needs. 40% distrust the doctor's competences, and communications skills towards patients. Attitudes towards physicians from 1998 were more negative than those from 1976.
Rawaf, M. M. et al., 2007. USA	Hypertension patients	Trust in Physician Scale (TPS)	Racial differences in the patient-doctor relationship and how do they relate with trust	Participants highly trusted physicians. Caucasians showed higher levels of trust in doctors than blacks (means: white 82.47 vs. black 78.19, $p<0.0001$), and the employed vs. unemployed (employed 82.31 vs. unemployed 79.52, $p=0.0067$). Trust score (max 100).
Sloan, F. A. et al., 2005. USA	Public	Household Survey instrument	Effects of patient protection laws on public trust in doctors	Participants showed in general high levels of trust in physicians. Patient protection laws had no influence on trust. Persons in good physical and mental health, females, and higher-incomers were more satisfied. Blacks and Hispanics were less satisfied. Patterns by education were mixed. Elderly had more trust in doctors than young participants. Low-income persons had a higher level of trust after patient-protection laws were implemented.
Tarrant, C. et al., 2003. UK	Outpatients	None	Patients' trust in their physicians	76% of patients had overall trust scores of 8 or over, meaning that doctors were highly trusted (mean:8.45; SD=1.86, max:10). GP–patient communication, interpersonal care, and knowledge of the patient were independently associated with trust, also age and race (Caucasians and elderly trusted more doctors).
Torke, A. M. et al., 2004. USA	Outpatients	Open questions/ transcripts from audio recordings	Perspectives of older African American patients in a primary care clinic as they consider a medical decision.	Many responses demonstrated the importance of trust in the doctor-patient relationship, such as the doctor is good at communicating and explaining, honesty, truthfulness, patience, kindness, showing an interest in the patient, and continuity in the clinical setting. Dishonesty and withholding information to a patient damaged that trust in doctors.
Weng, H. C., 2008. Taiwan	Outpatients	Hall's Trust in Physicians Scale	Impact of the physician's emotional intelligence on trust in the patient-doctor relationship	Patients trusted more doctors that showed better control on emotion regulation ($p < .05$) and older physicians. Follow-up rates were positively correlated with trust in doctors ($p < .01$), patient–physician relationship ($p < .05$), and patient satisfaction.
Weng, H. C. et al., 2011. Taiwan	Outpatients	Hall's Trust in Physicians Scale	Influence of Emotional Intelligence of specialists on public or patients' trust	Patients had higher trust for their internists (mean: 3.94 - very high trust:5) than they had for their surgeons (mean:3.88), showing several degrees of trust between physicians. Doctors' emotional intelligence was correlated with patients' trust. Older patients showed more trust in doctors.

Appendix 2. Characteristics and outcome about public trust in each of the stakeholders of the pharmaceutical sector from the public polls and surveys from non-academic independent institutions (complete - outcome).

Institute, year, region	Title	Public or patients	Instrument	Topic	Population	Outcome about trust
KFF, 2000, USA	The public and prescription drugs	Not reported	Open questions	Public and prescription drugs	Not reported	Trust in doctors was high (95% of the participants), followed by regulatory authorities (80% trusted FDA). Trust in pharmaceutical companies was low - 45% thinks that companies are doing a good job in serving consumers (quality, costs and convenience)
Gallup, 2002, USA	Health Care, Lawyers, Energy and Accounting Suffer in Public's Eye	Public - random	Open questions	Perception of several industries	Adults (18 years and older)	Public trust in doctors and health care was low (49% negative vs. 30% positive), while in pharmaceutical companies was less negative (43% vs. 33%)
Gallup, 2004, USA	Vioxx Recall Hits a Low-Rated Industry	Public - random	Open questions	Public perception of 25 industries and the FDA	Adults (18 years and older)	Public trust in doctors and health care was low (50% vs. 33% positive), while in pharmaceutical companies was less negative (48% vs. 31% positive). Regulatory authorities were trusted a great deal to moderate (70%)
Gallup, 2005, USA	Restaurants Highest-Rated Industry; Oil and Gas Lowest	Public - random	Open questions	Public perception of 20 industries	Adults (18 years and older)	Public trust in doctors and health care was lower (50% negative vs. 32% positive) compared with pharmaceutical companies (47% negative vs. 29% positive)
KFF, 2005, USA	Views On Prescription Drugs And The Pharmaceutical Industry	Not reported	Open questions	Views on prescription drugs and the pharmaceutical industry	Not reported	82% of the participants had favorable opinion of doctors. 55% of the participants were somewhat confident and 22% very confident about regulatory authorities. 50% of the participants had an unfavorable view of pharmaceutical companies, while 60% highly and 31% somewhat consider that pharmaceutical companies make an important contribution to society by R&D drugs.
Harris, 2006, USA	Large Numbers of People Do Not Trust the Institutions They Identify as Most Responsible for Drug Safety	Public - random	Open questions	Public perception of FDA and pharma	Adults (18 years and older)	58% trusted doctors (strongly and somewhat). While 75% of the public considers the FDA as responsible for drug safety, only 45% trusted the FDA. While 70% of the public considers pharmaceutical companies as responsible for drug safety, only 27% trusted pharmaceutical companies, and 42% distrusted them. 57% distrusted pharmaceutical companies to release information about adverse reactions.
Harris, 2006, USA	The FDA's Reputation with the General Public is Under Assault	Public - random	Open questions	Public perception of FDA	Adults (18 years and older)	70% don't trust FDA's capacity to ensure the safety and efficacy of prescription drugs. 82% of adults think the FDA takes decisions based on political influence rather than medical science. In 2004 was the other way around, 56% had a positive view of the FDA on doing its job and 37% were negative.
Gallup, 2007, USA	Annual Update: Americans Rate Business and Industry Sectors	Public - random	Open questions	Public perception of 25 industries	Adults (18 years and older)	Doctors and health care were distrusted by 56% and trusted by only 28% of the public. 50% don't trust pharmaceutical companies, while 33% do trust them.

Institute, year, region	Title	Public or patients	Instrument	Topic	Population	Outcome about trust
Harris, 2007, USA	Large Numbers of People Are Not Very Confident in their Own Knowledge and the Safety of Prescription Medications and this Often Leads to Non-Adherence	Public - random	Open questions	Public perception of the safety of medicines	Adults (18 years and older)	46% of the public was fairly, somewhat or not at all confident that their prescribed medications were safe.
KFF, 2008, USA	Views on Prescription Drugs and the Pharmaceutical Industry (Spotlight)	Not reported	Open questions	Public and prescription drugs	Not reported	52% of the public thinks the FDA moves too slow when reviewing and approving new medicines. 47% were positive about drug companies, while 44% were negative. 60% thinks that pharmaceutical companies are doing a good job in serving their consumers. 80% trust pharma to develop new and safety drugs. 72% trust pharma in providing information about drug effectiveness, safety and side effects. 58% don't trust pharma due to the high prices of drugs. Lack of trust is reflected in pharma's profits; (74%) thinks pharma makes too much profits. 50% of the public thinks higher costs in health care are derived due to the high prices of medicines.
Gallup, 2009, USA	On Healthcare, Americans Trust Physicians Over Politicians	Public - random	Open questions	Perception of public on doctors	Adults (18 years and older)	73% of the public trusts doctors to recommend the right thing during the healthcare reform. Only 40% trust pharma to recommend the right thing for the healthcare reform.
Gallup, 2010, USA	In U.S., More Than 8 in 10 Rate Nurses, Doctors Highly	Public - random	Open questions	Perception of public on doctors	Adults (18 years and older)	26% have excellent and 58% good trust in the services doctors provide. 42% have good and 26% fair trust in the pharmaceutical industry and their services
Gallup, 2010, USA	Obama Retains More Trust Than Congress on Healthcare	Public - random	Open questions	Perception of public on doctors	Adults (18 years and older)	77% trust doctors to recommend the right thing for reforming health care. Only 30% trust pharma to recommend the right thing for health care reform
Harris, 2010, USA	Oil, Pharmaceutical, Health Insurance, and Tobacco Top The List Of Industries That People Think Should Be More Regulated	Public - random	Open questions	Perception of several industries	Adults (18 years and older)	46% of the public do not trust pharma and believe it should be more regulated. On the other hand, 53% of the public trusts pharma to handle personally identifiable information on a confidential and secure manner. In 2010, only 11% of the public considered pharma as honest and trustworthy.
Harris, 2012, USA	American Red Cross, Nature Conservancy, Consumers Union and AARP are Organizations Inside the Beltway Most Trusted by Public	Public - random	Open questions	Public perception of several organizations	Adults (18 years and older)	Only 19% of the public was familiar with PhRMA (Pharmaceutical Research and Manufacturers of America). Yet, 47% of the public does not trusted PhRMA, while 84% think this institution has a great amount of power and influence at governmental level.

CHAPTER

4

Publication trends in newspapers and scientific journals for SSRIs and suicidality

A systematic longitudinal study

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Abstract

Background - In the period 2003–2008, the regulatory authorities issued several warnings restricting the use of SSRIs in pediatrics, in reaction to safety concerns regarding the risk of suicidality. In this study, the SSRIs and suicidality controversy serves as a template to analyze the long-term publication trends regarding the benefit/risk profile of medications. The aim is to ascertain differences (in terms of numbers, categories and timing) between negative and positive newspaper and journal articles on SSRIs and suicidality, and ascertain correlations between changes in the reports and regulatory warnings.

Methods - A systematic review of scientific articles (Embase), and NL and UK newspapers (LexisNexis) was performed between 2000-2010. Categorization was done by 'effect' (related treatment effect), 'type of article' and 'age group'. The articles' positive–to–negative effect ratio was determined. Differences in distribution of 'effect' categories were analyzed across sources, 'type of article', and 'age group' using the Mann–Whitney (2 sub–groups) or Kruskal–Wallis test (3 or more).

Findings - In total, 1141 articles were categorized: 352 scientific, 224 Dutch, and 565 British newspaper articles. Scientific articles were predominantly on research and were positive, whereas newspaper articles were negative (ratios=3.50–scientific, 0.69–NL and 0.94–UK; P<0.001). Articles on pediatrics were less positive in scientific journals and more negative in newspapers (ratios=2.29–scientific, 0.26–NL, and 0.20–UK; P<0.001), while articles on adults were positive overall (ratios=10.0–scientific, 1.06–NL, and 1.70–UK; P<0.001). In addition, negative-effect reporting trends were exacerbated following regulatory warnings and were generally opinion articles, both in scientific journals and newspapers (2003/4 and after 2007).

Interpretation - We found a positive publication tendency inherent in journal research articles. This apparent positive publication bias present in scientific journals, however, does not seem to prevent the dissemination of 'bad' news about medications. The negative tendency present in Dutch and British newspapers was perceivable in the pediatrics group and during the warnings, indicating that national news media have informed the public about this international drug safety controversy on time.

Introduction

The news media are an important source of information about therapeutic drugs and health [1]. Coverage varies from communicating the benefits and risks of medications, to drug regulation and litigation, among others [2, 3]. Scientific journals are a significant source of information for journalists writing about medicine [4]. However, this does not necessarily mean that 'good' or 'bad' news about medicines in the news media is determined by the scientific literature [4, 5]. The 'good' news and 'bad' news in both news media and scientific and medical journals may be in agreement, but may also differ dramatically depending on the situation [6, 7].

Health care providers and consumers alike seek medical information from the news media and act on it accordingly, changing their perceptions and behavior [8, 9]. Coverage of medical news exemplifies how information from the news media and scientific journals can have a significant impact, yet be confusing [7, 10, 11]. Most newspapers' coverage studies of the benefits and risks of medications, although valuable, are short–term and lack a comparative perspective among countries [2, 8, 12]. In this study, we analyzed the long-term publication trends regarding the benefit/risk profile of medications in the context of the SSRIs and suicidality controversy (see box) from 2000 to 2010 in scientific journals and newspapers in the Netherlands (NL) and in the United Kingdom (UK). The aim is to ascertain the differences (in terms of numbers, categories, and timing) between negative and positive newspaper and scientific journal articles on SSRIs and suicidality.

Box 1. The SSRI and suicidality controversy

In the period 2003–2008, regulatory authorities (FDA, MHRA and EMA, among others) issued several warnings restricting the use of SSRIs in pediatrics, in reaction to safety concerns regarding suicidal ideation [13-15]. While some scientists adulated the warnings, others expressed their concerns about the implied consequences [16, 17]. The safety issue arose following GlaxoSmithKline's (GSK) request for a 6-month market exclusivity extension with the FDA for the use of paroxetine (a SSRI) to treat pediatric depression in response to the Food and Drug Administration Modernization Act (FDAMA). Consequently, GSK submitted the results from unpublished pediatric clinical data to the FDA. Meanwhile, the BBC aired a documentary entitled 'The secrets of Seroxat' on October 13 2002 in which it was alleged that internal documents of GSK showed that the dissemination of trial data on paroxetine in childhood depression was spun 'to minimize any negative commercial impact' [18]. GSK was accused of underplaying the association between SSRIs and suicidality. The ensuing worldwide media exposure played a role in driving the SSRI suicide controversy. In the process, confidence in the pharmaceutical industry and regulatory authorities decreased significantly [19]. To date, the controversy remains unsettled, albeit evidence also suggests that SSRIs are useful first–line treatments for depression and most anxiety disorders but exhaustive monitoring is recommended during the initiating phase [20].

Methods

Time frame

Content analysis was performed on articles published in the period January 2000 to December 2009, including the period in which the regulatory warnings were repeatedly enforced, i.e., 2003 to 2004 and 2007.

Data sources

Scientific articles were extracted from Embase (compilation of Medline and 2000 extra journals not covered by Medline) using two sets of keywords, i.e., first: 'serotonin uptake inhibitor' NOT 'serotonin noradrenalin reuptake inhibitor' AND 'suicidal behavior' or 'automutilation' or 'aggression' AND 'depression'; and second: 'serotonin uptake inhibitor' NOT 'serotonin noradrenalin reuptake inhibitor' AND 'suicide'. The search string was limited to 'humans', and 'Dutch' and 'English' language.

Newspapers articles were extracted using the LexisNexis database from a selection of high–circulation newspapers in NL (n=6) and in UK (n=4). The newspapers analysed were: De Telegraaf, Algemeen Dagblad, De Volkskrant, NRC Handelsblad, Trouw and Het Parool for NL; and The Sun, Daily Mail, The Daily Telegraph and The Times for UK. The newspapers' circulation figures (per country) covered 11% of each total resident population [21, 22]. Search queries were performed in the language of the papers (Dutch and English). Dutch articles were retrieved using the terms 'antidepressiv!' or 'anti–depressiv!' or 'SSRI!' or 'serotonine!' AND 'zelfmoord!' or 'aggressi!' or 'geweld!' or 'kwaad!' or 'suicid!' AND 'depressi!'. British articles were extracted using the terms 'antidepress!' or 'anti–depress!' or 'SSRI!' or 'serotonin!' AND 'suicid!' or 'aggressi!' or 'violen!' or 'harm!' AND 'depressi!'.

Data classification

All articles addressing SSRIs, depression, suicidal thoughts, or suicide as the main topic were eligible for analysis. If that was not the case, such an article was categorized as 'out of context', e.g., articles reporting the use of SSRIs to treat premature ejaculation or neuralgia. All scientific and newspaper articles were analyzed on the content of full–text, except for scientific articles where the abstract information was regarded as sufficient for categorization. The 'effect', 'type of article', and 'age group' categories were independently determined for these articles by two researchers.

The 'effect' category was divided into positive, neutral, and negative. Articles reporting on positive therapeutic outcomes with no mention of an association between SSRIs and an increased risk on suicidal behavior were classified as positive. Consequently, articles affirmatively reporting on the association between SSRI use and suicidality, with no mention of positive therapeutic outcomes, were classified as negative. Articles with a balanced message (positive and negative effects) were classified as neutral.

The 'type of article' category was defined within scientific journals as: case study (i.e., represents a descriptive and intensive analysis of an individual patient), research (i.e., comprehends study results, such as RCTs (randomized clinical trials), meta–analyses,

observational studies (multiple patients), etc.), opinion (i.e., enclose articles, such as letters to an editor, commentaries, replies, etc.), and policy (i.e., comprehends articles discussing regulatory–related topics, etc.). The definition of 'type of article' in newspapers was based on the nature and elaboration of the news conveyed: interview (i.e., comprehends articles where the journalist questioned the interviewee to retrieve information), opinion (i.e., comprises articles where the author or journalist portrayed his/her personal perspective), news report (i.e., covers general articles with informative news or general journalism), science journalism (i.e., comprehends articles presenting scientific information or reports), and policy (i.e., comprehends articles discussing regulatory–related topics, such as reimbursement, change of indication, etc.). The 'age group' category considered adults (above 18 years old), pediatric (18 years old or younger), both (adult and pediatric) or unspecified.

Scoring discrepancies between the two researchers occurred in approximately 5% of all articles. In a case of discrepancy, the categorization of the article in question was settled by consensus.

Data analysis

The positive–to–negative ratio of the 'effect' category was calculated (per source, 'type of article', and 'age group' categories). For the statistical analyses, the total count of articles per category was used. Differences in distribution of the 'effect' categories (i.e., positive, neutral and negative) were analyzed across the sources (Embase, Dutch and/or UK newspaper articles); 'type of article', and 'age group' were analyzed using the Mann–Whitney (2 sub–groups) or Kruskal–Wallis test (3 or more). Statistical significance was defined as $P<0.05$. Statistical analyses were performed using SPSS software (release 18.0.3).

To assess the publication dynamics, the number of articles (in scientific journals and/or in newspapers) was plotted per year (2000–2010), and per category ('effect', 'type of article', or 'age group').

Results

A total of 1736 articles were retrieved based on the predefined key word sets. Of these, 1141 articles were fully categorized: 352 scientific, 224 Dutch newspaper articles and 565 British newspaper articles (Figure 1). The characteristics of the articles are listed in Table 1.

Publication patterns of the 'effect' category

Of all 1141 articles (scientific and newspapers), the positive-effect category (39%) was significantly larger than the negative-effect (31%) or the neutral-effect categories (30%; $P<0.001$). The differentiation of the 'effect' category by source showed that scientific journals were predominantly positive (ratio=3.5), whereas Dutch and British newspapers coverage of 'effect' was mainly negative (ratios=0.69–NL and 0.94–UK, Table 1). Statistically significant differences were observed in 'effect' classification for scientific journals and newspapers (both $P<0.001$), but not between NL and UK dailies ($P=0.116$, Table 2).

Table 1. Characteristics of the 1141 articles in NL & UK newspapers and in scientific journals (2000–2009)

Characteristics	Scientific Journals (n=352)	NL newspapers (n=224)	UK newspapers (n=565)
Effect*			
Positive	191 (54)	65 (29)	192 (34)
Neutral	106 (30)	66 (29)	169 (30)
Negative	55 (16)	93 (42)	204 (36)
Positive to negative ratio	3.5	0.69	0.94
Type of article			
Case study	13 (4)	N/A	N/A
Research	210 (60)	N/A	N/A
Opinion	121 (34)	25 (11)	107 (19)
Policy	8 (2)	11 (5)	10 (2)
Interview	N/A	38 (17)	77 (14)
News report	N/A	110 (49)	291 (52)
Science journalism	N/A	40 (18)	80 (14)
Age group			
Adults	89 (25)	128 (57)	313 (55)
Pediatric	108 (31)	30 (13)	92 (16)
Both	80 (23)	32 (14)	66 (12)
Unspecified	75 (21)	34 (15)	94 (17)

**Statistically significant differences in effect classification were observed between scientific journals and newspapers (P<0.001), but not between NL and UK dailies (P=0.116). N/A=not applicable.*

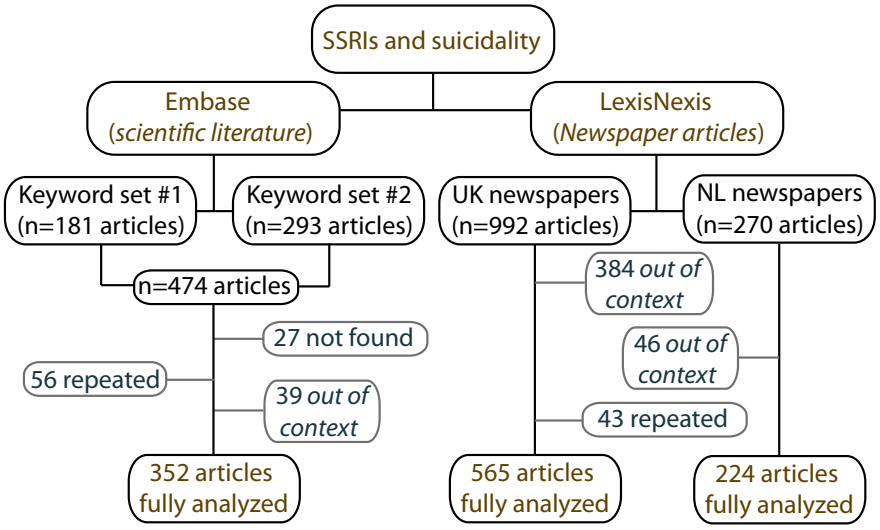

Figure 1. Scheme of the search process performed in the scientific and medical literature and in NL & UK newspapers.

Table 2. Allocation of effect categories related to types of article and age groups, and differentiated by source (NL & UK newspaper articles combined)

Categories		Positive	Neutral	Negative	Positive to negative ratio	p-value
NL newspapers		65	66	93	0.69	0.116
UK newspapers		192	169	204	0.94	
Scientific journals		191	106	55	3.5	<0.001
NL & UK Newspapers (mixed)		257	235	297	0.86	
Type of article						
Scientific journals	Case study	4	4	5	0.8	<0.001
	Research	144	49	17	8.47	
	Opinion	39	49	33	1.18	
	Policy	3	5	0	3	
Newspapers*	Interview	69	30	16	4.31	<0.001
	News report	88	125	188	0.47	
	Science journalism	38	30	52	0.73	
	Opinion	60	43	29	2.07	
	Policy	2	7	12	0.17	
Age group						
Scientific journals	Adults	70	12	7	10	<0.001
	Pediatric	48	39	21	2.29	
	Both	33	29	18	1.83	
	Unspecified	40	26	9	4.44	
Newspapers	Adults	176	145	120	1.47	<0.001
	Pediatric	18	20	84	0.21	
	Both	22	33	43	0.51	
	Unspecified	41	37	50	0.82	

**Statistically significant differences in effect distributions related to types of article were also observed in UK newspaper articles (P<0.001), and in NL newspaper articles (P=0.011).*

Although the overall coverage of 'effect' was generally positive in scientific journals, temporal changes were observed in the positive–to–negative 'effect' ratio per year, indicating a less positive-effect trend during 2003/4 and after 2007. Newspaper reporting revealed a similar trend as scientific journals. However, the positive–to–negative 'effect' ratio per year in newspapers shifted to the negative side from 2003 to 2005 and after 2007 (Figure 2B). This specific increase in negative–effect articles in newspapers was characterized by repetitive reports about lawsuits (e.g., lawyers' unsubstantiated claims of a causal association between murder and suicide attempts and the use of SSRIs), whistle–blowers or other media interventions, which fuelled the discussion.

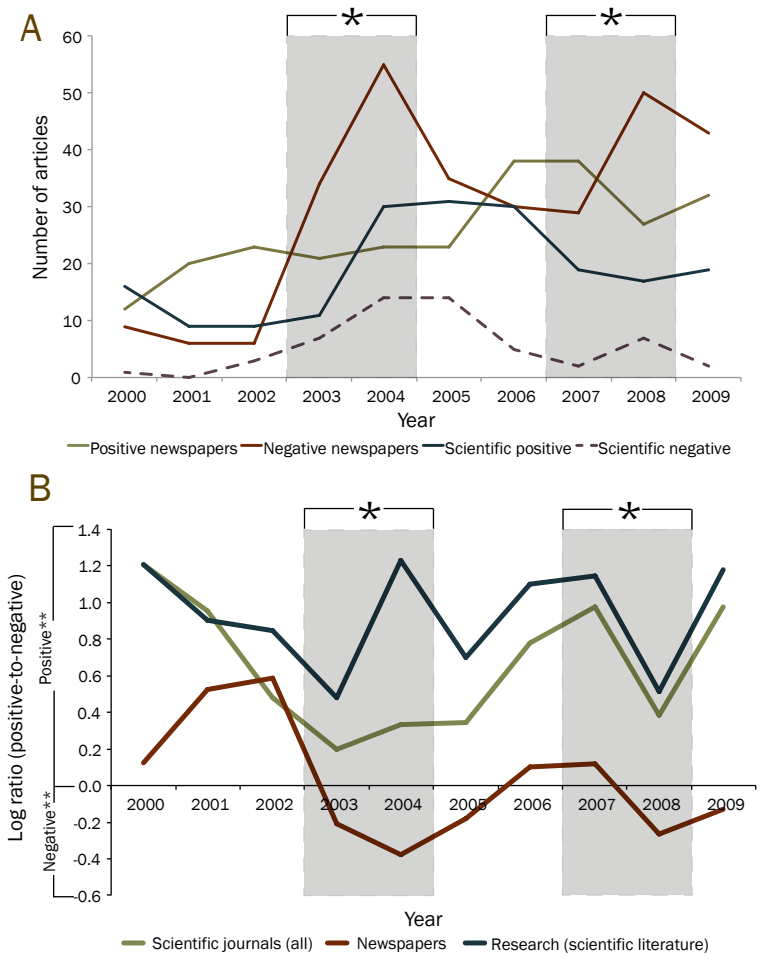

*Figure 2. (A) Effect messages (positive and negative) organized along the research period, per year (2000–2009) and according to the source (scientific-medical journals and newspapers). (B) The natural logarithm of the positive–to–negative ratio was calculated and also plotted for the accumulated scientific-medical articles (green line), accumulated newspaper articles (red line), and solely research articles from the scientific-medical literature (dark blue line). *The grey zone illustrates the period where most of the regulatory warnings were issued. **Articles with a positive–effect trend are located above zero, whilst articles conveying a negative¬–effect trend are located underneath zero.*

Publication patterns of the 'type of article' category

Scientific journals published generally research articles (60%), carrying a positive-effect message (ratio=8.5, Table 2). To a lesser extent, scientific journals published opinion articles (34%), which conveyed an overall positive–effect message (ratio=1.2, Table 2). However, scientific opinion articles displayed major temporal changes in the positive–to–negative 'effect' ratio following regulatory warnings, showing more negative–effect articles. Differences of 'effect' distributions related to 'types of article' were statistically significant (P<0.001, Table 2).

Newspapers published mainly news report articles (50.5%) and carried an overall negative–effect message (ratio=0.5, Table 2). A similar negative–effect trend was measured in scientific journalism articles (ratio=0.7). Newspaper opinion articles also portrayed an overall positive–effect message (ratio=2.1), as observed for opinion articles in scientific journals (ratio=1.2, Table 2). Major temporal changes in the positive–to–negative 'effect' ratio of newspaper articles were visible in the period of regulatory warnings (2002–2005 and 2007–2008, Figure 2B). Differences between 'effect' distributions related to 'types of article' were statistically significant in the accumulated newspaper articles group, UK newspaper articles (P<0.001), and in NL newspaper articles (P=0.011).

Publication patterns of the 'age group' category

Scientific journals reported more frequently on pediatrics (31%) than on adults (25%; P<0.001). Articles on adults were notably more positive concerning 'effect' compared to pediatric articles (ratio=10 and 2.3, Table 2).

Newspapers paid more attention to adults (56%) than pediatrics (15%, Table 1). Reporting trend for articles on adults was primarily positive about 'effect', whereas those on pediatrics were mainly negative (ratio=1.5 and 0.2). Significant differences were found between 'effect' distributions in newspapers related to 'age group' (P<0.001). Reporting patterns between NL and UK dailies were comparable in all three categories (P=0.116, Table 2).

Articles on pediatrics in scientific journals and in newspapers displayed similar publication dynamics, i.e., a significant peak in 2004, following the warnings. The publication dynamics of articles on adults in scientific journals and newspapers also showed a similar pattern. Thereafter, newspaper articles on adults continued to increase until 2010, while their scientific counterparts remained more or less stable (Figure 3).

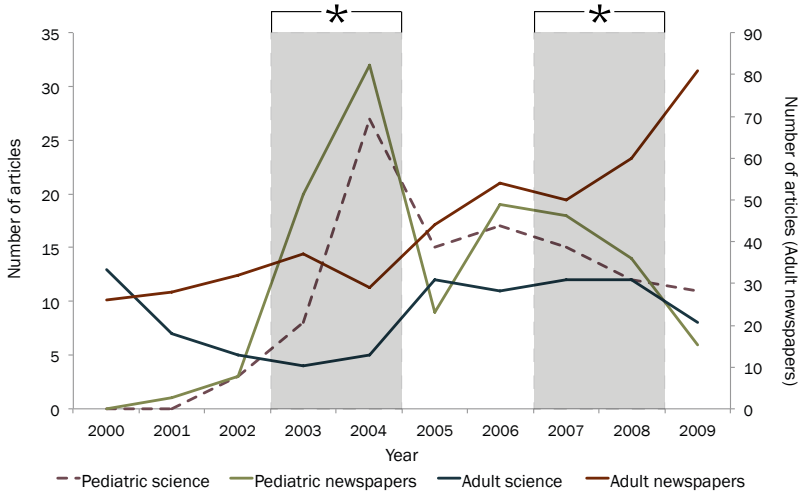

*Figure 3. Articles indexed into age groups (pediatric and adult) in scientific-medical journals and in newspapers from 2000 to 2009. The scale of newspaper articles on adults is portrayed on the right y-axis. *The grey zone illustrates the period where most of the regulatory warnings were issued.*

Discussion

This study assessed the characteristics and dynamics of SSRIs and suicidality coverage by scientific and medical journals in general, and newspapers in NL and UK from 2000 to 2010. Scientific journals published predominantly research articles about positive therapeutic outcomes with little mention of an association between SSRIs and suicidality, particularly in adults. Despite different ethnic backgrounds (e.g., tabloid culture in UK, among others) and language, newspaper reporting trends in NL and UK were comparable; and were overall negative regarding the therapeutic effect of SSRIs in pediatrics, while positive–effect reporting prevailed for adults.

The present study has several limitations. It covered 11% of the total population per country based on newspaper circulation figures. Nevertheless, the random sample is representative (n=789 newspaper articles) given the aim to ascertain differences (in terms of numbers, categories, and timing) between negative and positive newspaper and journal articles on SSRIs and suicidality. The categories 'effect' and 'type of article' might be limited by our definition, and their interpretation could differ between readers. We attempted to avoid subjectivity by analyzing the data independently by two researchers. We achieved more than 95% agreements during article categorization (effect, type of article, and age group categories). We did not, however, ascertain the context of the articles in terms of construction of the newspaper and opinion articles from its original source. Neither did we explore other forms of media coverage (television, radio, magazines, or the Internet). The content analysis method used in this study does not allow for these additional more complex queries.

Our results showing a positive publication tendency in scientific journals are consistent with previous work, which demonstrated that antidepressant trials with a positive outcome were published more often than those with negative outcomes [23]. This positive publication tendency continued even after the regulatory warnings, and could potentially leave physicians with a biased view of the medications that they are prescribing to patients. Studies questioning these warnings, and the possible disservice they did to public health (e.g., the possible inverse association between SSRIs prescriptions and suicidality, or the decline in treatment of depression in pediatrics) contributed to this post–warning positive–effect trend [16, 17]. On the other hand, this positive publication tendency in scientific journals does not seem to prevent the dissemination of 'bad' news about medications. For instance, science journalism articles (newspapers) that presented a negative publication tendency regarding SSRIs (ratio=0.7), could not be related to the positive publication tendency found in scientific journals. These findings indicate that either newspaper journalists may selectively report scientific outcomes to the public, as also stated in the CHMP assessment report on antidepressants [24] or that controversial topics might be selected to increase readership [4, 11, 25, 26]. Such practices might generate confusion, since the translation of evidence–based medicine to the public is not uniform [2, 12, 27, 28], and may have implications for patients compliance with medications, willingness to see physicians, and trust in the doctor-patient relationship. However, scientific and medical journals might also do disfavor to the scientific community by favoring positive outcome

studies, thus limiting the journalists' sources of accurate and critic information to communicate to the public new scientific and medical evidence.

The uncertainties regarding the SSRIs' benefit/risk balance, primarily in pediatrics, have led to the restriction of almost all SSRIs under 18 year olds in 2003 and further restrictions for young adults (18 to 24 years old) in 2007 [13-15, 29]. In the same periods, our data revealed shifts towards negative–effect reporting trends in scientific and newspaper articles on pediatrics and opinion articles. The timing between the warnings and the observed increase in articles substantiate the possible influence of warnings on media publication trends. Moreover, this increment in the number of articles suggests that newspapers informed the public about this particular drug safety event in a timely fashion. Studies have underlined the relevance of informing the public about medical news within a suitable time frame [6, 30]. However, these studies only focused on a subset of scientific journals, whereas we did not discriminate among scientific journals. A balance between timely coverage, consistent, and adequate information is fundamental when reporting on drug safety controversies. Ideally, this balance should be the result of an open dialogue between healthcare practitioners, academia, governmental agencies, the pharmaceutical industry, journalists and the public. However difficult, educating the public properly and on time about the benefits and the risks of medicines will help to maintain public trust during unsettling periods [31].

Finally, the possible implications of the discovered tendencies in scientific journals and newspapers for patients and doctors have not been addressed in this paper. It has been shown that news media reports (on suicide, or related to suicide) have an influence on suicidal behavior, and on drug usage [32, 33]. It might be valuable in this regard to determine the long-term influence of media coverage and the regulatory warnings on prescription patterns.

Conclusion

Our study of the SSRIs and suicidality controversy showed several publication tendencies in scientific journals and newspapers. We identified a positive publication tendency inherent in journal research articles, which could potentially affect doctors' assessment of the safety and effectiveness of the medications that they are prescribing to patients. This apparent positive publication bias in scientific journals, however, does not seem to prevent the dissemination of 'bad' news about medications. The occurrence of 'good' or 'bad' news in scientific journals and newspapers was found to be dependent on the news category or type of article. Opinion reports in scientific journals did not differ significantly in the nature and timing of reporting from opinion articles in Dutch and British dailies. Differences between the Dutch and British newspaper reporting patterns were minor. The negative tendency present in Dutch and British newspapers was perceivable in the pediatrics group and during the warnings, indicating that newspapers have informed the public about this drug safety controversy on time. It also shows that a proactive and transparent risk communication strategy of regulatory offices and the pharmaceutical industry might pay off in the long run for reporting on the benefits and risks of medications.

References

1. Wilson A, Bonevski B, Jones A, Henry D. Media reporting of health interventions: signs of improvement, but major problems persist. PLoS One. 2009;4(3):e4831.
2. Moynihan R, Bero L, Ross-Degnan D, Henry D, Lee K, Watkins J, et al. Coverage by the news media of the benefits and risks of medications. N Engl J Med. 2000 Jun 1;342(22):1645-50.
3. Ries NM, Rachul C, Caulfield T. Newspaper reporting on legislative and policy interventions to address obesity: United States, Canada, and the United Kingdom. J Public Health Policy. 2011 Feb;32(1):73-90.
4. Bartlett C, Sterne J, Egger M. What is newsworthy? Longitudinal study of the reporting of medical research in two British newspapers. BMJ. 2002 Jul 13;325(7355):81-4.
5. Lai WY, Lane T. Characteristics of medical research news reported on front pages of newspapers. PLoS One. 2009;4(7):e6103.
6. Canales MK, Breslau ES, Nelson DE, Ballard-Barbash RR. Did news reporters get it right? Translation of the 2002 hormone study findings. American Journal of Preventive Medicine. 2008 Jan;34(1):61-8.
7. Dentzer S. Communicating Medical News — Pitfalls of Health Care Journalism. New England Journal of Medicine. 2009;360(1):1-3.
8. Archer DF. Medical decisions regarding hormone therapy for menopausal women are significantly influenced by the media. Pharmacoepidemiology and Drug Safety. 2007;16(1):28-31.
9. Williams D, Kelly A, Feely J. Influence of media and regulatory changes on prescribing of Cotrimoxazole and Trimethoprim in Ireland. Pharmacoepidemiol Drug Saf. 2000;9(4):313-7.
10. Grilli R, Ramsay C, Minozzi S. Mass media interventions: effects on health services utilisation. Cochrane Database Syst Rev. 2002 (1):CD000389.
11. Mebane FE. The importance of news media in pharmaceutical risk communication: proceedings of a workshop. Pharmacoepidemiol Drug Saf. 2005 May;14(5):297-306.
12. Danovaro-Holliday MC, Wood AL, LeBaron CW. Rotavirus vaccine and the news media, 1987-2001. JAMA. 2002 Mar 20;287(11):1455-62.
13. EMA. European Medicines Agency finalises review of antidepressants in children and adolescents London: EMA; 2005 [cited 2011 4th February]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/12/news_detail_000882.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1.
14. FDA. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications Rockville, MD: Department of Health and Human Services; 2004 [cited 2011 20th January 2011]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm.
15. MHRA. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. London: Committee on Safety of Medicines, 2004.
16. Cheung A, Sacks D, Dewa CS, Pong J, Levitt A. Pediatric prescribing practices and

the FDA Black-box warning on antidepressants. Journal of developmental and behavioral pediatrics : JDBP. 2008;29(3):213-5.
17. Wheeler BW, Gunnell D, Metcalfe C, Stephens P, Martin RM. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: Ecological study. BMJ. 2008;336(7643):542-5.
18. BBC. Panorama: The Secrets of Seroxat London: BBC; 2002 [cited 2011 7 February]. Documentary]. Available from: http://news.bbc.co.uk/panorama/hi/front_page/newsid_8425000/8425414.stm.
19. Olsen AK, Whalen MD. Public perceptions of the pharmaceutical industry and drug safety: implications for the pharmacovigilance professional and the culture of safety. Drug Saf. 2009;32(10):805-10.
20. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. J Clin Psychiatry. 2011 Jul;71(7):839-54.
21. Department of statistics UK 2010 [cited 2010 August]. Available from: http://www.statistics.gov.uk/cci/nugget.asp?id=6.
22. CBS. Bevolkinsteller (Centrale Bureau van Statistiek) 2010 [cited 2010 August]. Available from: http://www.cbs.nl/en-GB/menu/themas/bevolking/cijfers/extra/bevolkingsteller.htm.
23. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008 Jan 17;358(3):252-60.
24. EMA. CHMP Assessment Report on Antidepressants. London: European Medicines Agency, 2008 30 May 2008. Report No.
25. Franklin B, Hamer M, Hanna M, Kinsey M, Richardson J. Key concepts in journalism studies. Sage, editor. London. Thousand Oaks, California: Sage 2005.
26. Iggers J. Good news, bad news: journalism ethics and the public interest Schiller HI, editor. Boulder, Colorado: Westview press; 1999.
27. Lai WYY, Lane T. Characteristics of Medical Research News Reported on Front Pages of Newspapers. PLoS One. 2009 Jul 1;4(7).
28. Koren G, Klein N. Bias against negative studies in newspaper reports of medical research. JAMA. 1991 Oct 2;266(13):1824-6.
29. FDA. Antidepressant Use in Children, Adolescents, and Adults Rockville, MD: Department of Health and Human Services; 2007 [cited 2011 7th February 2011]. Available from: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm.
30. Stryker JE. Reporting Medical Information: Effects of Press Releases and Newsworthiness on Medical Journal Articles' Visibility in the News Media. Preventive Medicine. 2002;35(5):519-30.
31. Karacsony A, Rosembaum J. Recapturing the vision: restoring trust in the pharmaceutical industry by translating expectations into actions. Report. PwC, Pharmaceuticals; 2007 January 2007. Report No.
32. Pirkis J, Blood RW. Suicide and the media. Part I: Reportage in nonfictional media. Crisis. 2001;22(4):146-54.

33. Martin RM, May M, Gunnell D. Did intense adverse media publicity impact on prescribing of paroxetine and the notification of suspected adverse drug reactions? Analysis of routine databases, 2001-2004. Br J Clin Pharmacol. 2006 Feb;61(2):224-8.

CHAPTER

5

A 10-year analysis of the effects of media coverage and regulatory warnings on antidepressant use in The Netherlands and UK

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Abstract

Background - In 2003 - 2004 and 2007 - 2008, the regulatory banning of SSRI use in pediatrics and young adults due to concerns regarding suicidality risk coincided with negative media coverage. SSRI use trends were analyzed from 2000 - 2010 in the Netherlands (NL) and the UK, and whether trend changes might be associated with media coverage of regulatory warnings.

Methods - Monthly SSRIs sales were presented as DDDs/1000 inhabitants/day. SSRI-use trends were studied using time-series segmented regression analyses. Timing of trend changes was compared with two periods of media coverage of warnings. Annual Dutch SSRI prescription data were analyzed by age group.

Results - Trend changes in SSRI use largely corroborated with the periods of media coverage of warnings. British SSRI use declined from 3.9 to 0.7 DDDs/month (95% CI: 3.3; 4.5 & 0.5; 0.9, respectively) before the first warning period (2003 - 2004). A small decrease of -0.6 DDDs/month (-1.2; -0.05) was observed in Dutch SSRI use shortly after 2003 - 2004. From 2007 - 2008, British SSRI use stabilized, whilst Dutch SSRI use diminished to -0.04 DDDs/month (-0.4; 0.3). Stratified analyses showed a rapid decrease of -1.2 DDDs/month (-2.1; -1.7) in UK paroxetine use before 2003 - 2004, but only a minimal change in Dutch paroxetine use (-0.3 DDDs/month -0.8; 0.2). Other SSRI use, especially (es-) citalopram, increased during 2003 - 2004 in both countries. Significant reductions in Dutch paroxetine use were observed in pediatrics, adolescents, and young adults after 2003 - 2004.

Conclusion - Changes in SSRI use (NL & UK) were associated with the timing of the combined effect of media coverage and regulatory warnings. Our long-term assessment illustrates that changes in SSRI use were temporal, drug-specific and more pronounced in pediatrics and young adults. The two-fold increase in SSRI use over one decade indicates that regulatory warnings and media coverage may come and go, but they do not have a significant impact on the overall upward trend of SSRI use as a class in both countries.

Introduction

Health care providers and consumers alike seek health and medical information from the news media and act accordingly, changing their perceptions and behavior [1, 2]. Several studies have documented the effects of media and regulatory interventions on medical decisions, health services utilization, and pharmaceutical sales patterns [3, 4]. The influence of news media reports or pharmaceutical regulatory warnings for antidepressants has been studied. For instance, Martin et al. identified a correlation between increased negative media attention on the safety of paroxetine (a Selective Serotonin Reuptake Inhibitor-SSRI) and the temporal and voluntary reporting of adverse drug reactions (ADRs). The measured decrease in paroxetine prescriptions in England, after 2002, was attributed to regulatory warnings and lawsuits (see Box 1), rather than media reports [5]. Another study also found a temporal decline in pediatric antidepressant prescriptions in the United Kingdom (UK) related to regulatory actions after 2003 [6]. This regulatory-driven fall in antidepressant use in pediatrics was also reported in a study establishing a greater impact of warnings in the UK than in the United States (US) or the Netherlands (NL) from 2003-2005 [7]. Volkers et al. added more evidence to this drop in antidepressant prescriptions (2001-2005) in Dutch pediatric patients [8]; and two other studies also showed the influence of the warnings in the US [9, 10]. However, none of abovementioned studies analyzed the long-term influence of regulatory warnings on antidepressant use; thus, a second set of warnings (updates 2007-2008) were not included in those analyses. In addition, the influence of both warning periods has not been studied in combination with the long-term influence of media coverage, nor has the differential impact on use in various age groups been examined.

In a previous study, we analyzed the long-term dynamics of 'good' and 'bad' news in scientific journals and Dutch and British newspapers in the context of the SSRIs and suicidality controversy [11]. We found an increase in the number of articles discussing the positive (protective) effect of antidepressants for the treatment of depression or to prevent suicidality in scientific journals. This "positive publication tendency" did not influence the dissemination of negative news in Dutch and British dailies. However, negative reporting in the same newspapers was predominantly about the pediatric use of SSRIs and correlated with regulatory warnings in 2003-2004 and in 2007-2008. We hypothesize that in both the NL and the UK, the use of SSRIs was influenced by the synergetic interaction of regulatory warnings (black box warning and updates) and scientific and media attention to the SSRI and suicidality controversy in 2003-2004 and 2007-2008. The aim of this study was to specifically analyze trends of SSRI use between January 2000 and January 2010 in the NL and the UK. In addition, we evaluated whether trend changes could be associated with the combined and long-term effects of the periods of intense media coverage of the warnings. In the NL, we also analyzed the differential impact of media coverage by the type of prescriber and age group.

Methods

Data source

IMS Health provided monthly antidepressant sales data in the NL and the UK for time trends assessment on a national (aggregated) level. Antidepressant sales data in the NL

were available from January 2000 to January 2006 for tricyclic antidepressants (TCAs) and other antidepressants (monoamine oxidase inhibitors (MAOIs), as well as serotonin-norepinephrine reuptake inhibitors (SNRIs, etc.). Sales data for SSRIs were available from January 2000 to July 2010. Antidepressant sales data in the UK were available from January 2000 to January 2010 for all antidepressants. Escitalopram entered the market in August 2004 in the NL and in June 2002 in the UK. The sales data provided by IMS Health consisted of wholesaler information from ambulatory care and hospitals that cover, on average, 90% of the total therapeutic drug sales in the NL and UK. IMS Health also provided monthly Dutch SSRIs prescription data stratified by specialty from January 2000 to January 2010. This dataset was used to ascertain changes in the prescribing habits of general practitioners (GPs), and specialists (psychiatrists, cardiologists, oncologists, etc.). The GIP-database (Dutch insurance data retrieved from ambulatory care; not hospitals) provided yearly aggregate SSRI prescription data stratified by age groups from 2000 to 2010. The GIP-database covers, on average, 83% of the insured population in the NL [12].

Data presentation

Sales data were classified into three main groups: a) SSRIs, b) TCAs, and c) other antidepressants (other ADs). IMS Health's sales data were delivered in standard counts, which is the volume unit used to describe sales per counting unit (i.e., tablet, capsule, etc.), together with the given concentration of the active compound. For each antidepressant, monthly use was converted into defined daily doses (DDD)/1000 inhabitants/day, using the standard counts sold, dosage strength, and monthly population estimates per country. The DDD is the international unit of drug utilization approved by WHO for drug utilization studies and is defined as the average maintenance dose of the studied drug when used for its major indication in adults [13]. Yearly Dutch SSRI use in DDD/1000/day per age groups (GIP-database) was adjusted for the age distribution of the population. Monthly Dutch population estimates, as well as yearly age-group population estimates (per strata), were obtained from the Office of Statistics Netherlands (CBS), and UK estimates from the European Commission statistics database (Eurostat) [14, 15].

Age groups categorization (NL only)

The age groups were defined as pediatrics (0-14 years old), adolescents (15-19 years old), young adults (20-24 years old), adults (25-64 years old), and elderly (65 years and older). However, the GIP data combined the use of antidepressants for 15 to 24-year-olds between 2000-2001 hindering a differentiation between adolescents and young adults. Therefore, the ratio of use for adolescents and young adults in 2002-2010 was used to extrapolate use in 2000-2001.

Periods of intense media coverage of regulatory warnings

Based on our analysis of scientific and newspaper coverage, we chose the following periods of intense media coverage of regulatory warnings: a) January 2003 to December 2004, and b) January 2007 to December 2008. The control periods were: a) January 2000 to December 2002, b) January 2005 to December 2006, and c) January 2009 to December 2009 [11].

Statistical analyses

To assess whether trend changes in antidepressant use were associated with the combined and long-term effects of both periods of regulatory warnings and scientific and newspaper coverage, we performed time-series analyses for overall SSRI, TCA and other ADs use, and per specific SSRI. The algorithm that describes the principle of our time-series analyses based on change-points was previously reported [16, 17]. This algorithm creates segments within the time-series under two distinct circumstances. First, each segment is created based on the change of the slope over time by fitting linear regressions with autoregressive (AR) models of the second order for random error to correct for the autocorrelation of monthly medication use over time. Second, if the average change of the slope is similar, but there is excessive variation, then a segment is created. The predicted values at the end of a segment and at the beginning of the consecutive segment were fitted as closely as possible. The segment with the lowest minimal number of change-points was selected. Segments were created without consideration of the periods of media coverage of regulatory warnings; however, the selected segments were compared to determine if they coincided with these periods.

Differences in SSRI use (mean) within Dutch age groups were compared with an ANOVA test, assuming that the means of each age group were equal. A Tukey HSD (honest significant difference) post-hoc test was used to determine which age group's means were significantly different from one another. Statistical significance was set at $P<0.05$. Analyses were performed using the statistics software program "R" version 2.12.2 [18].

Results

The use of SSRIs increased in the NL from 16.7 in January 2000 to 27.9 DDDs/1000/day in July 2010, while in the UK, SSRI use doubled from 24.7 in January 2000 to 50.1 DDDs/1000/day in December 2009. The use of other ADs increased from 3.3 in 2000 to 8.3 DDDs/1000/day in December 2005 in the NL, and from 3.4 in 2000 to 12.1 DDDs/1000/day in December 2009 in the UK. TCAs use increased from 4.2 in January 2000 to 5.2 DDDs/1000/day in December 2005 in the NL, whereas in the UK, TCAs use increased from 9.5 in January 2000 to 10.6 DDDs/1000/day in December 2009. On average, the UK population used 1.5-fold more SSRIs, 1.1-fold more other ADs, and 2.1-fold more TCAs than the Dutch did; both populations are comparable with respect to gender and age distributions (Table 1).

Table 1. Demographics for the Netherlands and the United Kingdom (2000-2009)

	Netherlands					United Kingdom				
Population characteristics	**2000**		**2009**		**Growth rate (%)**	**2000**		**2009**		**Growth rate (%)**
Population	15987075		16574989		3.7	58981904		61990973		5.1
Female (%)	8017633	(50.5)	8329391	(50.5)	3.9	30296500	(50.7)	31399890	(50.6)	3.6
Age groups										
0-20	3873008	(24.4)	3933585	(23.9)	1.6	12076300	(20.2)	11227401	(18.1)	-7.0
20-65	9838500	(62.0)	10080387	(61.1)	2.5	38362500	(64.2)	40680109	(65.6)	6.0
>65	2152442	(13.6)	2471815	(14.9)	14.8	9316600	(15.6)	10083462	(16.3)	8.2

SSRI use in the NL and the UK

Regression analyses indicated a short and temporal effect of the regulatory warnings on overall SSRI use in the NL. From 2000, SSRI use increased in a trend that continued until November 2004 (Figure 1A+B). After the first period of intense media coverage of regulatory warnings, the growth trend slowed until September 2005 when it increased again until August 2007. SSRI use then plateaued, after the second period of intense media coverage of the warnings and stagnated until July 2010. SSRI use in the UK showed no negative trends during this period, with episodes of rapid increase outside the periods of media coverage of regulatory warnings and episodes of slowed growth during the periods of media coverage of regulatory warnings (Figure 1A+C).

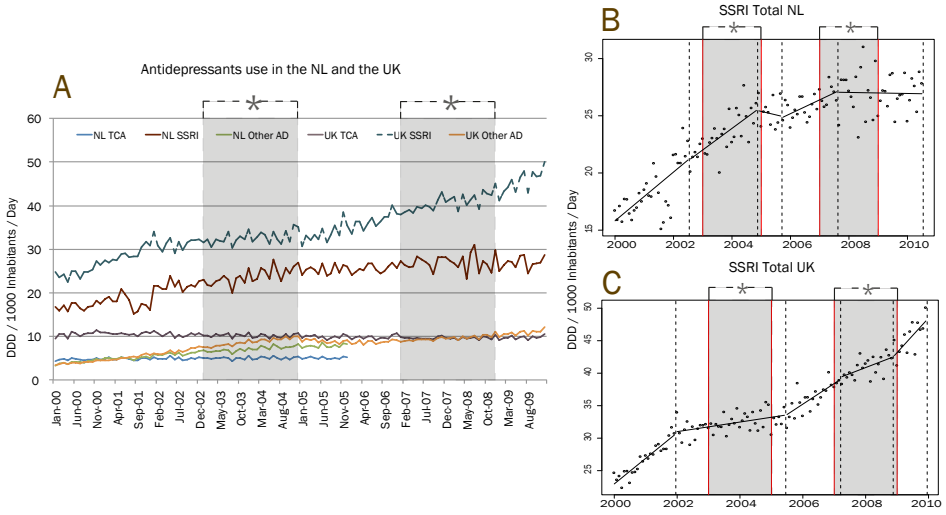


*Figure 1. Antidepressant use in the NL and the UK (SSRIs, TCAs, and other antidepressants) (A). Segmentation of SSRI use in the NL (B), and in the UK (C). Dotted lines represent a change in use trend and therefore a new, or the end of a segment. *The grey periods represent the periods of media coverage of regulatory warnings.*

When analyzing individual SSRI use in the NL, citalopram and escitalopram showed rapid growth (Figure 2A). Although the overall increase in paroxetine use was modest (8.2 to 10.0 DDD/1000/day), it remained the most frequently used SSRI in the NL. Regression analysis of paroxetine use demonstrated a rapid increase from January 2000 to May 2002, followed by a period of slowed growth until October 2004. At the end of the first period of media coverage of regulatory warnings, paroxetine use in the NL decreased consistently until July 2010 (Figure 2B).

As in the NL, the use of citalopram and escitalopram increased exponentially in the UK in the period under survey. Fluoxetine, the most frequently used SSRI in the UK, demonstrated a modest increase of 11.2 to 13.9 DDD/1000/day during the period 2000-2010. Fluvoxamine use also demonstrated a consistent decrease during the entire study period in the UK, as

was also documented in the NL. Overall paroxetine use decreased from 7.3 in January 2000 to 4.3 DDD/1000/day in December 2009 (Figure 2C). Segmented regression analysis of paroxetine use revealed a rapid increase from January 2000 to January 2002, followed by a rapid decrease prior to the first period of media coverage of regulatory warnings. This downward trend persevered until December 2009 (Figure 2D).

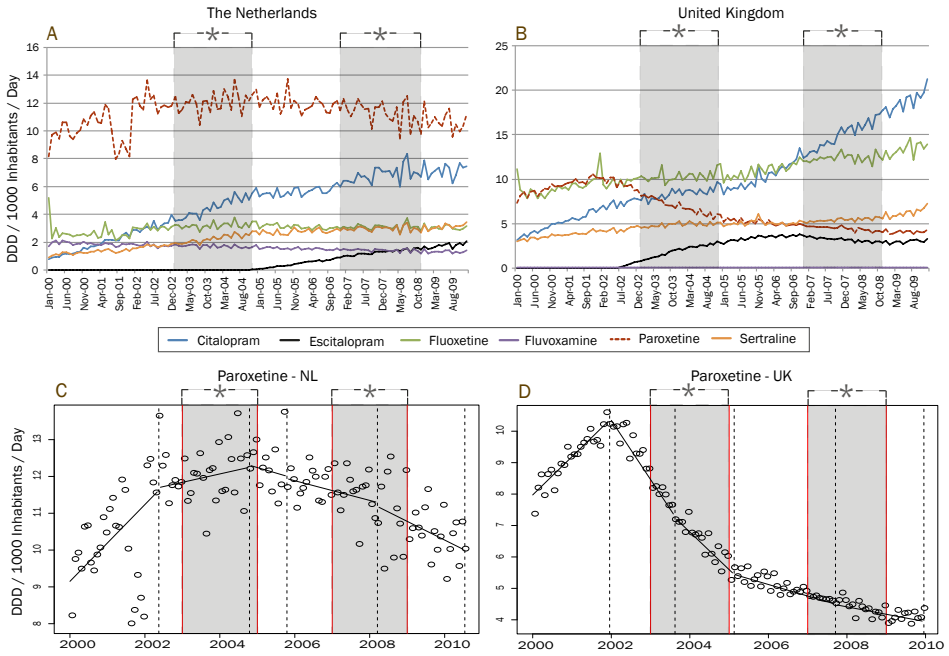


*Figure 2. SSRI use in the NL (A) and in the UK (B), Segmentation of paroxetine in the NL (C) and in the UK (D). Dotted lines represent a change in use trend and therefore a new, or the end of a segment. *The grey period illustrates the periods of media coverage of regulatory warnings.*

SSRI use in the NL stratified by specialty

Dutch GPs prescribed the largest share of SSRIs (mean: 80.4%, 95% CI: 80.3; 80.6, Table 2). Therefore, national SSRI use trends and GPs' SSRI prescribing trends were comparable (Figure 3A+B). Segmented regression analysis demonstrated that GPs steadily prescribed more SSRIs from January 2000 to September 2004. At the end of the first period of media coverage of regulatory warnings, SSRI prescriptions by GPs slightly decreased until January 2006 and then recovered to eventually reach a plateau from April 2008 to December 2009. Paroxetine GP prescriptions revealed an upward trend from January 2000 to September 2004. Towards the end of the first period of media coverage of regulatory warnings, GPs' prescriptions for paroxetine showed a negative trend and continued decreasing until December 2009 (Figure 3C). By December 2009, Dutch GPs' citalopram prescriptions were almost level with paroxetine use (Figure 3A). As far as paroxetine use is concerned, we see a downward trend in specialist prescriptions similar to the decrease in GPs' prescriptions after the first period of media coverage in the

NL (Figure 3D). The downward trend continued until December 2009 (Figure 3D) and was molecule specific. Specialists' prescriptions for citalopram grew exponentially until the end of the first period of media coverage of regulatory warnings. Thereafter, growth slowed and following the second period of media coverage of regulatory warnings citalopram use stabilized.

Table 2. Amount of DDD/1000 inhabitants/day of SSRIs in the Netherlands, and percentage between January 2000 and December 2009 stratified by specialty

Specialty	**General Practitioner**				**Specialists**				**Unidentified**			
SSRI/Year	**2000**		**2009**		**2000**		**2009**		**2000**		**2009**	
Citalopram	0.3	(2.2)	7.6	(32.8)	0.4	(12.5)	1.8	(35.9)	0.02	(7.1)	0.2	(52.4)
Escitalopram*	0.0	(0.0)	1.2	(5.3)	0.0	(0.5)	0.7	(13.8)	0.00	(0.3)	0.0	(6.5)
Fluoxetine	2.5	(18.8)	2.0	(8.6)	0.5	(16.6)	0.6	(11.6)	0.06	(17.3)	0.0	(6.3)
Fluvoxamine	1.6	(12.1)	1.1	(4.9)	0.4	(14.0)	0.2	(4.7)	0.03	(10.0)	0.0	(4.4)
Paroxetine	8.4	(62.8)	9.4	(40.2)	1.5	(44.8)	1.0	(19.0)	0.20	(59.5)	0.1	(21.7)
Sertraline	0.5	(4.0)	1.9	(8.3)	0.3	(10.5)	0.7	(14.9)	0.01	(4.4)	0.0	(9.6)
Total	13.3	-100	23.3	-100	3.1	-100	5.0	-100	0.33	-100	0.4	-100
Total (%) per specialty	(79.5)		(81.1)		(18.5)		(17.4)		(2.0)		(1.5)	

** Data available from October 2004*

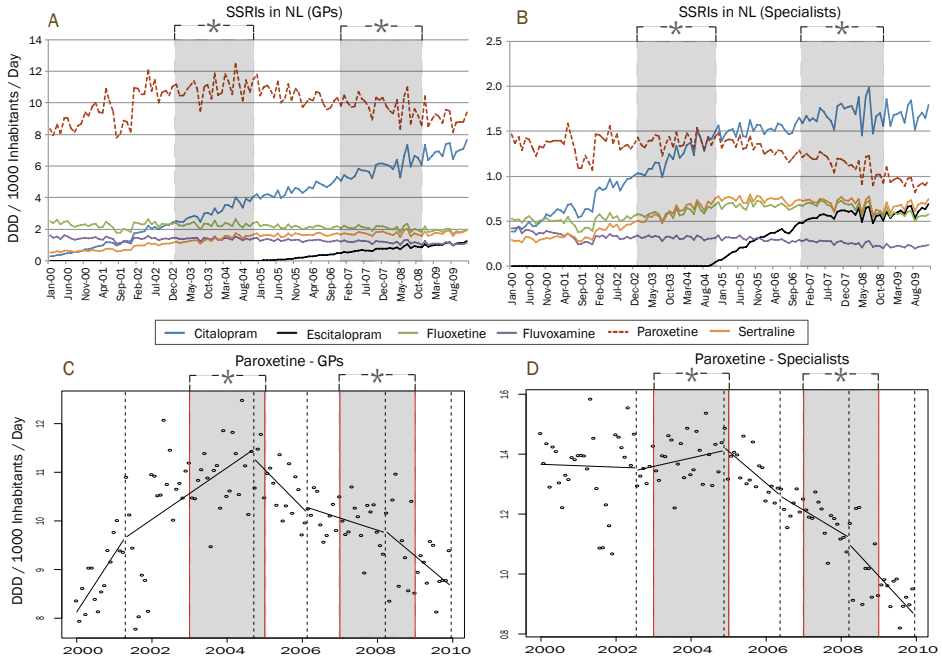


*Figure 3. SSRI use in the NL through GPs (A) and specialists (B), segmentation of paroxetine use in the NL through GPs (C) and specialists (D). Dotted lines represent a change in use trend and therefore a new, or the end of a segment. *The grey period illustrates the periods of media coverage of regulatory warnings.*

SSRI use in the NL stratified by age group

In the NL, SSRI use in pediatrics, adolescents, and adults modestly decreased after the first period of media coverage of the warnings, and then recovered. Initially, the use of SSRIs increased in young adults; however, by the end of the first period of media coverage the use dropped until 2010. SSRI use by the elderly grew during the entire study period (data not presented). Specific Dutch SSRI trends revealed a growth in the use of citalopram, escitalopram, and sertraline across all age groups (Figure 4A-D). This growth was partially interrupted towards the end of the first period of media coverage of regulatory warnings, mainly in the younger groups (pediatrics, adolescents and young adults). The use of fluoxetine increased; however, only in pediatrics and adolescents. In adults and the elderly, the use of fluoxetine either remained stable or decreased modestly. A constant reduction in paroxetine use was measured prior to the first period of media coverage of regulatory warnings (2002) in pediatrics (from 0.06 to 0.005 DDDs/1000/day), adolescents (1.9 to 0.3 DDDs/1000/day), and young adults (6.7 to 2.2 DDDs/1000/day). Conversely, adults used more paroxetine in the period from 2000-2004 (15.5 to 18.4 DDDs/1000/day) than after the first period of media coverage of regulatory warnings when their use decreased to 13.5 DDDs/1000/day in 2010. A similar effect was measured in the elderly, as paroxetine use peaked in 2004 (14.5 DDDs/1000/day) and then decreased modestly after the first period of media coverage of regulatory warnings to 13.3 DDD/1000/day in 2010.

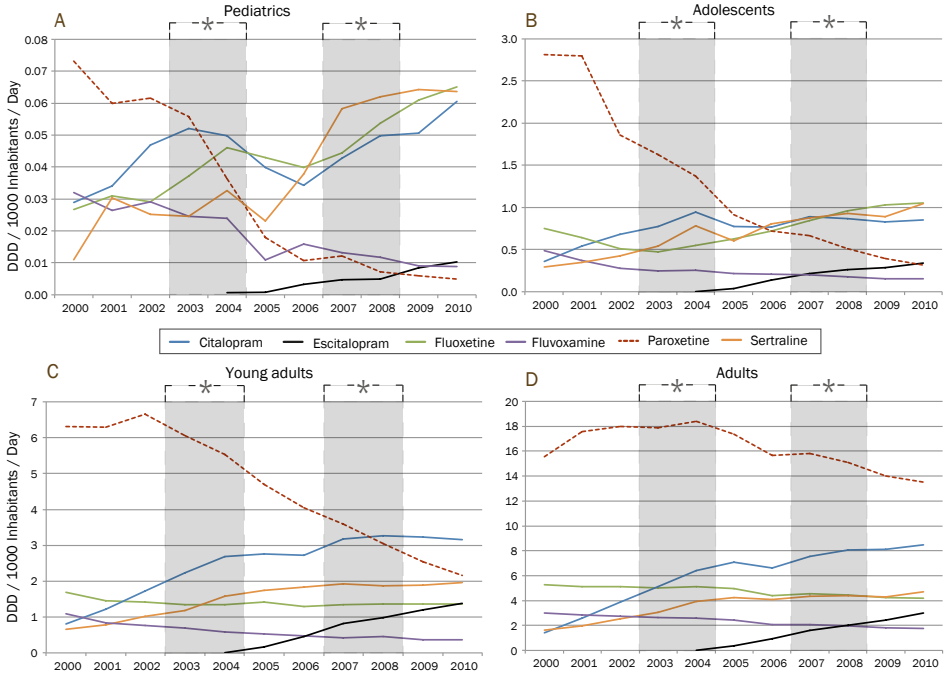


*Figure 4. SSRI use in the NL in pediatrics (A), adolescents (B), young adults (C), and adults (D). *The grey period illustrates the period of media coverage of regulatory warnings.*

Discussion

The regulatory authorities issued several warnings restricting the use of SSRIs in patients younger than 18 years of age between 2003 and 2004 due to uncertainties regarding the benefit/risk balance, and included further restrictions for young adults (18 - 24-years-old) in 2007 and 2008 [19-22]. During these years, scientific journals and Dutch and British newspapers increased their (negative) coverage about the SSRI and suicidality controversy [11]. We analyzed British and Dutch SSRI use trends in 2000 - 2010 and assessed whether trend changes could be associated with the combined and long-term effect of both periods of media coverage of regulatory warnings. To our knowledge, this is the first study that presents such evidence on long-term use patterns of SSRIs and possible associations with media coverage of regulatory warnings.

Trend changes in overall SSRI use largely corroborated with the periods of media coverage of the warnings. Both post-warning periods were associated with upward trends in SSRI use in the UK. Contrarily, Dutch post-warning periods were associated with limited reductions in overall SSRI use. However, these associations were not causal. In general, we found evidence of a temporal and limited association between overall SSRI use in both countries and both periods of media coverage of regulatory warnings. The effect of the periods of media coverage of regulatory warnings varied significantly per specific SSRI, country, and Dutch age groups. Stratified analyses showed a significant decrease in paroxetine use prior to the first period of media coverage of regulatory warnings in the UK overall and in Dutch pediatric, adolescent, and young adult age groups. Other SSRI use, especially (es) citalopram, continued to increase during the first period of media coverage of regulatory warnings in both the NL and UK . Still, paroxetine remained the most frequently used SSRI in the NL, whilst fluoxetine was used most frequently in UK in the 10-year period.

The present study has several strengths and limitations. The main strengths of this paper are the long-term analysis of trends of antidepressant use in the UK and the NL (based on national data), the comparison between two northern European countries, and the inclusion of all classes of antidepressants (not only those subject to safety advisories). Although media coverage represents only one of the many factors that may influence use (other factors might be reimbursement systems and policies, guidelines or patient compliance), our choice of the periods of media coverage of regulatory warnings is substantiated by a systematic analysis, which is also an important strength of the present study [11].

The limitations of the present study are explained below. Two distinct types of data on SSRI use were analyzed (IMS sales data for the NL and UK and Dutch GIP-prescription data). None of the datasets provided information on patient characteristics or detailed information on prescription dynamics at a patient level. Patient-level data can be used to assess trends in use over time on a more detailed level, such as rates of initiation of new prescriptions, discontinuation, or switching. However, these data were not available for the present study. We assessed a possible association between changes in Dutch and British antidepressant use and media or regulatory warnings on a national level, not on a micro level. Therefore, we used DDDs/1000/day to present drug utilization patterns. One

of the greatest advantages of using the DDDs methodology when conducting drug utilization studies is that it enables comparisons between distinct molecules within and between countries. We consider that the quality of our data, the quantity, and interpretation in DDDs, were sufficient to answer our research question. However, further research in this direction could focus on analyzing antidepressant use and the influence of media and regulatory warnings at a patient level as mentioned above. Another weakness of our study is the lack of adjustment for pediatric doses. Unfortunately, the DDD-methodology is limited to adults, since the standard value assigned by the WHO is based on the main indication in adults. The lack of adjustment in our results creates an underestimation of the amount of antidepressant use in younger groups; this is unavoidable for drug utilization studies when analyzing pediatric off-label use. Unfortunately, due to the limited clinical evidence about the use of antidepressants in children, and the fact that dose calculations in children carry greater risks of error when compared with adults (differences in age and weight), no standardized guidelines for the use and dosage of antidepressants in children have been developed to date [23, 24]. Since we were interested in the macro-level dynamics/patterns of antidepressant use in children and the influence of media coverage of the warnings on use, we decided to present pediatric antidepressant use in DDDs despite all limitations. However, caution ought to be taken when interpreting the absolute level of use (number of DDDs/1000/day) in these young age groups.

The periods of media coverage of regulatory warnings had a limited and temporal effect on overall SSRI use in both the UK and NL. Significant reductions in SSRI use were not clearly observed during these periods. Overall SSRI use doubled during the period 2000-2010, which has been previously reported for other countries as well [6, 7, 10, 25-31]. It should be noted that overall antidepressant use could have increased significantly in the absence of regulatory actions or their coverage in the media, so the full effect of the regulatory actions or their coverage in the media may have been underestimated. When split by age groups, we observed that the increasing trend for Dutch SSRI use was temporarily interrupted in pediatrics, adolescents, and in less intensity in adults after the first period of media coverage of the warnings. Thereafter, SSRI use in these age groups recovered. Contrarily, SSRI use consistently decreased in young adults, whereas use by the elderly continued to increase despite media coverage of the warnings. These temporal decreases in SSRI use could indicate the prescribers' attention and reaction to the warnings or media coverage. A similar response from prescribers to the regulatory advisories in children was reported for the UK, albeit without evidence of media influence [32].

Recent research on prescribing behaviors in the UK demonstrated that the increase in the prescriptions of antidepressants was not attributed to an increase of new patients (initiation), but to an increase in the number of long-term prescriptions [33]. Reasons for this growth in long-term use of antidepressants are to prevent relapses or recurrences, and to reduce the occurrence of withdrawal symptoms by titration and maintenance dosing. Research on antidepressant use in the NL in the 1990s demonstrated a similar cumulative effect in use, namely an increase in SSRI use both in terms of prevalence and incidence [34]. During the 2000s, the Dutch Health Insurance Board reported an increase in overall antidepressant use, while the number of SSRI users remained constant [35], demonstrating

a shift in the 2000s when the prevalence of SSRI use increased, but the incidence did not. All in all, changes in the management of depression would be expected to affect population-level DDDs. Although this cumulative effect on antidepressant use was reported for both countries, UK national use was nearly two-fold higher than in the NL despite the use of DDDs as equivalent measure.

Towards the end of our study period in 2008, two important systematic reviews were published calling into question the effectiveness of SSRIs not only in pediatrics, but in adults and elderly, as well. In a meta-analysis, Kirsch et al. concluded that antidepressants were no better than placebo, and that in more severely depressed patients these drugs showed some effect, but only because of a poor response to placebo [36]. In the second publication, Turner et al. demonstrated that antidepressant trials with positive outcomes were published more often that those reporting negative outcomes [37]. This publication bias seemed to provide an incomplete picture when analyzing the efficacy of antidepressants by overestimating their efficacy. The publication of both systematic reviews, in particular Kirsch et al., evoked several media responses with controversial headers such as “depressing news, the happy pills don’t work”, or “anti-depressants taken by thousands of Brits ‘do NOT work’, major new study reveals” [38, 39]. Such publications, not related to the safety controversy, may also influence SSRI use. Despite this negative coverage in scientific journals and newspapers, SSRI use remarkably continued to grow in both countries after 2008.

Overall SSRI growth in the UK was mainly driven by the use of citalopram, escitalopram, and fluoxetine. The UK guideline (NICE) for the treatment of depression recommends SSRIs, in particular (es)citalopram and fluoxetine, as first-line pharmacological interventions for the treatment of mild to severe depression based on their positive benefit/risk profile [40-42]. SSRIs growth could be attributed to these recommendations and the prescribers’ compliance. Another factor that could have influenced the increase in the use of escitalopram is its patented status (approved in 2002). However, this was not the case for citalopram that hitherto had shown a constant upward trend when its patent expired in 2003. Contrary to citalopram, paroxetine use dropped in February 2002, the same year that its patent status expired, and prior to the first period of increased (negative) media coverage and regulatory warnings. Most of the negative media coverage was directed towards paroxetine in both the NL and UK. In 2001, GlaxoSmithKline (GSK) lost its first lawsuit concerning paroxetine’s association with murder and suicide [43, 44], and this resulted in a FDA product warning [45]. In 2002, the BBC aired a documentary ‘The Secrets of Seroxat’ (paroxetine’s trademark) that highlighted safety concerns about this product, both in terms of suicidality and difficulties with discontinuing use [46]. These series of events may have induced the plunge in paroxetine use in the UK observed in our results prior to the first period of media coverage of regulatory warnings, in February 2002.

Specific SSRI use in the NL was comparable with the UK to a limited extent. Citalopram, escitalopram, and sertraline use also showed upward trends in the period under survey, albeit with limited signs of diminished use towards the end of the survey period and after the periods of media coverage of regulatory warnings. The Dutch GP guideline for the treatment of depression in adults recommends either a TCA or an SSRI as first-

line treatment, giving priority to fluvoxamine, paroxetine, sertraline and a lower priority to fluoxetine due to the long-half life [47]. Remarkably, individual SSRIs with a large market uptake and a positive benefit/risk profile, such as citalopram and escitalopram [40-42] are not mentioned, nor recommended in the Dutch guidelines. The Dutch guideline for specialists extensively considers the benefits and risks of citalopram and escitalopram [48]. The preference for paroxetine in GP guidelines may be one of many factors why its use was less affected in the NL by media coverage of regulatory warnings compared to the UK [47] where citalopram, escitalopram, and fluoxetine are recommended for GP use.

Most of the SSRI prescriptions in the NL were issued by a GP (±80%), confirming previous research [49]. Dutch GPs and specialists started prescribing less paroxetine towards the end of the first period of media coverage of regulatory warnings, apparently indicating a timely reaction from prescribers to the regulatory advisories or media attention. On the other hand, the increasing prescription rate of citalopram by both Dutch GPs and specialists demonstrated little or no effect during both periods of media coverage of regulatory warnings, as well as either prescribers' disregard of the regulatory warnings or switching. The influence of guidelines, reimbursement policies, and prescribing habits for SSRI use should be further studied to better understand the differences for specific SSRIs and between countries.

Notwithstanding the modest reduction in paroxetine use in the NL, we measured significant drops in use for pediatrics, adolescents, and young adults prior to the period of media coverage of regulatory warnings. Therefore, no direct association between the periods of media coverage of regulatory warnings and decreased paroxetine use was found in young groups. Conversely, both periods of media coverage of regulatory warning were associated with decreased paroxetine use in adults and elderly, although the warnings (and updates) were originally not thought to affect these age groups. Presumably, disadvantages regarding the use of paroxetine, such as the high risk of withdrawal effects or akathisia, could have caused this reduction in use [50]. The first period of media coverage of regulatory warnings (2003 - 2004) was associated with a temporal dip in citalopram, and sertraline use in pediatrics, and adolescents in NL. Similar reductions in SSRI use by children and adolescents were also reported in other countries [6, 7, 9, 51-53]. However, our data demonstrate that this temporal decrease in use by Dutch children and adolescent user groups recovered between the first and second period of media coverage of regulatory warnings. These results may indicate that doctors outweighed the benefits of SSRIs compared to the risks. Wijlaars et al. have reported similar long-term use patterns for British children, but without systematically accounting for the effects of the media coverage of the warnings, or differential antidepressant use by various young age groups [32].

Conclusion

The timing of the media coverage of regulatory warnings about the suicidality risk associated with SSRI use coincided with changes in overall use in the NL and UK from 2000 to 2010. The results of this study demonstrate that short-term investigations only provide a

snapshot of the potential implications of media coverage and regulatory warnings. We confirmed a strong, but not causal, association between periods of intense media coverage of regulatory warnings and significant changes in SSRI use over a ten-year period in both countries. However, our long-term assessment illustrated that the changes were temporal, drug-specific and more pronounced in pediatrics and young adults. The twofold increase in SSRI use over the 10-year period indicates that regulatory warnings and media coverage may come and go, but they do not have a significant impact on the overall upward trend of SSRI use as a drug class in both countries.

References

1. Williams D, Kelly A, Feely J. Influence of media and regulatory changes on prescribing of Cotrimoxazole and Trimethoprim in Ireland. Pharmacoepidemiol Drug Saf. 2000;9(4):313-7.
2. David F, Archer M. Medical decisions regarding hormone therapy for menopausal women are significantly influenced by the media. Pharmacoepidemiol Drug Saf. 2007;16(1):28-31.
3. Mebane FE. The importance of news media in pharmaceutical risk communication: proceedings of a workshop. Pharmacoepidemiol Drug Saf. 2005 May;14(5):297-306.
4. Brouneus F, Dahlin A, Beermann B. Press coverage and sales of Xenical in Sweden, 1998-2000. Eur J Clin Pharmacol. 2005 Jun;61(4):285-9.
5. Martin RM, May M, Gunnell D. Did intense adverse media publicity impact on prescribing of paroxetine and the notification of suspected adverse drug reactions? Analysis of routine databases, 2001-2004. Br J Clin Pharmacol. 2006 Feb;61(2):224-8.
6. Wheeler BW, Gunnell D, Metcalfe C, Stephens P, Martin RM. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. BMJ. 2008 Mar 8;336(7643):542-5.
7. 7. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry. 2007 Sep;164(9):1356-63.
8. Volkers AC, Heerdink ER, van Dijk L. Antidepressant use and off-label prescribing in children and adolescents in Dutch general practice (2001-2005). Pharmacoepidemiol Drug Saf. 2007 Sep;16(9):1054-62.
9. Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry. 2007 Jun;164(6):884-91.
10. Olfson M, Marcus SC, Druss BG. Effects of Food and Drug Administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry. 2008 Jan;65(1):94-101.
11. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, Belitser SV, Raaijmakers JAM, Pieters T. Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study. BMJ Open. 2011 January 1, 2011;1(2).
12. GIPdatabank. GIPdatabank Utrecht: CVZ; 2011 [cited 2012 January 13]. Available from: http://www.gipdatabank.nl/.
13. WHO. ATC/DDD Index 2011 Geneva: WHO; [cited 2011 4 October]. Available from: http://www.whocc.no/atc_ddd_index/.
14. CBS. Bevolkinsteller (Centrale Bureau van Statistiek) 2011 [cited 2011 23 October]. Available from: http://www.cbs.nl/en-GB/menu/home/default.htm?Languageswitch=on.
15. Commission E. Eurostat 2011 [cited 2011 5 October]. Available from: http://epp.

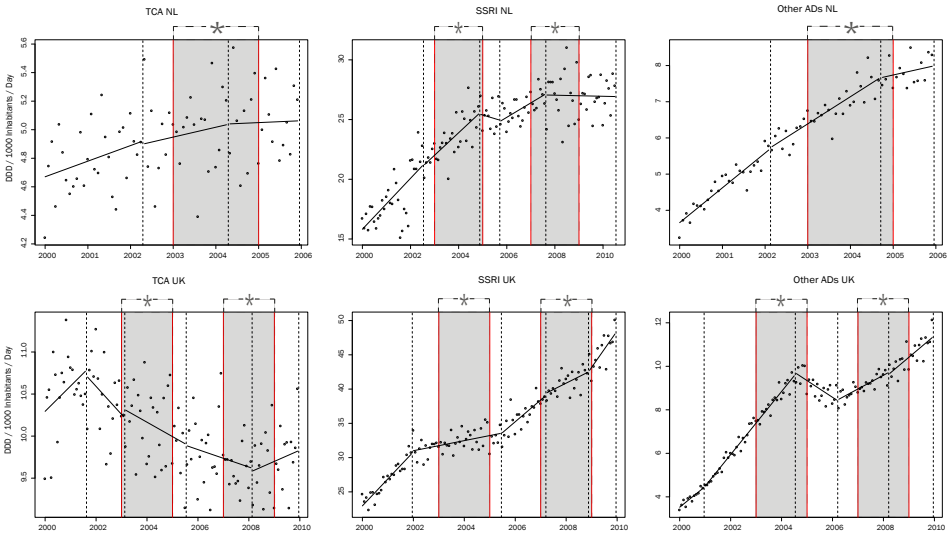
eurostat.ec.europa.eu/portal/page/portal/statistics/themes.
16. Xianping G. Segmental Semi-Markov Models and Applications to Sequence Analysis: University of California; 2002.
17. Stolk P, Belitser SV, Leufkens HGM, Heerdink ER. Variable Access to Clopidogrel in a Harmonized EU Market. Value in Health. 2008;11(5):989-95.
18. R-Project. The R Project for Statistical Computing Viena, Austria: R Foundation for Statiastical Computing; 2011 [cited 2012 13 February]. Available from: http://www.r-project.org/.
19. FDA. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications Rockville, MD: Department of Health and Human Services; 2004 [cited 2011 20 January]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm.
20. EMA. European Medicines Agency finalises review of antidepressants in children and adolescents London: EMA; 2005 [cited 2011 4 February]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/12/news_detail_000882.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1.
21. MHRA. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants London: Committee on Safety of Medicines; 2004 [cited 2012 24 August]. Available from: http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019472.pdf.
22. FDA. Antidepressant Use in Children, Adolescents, and Adults Rockville, MD: Department of Health and Human Services; 2007 [cited 2011 7 February]. Available from: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm.
23. WHO. Guidelines for ATC classification and DDD assignment 2010 [cited 2011 24 February]. Available from: http://www.whocc.no/filearchive/publications/2010guidelines.pdf.
24. Liem T, Heerdink E, Egberts A, Rademaker C. Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs. European Journal of Clinical Microbiology & Infectious Diseases. 2010;29(10):1301-3.
25. Hall WD, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P. Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. BMJ. 2003 May 10;326(7397):1008.
26. Milane MS, Suchard MA, Wong M-L, Licinio J. Modeling of the Temporal Patterns of Fluoxetine Prescriptions and Suicide Rates in the United States. PLoS Med. 2006;3(6):e190.
27. Grunebaum MF, Ellis SP, Li S, Oquendo MA, Mann JJ. Antidepressants and suicide risk in the United States, 1985-1999. J Clin Psychiatry. 2004 Nov;65(11):1456-62.
28. Korkeila J, Salminen J, Hiekkanen H, Salokangas R. Use of antidepressants and suicide rate in Finland: an ecological study. J Clin Psychiatry. 2007;68(4):505-11.
29. Bramness JG, Walby FA, Tverdal A. The sales of antidepressants and suicide rates in Norway and its counties 1980-2004. Journal of Affective Disorders. 2007;102(1-3):1-9.

30. Reseland S, Bray I, Gunnell D. Relationship between antidepressant sales and secular trends in suicide rates in the Nordic countries. The British Journal of Psychiatry. 2006 April 1, 2006;188(4):354-8.
31. Baldessarini RJ, Tondo L, Strombom IM, Dominguez S, Fawcett J, Licinio J, et al. Ecological studies of antidepressant treatment and suicidal risks. Harvard Review of Psychiatry. 2007;15(4):133-45.
32. Wijlaars LPMM, Nazareth I, Petersen I. Trends in Depression and Antidepressant Prescribing in Children and Adolescents: A Cohort Study in The Health Improvement Network (THIN). PLoS ONE. 2012;7(3):e33181.
33. Reid S, Barbui C. Long term treatment of depression with selective serotonin reuptake inhibitors and newer antidepressants. BMJ. 2010 2010-03-26 00:00:00;340.
34. Meijer WE, Heerdink ER, Leufkens HM, Herings RC, Egberts AG, Nolen W. Incidence and determinants of long-term use of antidepressants. European Journal of Clinical Pharmacology. 2004 2004/03/01;60(1):57-61.
35. CVZ. GIPeilingen: College voor zorgverzekeringen (CVZ); 2012 [cited 2012 21 May]. Available from: http://www.cvz.nl/publicaties/gipeilingen.
36. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. PLoS Med. 2008;5(2):e45.
37. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008 Jan 17;358(3):252-60.
38. Boseley S. Prozac, used by 40m people, does not work say scientists London, UK: Guardian Media Group; 2008 [updated Tuesday 26 February 2008; cited 2012 24 August]. Available from: http://www.guardian.co.uk/society/2008/feb/26/mentalhealth.medicalresearch.
39. McRae F. Anti-depressants taken by thousands of Brits 'do NOT work', major new study reveals London2008 [cited 2012 24 August]. Available from: http://www.dailymail.co.uk/health/article-518669/Anti-depressants-taken-thousands-Brits-NOT-work-major-new-study-reveals.html.
40. NICE. Depression: the treatment and management of depression in adults (National Clinical Practice Guideline 90) UK: National Institute for Health and Clinical Excellence (NICE); 2009 [cited 2011 19 December]. Available from: http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf.
41. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. The Lancet. 2003;361(9358):653-61.
42. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JPT, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. The Lancet. 2009;373(9665):746-58.
43. Guardian T. 'Four people dead is four too many' London: Guardian; 2001 [cited 2011 19 December]. Available from: http://www.guardian.co.uk/education/2001/aug/09/medicalscience.healthandwellbeing.

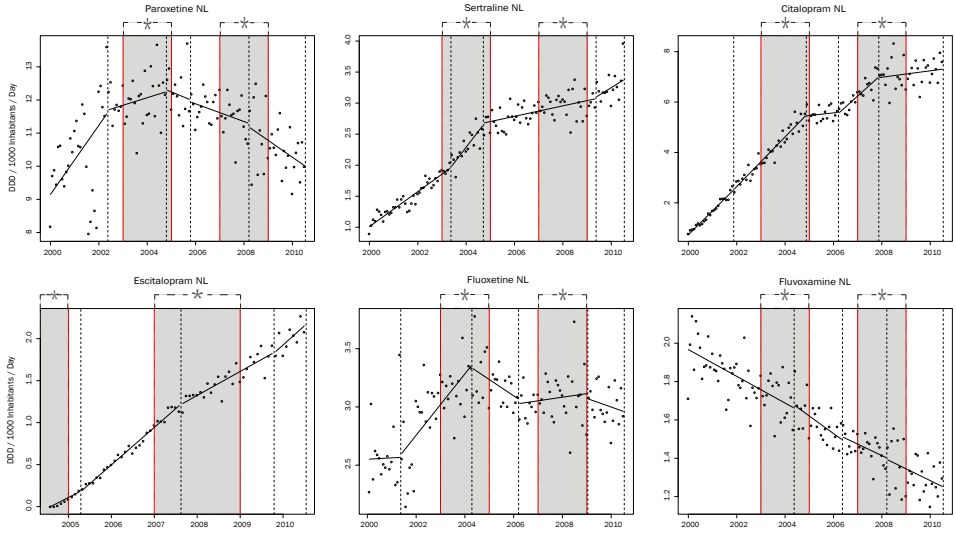
44. BBC. Antidepressant addiction warning London: BBC; 2001 [cited 2011 19 December]. Available from: http://news.bbc.co.uk/2/hi/health/1382551.stm.
45. Tonks A. Withdrawal from paroxetine can be severe, warns FDA. BMJ. 2002 2002-02-02 00:00:00;324(7332):260.
46. BBC. Panorama: The Secrets of Seroxat London: BBC; 2002 [cited 2012 1 February]. Available from: http://news.bbc.co.uk/panorama/hi/front_page/newsid_8425000/8425414.stm.
47. NHG. M44 NHG-Standaard Depressieve Stoornis (Depressie) Utrecht: Nederlands Huisartsen Genootschap; 2009 [updated 2009; cited 2012 13 February]. Available from: http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden.htm - clusterN.
48. CBO. Richtlijnherziening van de Multidisciplinaire richtlijn Depressie bij volwassenen Utrecht: Centraal BegeleidingsOrgaan; 2010 [cited 2011 15 December]. Available from: http://www.cbo.nl/thema/Richtlijnen/Overzicht-richtlijnen/Geestelijke-gezondheidszorg/?p=402.
49. Gardarsdottir H, Heerdink ER, Egberts AC. Potential bias in pharmacoepidemiological studies due to the length of the drug free period: a study on antidepressant drug use in adults in the Netherlands. Pharmacoepidemiology and drug safety. 2006 May;15(5):338-43.
50. Healy D, Herxheimer A, Menkes DB. Antidepressants and Violence: Problems at the Interface of Medicine and Law. PLoS Med. 2006;3(9):e372.
51. Nemeroff CB, Kalali A, Keller MB, Charney DS, Lenderts SE, Cascade EF, et al. Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States. Arch Gen Psychiatry. 2007 April 1, 2007;64(4):466-72.
52. Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment after FDA warnings. Arch Gen Psychiatry. 2009 Jun;66(6):633-9.
53. Isacsson G, Holmgren A, Ösby U, Ahlner J. Decrease in suicide among the individuals treated with antidepressants: A controlled study of antidepressants in suicide, Sweden 1995-2005. Acta Psychiatrica Scandinavica. 2009;120(1):37-44.

Appendixes

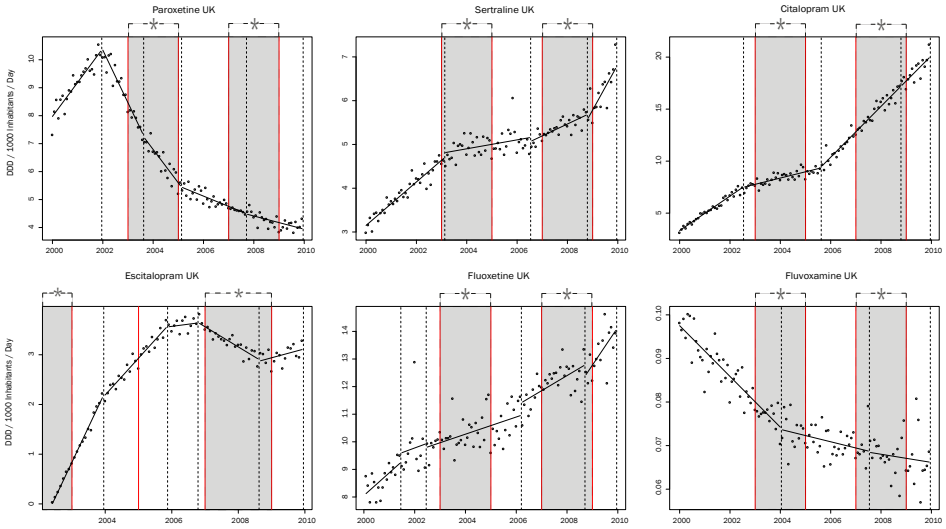
Appendix 1. Segmentation of antidepressants in NL and the UK (TCAs, SSRIs, and other antidepressants)



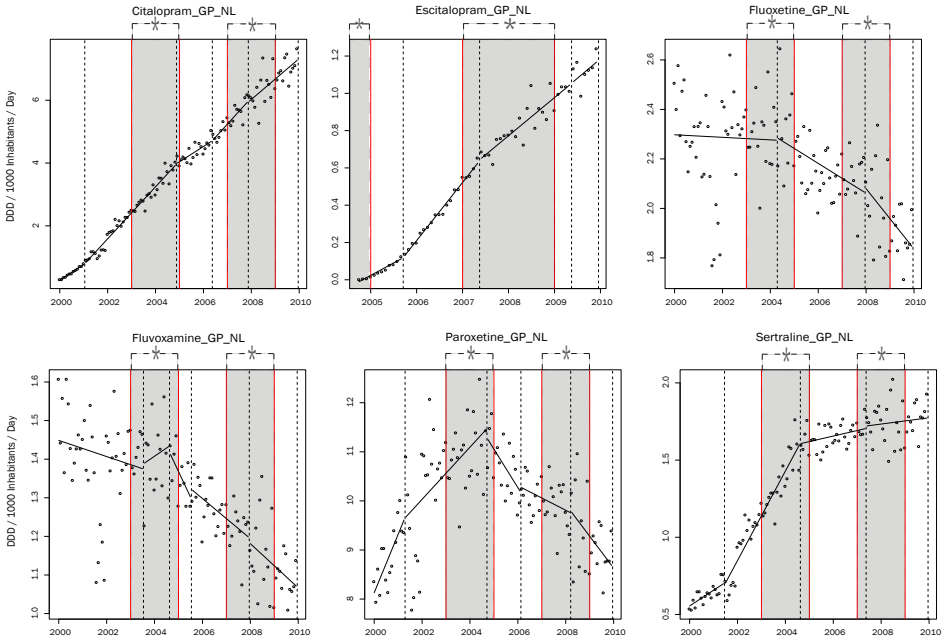
Appendix 2. Segmentation of all SSRIs in the NL (paroxetine, sertraline, citalopram, escitalopram, fluoxetine, and fluvoxamine).



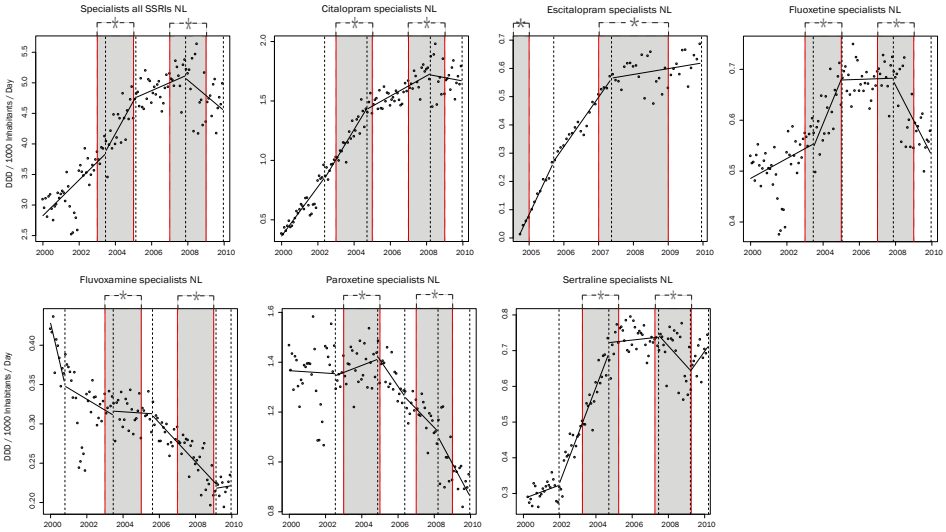
Appendix 3. Segmentation of all SSRIs in the UK (paroxetine, sertraline, citalopram, escitalopram, fluoxetine, and fluvoxamine).



Appendix 4. Segmentation of SSRI use in the NL through GPs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline).



Appendix 5. Segmentation of SSRI use in NL through specialists (SSRIs, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline).



CHAPTER

6

Restoring trust in the pharmaceutical sector on the basis of the SSRI case

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Abstract

The lack of public trust in the pharmaceutical sector (i.e., industry, authorities and doctors) may compromise the future of drug development and the regulatory system. Public trust integrates two important components, namely the vulnerability of the truster and the competence of the trustee. As trust appears to have eroded due to the occurrence of drug safety controversies, this paper analyzes the role of public trust during the SSRI and suicidality controversy focusing on the aforementioned trust components. As the competence component of trust is argued to be paramount in determining and maintaining public trust, the SSRI case shows that this component is a part of public trust where these institutions can build on and might therefore be better used to substantiate and reinforce public trust. Efforts to build trust should rely on the ethical, professional (competence) and societal commitment of institutions and individuals to protect the vulnerability of the public during controversies. Since shared values can create trust or increase its levels within a specific environment, industry, authorities and physicians ought to develop novel and cooperative strategies to highlight their shared values and motivations. Rules, regulations and settlements are indispensable tools but undue regulation is costly and can backfire on the rather sensitive trust relationships in the pharmaceutical sector.

Introduction

Drug safety controversies have evoked concerns regarding the structure and sustainability of drug development and regulatory systems. Editorials from renowned scientific/medical journals have argued that public trust in the pharmaceutical sector and medicines are the greatest victims of these controversies and that distrust may compromise the future of drug development and the regulatory system [1, 2]. An exemplary case that contributed to this discussion and distrust was the controversy about the increased risk of suicidality observed in patients using antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs). A chronological description of this controversy is reported in Appendix 1.

The SSRI case offers a practical learning opportunity about controversies because most pharmaceutical sector's stakeholders were blamed for the lack of trust at various points in time (e.g., industry, authorities and doctors) [1, 3-7]. Although news media coverage of the controversy was generally negative about the efficacy and safety of antidepressants, scientific journals were mainly positive [8]. Notwithstanding the negative series of events surrounding the SSRIs and suicidality controversy, the overall consumption of antidepressants increased despite short stabilization periods during the warnings in 2003 - 2004 and 2007 - 2008 [9]. This upward trend raises questions about the role of public trust in pharmaceutical stakeholders since the communication of regulatory (black-box) warnings, negative media coverage, and public polls/surveys indicating an erosion of trust did not lead to a persistent drop in antidepressant use. In this chapter, these contradictory trends of decreasing trust levels in the pharmaceutical sector and increasing antidepressant use will be explored by analyzing the role of public trust in the SSRIs and suicidality controversy.

Studies on public responses to technological advances, controversies or new risk management strategies (e.g., regulations or warnings) have revealed pivotal differences concerning the understanding and interpretation of risks between policy-makers (those who are responsible for overseeing, promoting and regulating health and safety) and the lay public [10]. To counter this problem, better understanding of risk perception and enhanced risk communication has been proposed to successfully educate, and warn the public about risks or the introduction of (new) regulations [10]. A shortcoming of most risk communication approaches is that its core primarily focuses on risk-related issues. Consequently, Renn and Levine (1991) emphasized the importance of acknowledging the fundamental role of credibility and trust in risk communication. Renn and Levine argue that trust is a necessary precondition for enabling credibility [11].

The terms "public trust" and an "erosion of trust" have almost become indicative to signal problems, or consequences, concerning the occurrence of drug safety controversies [1, 2, 5, 6, 12]. Although an erosion of trust may be plausible, most claims do not explicitly define trust, hampering the interpretation of what could be understood as trust. Given the complex nature of trust, we have proposed a definition of public trust that integrates important trust components, namely vulnerability and competence. Our definition of trust is given below. Having this definition as a background, we will analyze the role of public trust in the SSRI

and suicidality controversy. This analysis may offer lessons for the management of future drug safety controversies by underlining which trust components (i.e., vulnerability or competence) are important for which stakeholders and whether these have been optimally utilized. Public trust in the pharmaceutical sector and public health is utterly important since it may increase credibility, coherence, and motivate cooperation and innovation within the drug development and regulatory system, therefore making it more sustainable.

What is public trust in the pharmaceutical sector?

Trust has been studied in various disciplines resulting in manifold definitions for a single concept. Nonetheless, the value of trust has been widely recognized at interpersonal and organizational levels [13-16]. Since no clear definition of trust exists for the pharmaceutical sector, we examined the literature to provide an appropriate definition of public trust. Our literature search demonstrated the predominance of two major components of trust. We labeled these: the vulnerability and competence components. Hence, public trust in the pharmaceutical sector was defined as:

- "The willingness to assume a position of vulnerability in relation to the provision of care and the management and use of medicines [17-25]; and as
- The reliance on the competence of companies, authorities, and healthcare providers to perform the tasks they are responsible for and expected to do" [17, 18, 26-34].

This definition will be used as a template to discuss the factors related to the SSRI and suicidality controversy that may have affected trust and analyze the role of trust in the controversy.

The role of public trust within the SSRI and suicidality controversy

The initial reports suggesting an increased suicidality risk during SSRI therapy emerged in 1990 (Appendix 1) [35]. These reports prompted the Federal Drug Administration (FDA) in the United States (US) to call a public hearing in 1991 where it was concluded that the evidence was poor and unclear [36]. Regulatory authorities, such as the FDA, are (en-) trusted to oversee the safety and efficacy of medicines based on their scientific competence. By holding public hearings, the FDA aimed to include public opinion in their decision-making process. More importantly, the agency addressed the vulnerability of SSRI users (which may have been exacerbated by the suicidality reports), by reassuring the public about the safety and efficacy of SSRIs. While the agency used their competence to oversee the safety of antidepressants, attention was also paid to the vulnerability of patients/public as a part of public trust. The FDA's intervention was according to their expected societal role as expert public representatives and most likely stimulated public trust based on the agency's competence (Appendix 1) [37, 38].

In 2002, the alleged suicidality risk associated with SSRI use suddenly reemerged in public debate following GlaxoSmithKline's (GSK) application for a pediatric indication for

paroxetine. A BBC documentary reported that the data submitted by GSK was altered to veneer the increased suicidality risk. The documentary also showed patients' experiences with side effects of antidepressants [39]. This media intervention evoked a public scare. The claim of "altered data" to "veneer the risk" concerning antidepressants exposed disguised and dishonest corporate behavior, fomenting suspicion and public distrust [40]. The New York State Attorney General's accusation that GSK had concealed this suicidality risk added more suspicion and distrust [7]. According to the principles of corporate social responsibility, these negative reports may have affected the industry's reputation, detracting from corporate legitimacy and stirring distrust [41]. At this stage, public trust was not honored since disguising the suicidality risk exposed SSRI users directly or indirectly to unnecessary risks, thereby increasing their vulnerability [42-44].

Another component of public trust in pharmaceutical companies is the reliance on the industry's competence to develop and produce safe and efficacious medicines [20, 26, 27, 45-47]. So, trust was also harmed due to the company's incompetence to guarantee the safety/efficacy of their marketed products, or collaborate with other stakeholders in performing this task [48].

Although clinical data concealment was alleged and the pharmaceutical company was so accused, regulatory authorities appeared to have had this data before the accusations (Appendix 1). Regulatory analyses of the data confirmed the increased suicidality risk with SSRIs, but it was only communicated to the public six months later, after re-analyzes [4]. This cautionary action indicated that the authorities wanted to be certain about the increased suicidality risk before taking any measurements or communicating it to the public. However, it seemed that political interests upon and within the FDA impeded the timely release of these results and in fact resulted in two Congressional investigations [49] while receiving media attention [50]. Public trust in regulatory authorities may have been affected at this stage given the agency's apparent inability to distantiate themselves from political/bureaucratic interests [37, 48, 51]. This behavior of regulatory authorities may have revealed a certain degree of incompetence for not honoring the principles of ethics and altruism by which public representatives are expected to function [37, 41, 51]. Nevertheless, authorities issued a black-box warning after confirmatory results of increased suicidality risk were obtained [52-55]. By promoting and acting on public protection (warnings), using the agencies' scientific competences, authorities were able to substantiate and reaffirm the public's trust and exert their societal role [51].

The news media played a recurrent role in communicating information concerning the increased suicidality risk and other aspects of the SSRI controversy to the public. Studies, not related to this controversy, illustrate that media reports may tend to either overestimate or underestimate the benefit/risk profile of medicines [56-58]. However, during this controversy, news media showed a negative tendency towards the benefits of antidepressants for the treatment of depression [8]. As the tone and content of media communications may influence public perceptions and prescribing behavior [59, 60], public trust and antidepressant use might have decreased by the negative reporting trend. Regulatory authorities could have played a mediating role between those negative reports, the public and prescribers.

Trust is reinforced through open, honest and objective communication, while scant or subjective communication or secrecy generates suspicion and distrust [38, 40]. Alas, regulatory authorities assumed a reactive/passive role that did not contribute to enhancing the quality of news media reporting or alleviating patient's vulnerability [12, 13, 61].

Despite the temporal and limited association between overall SSRI use, negative media coverage and regulatory warnings, overall SSRI use continued to increase and antidepressant use simply shifted from one SSRI to another [9]. It does not seem logical that antidepressant users would maintain their level of trust in the industry after being confronted with disguised, dishonest corporate behavior or negative news about the efficacy of antidepressants [17, 46]. The increasing SSRI use may indicate that public distrust in pharmaceutical companies was counterbalanced by their trust in prescribers, which is generally known to be high [17, 18, 62, 63]. Doctors may have mediated the connection between pharmaceutical companies, antidepressants and patients, thus disassociating patients from the controversy and acting as a buffer between the patients' vulnerability and latent risks of abandoning SSRIs. The face-to-face nature of the patient-doctor relationship could explain the trusted role of doctors as gatekeepers in the healthcare system [62, 64, 65]. Previous positive experiences and a perception of doctors as overseeing, benevolent and caring all substantiate patients' trust in doctors [18]. Hence, the controversy surrounding companies, authorities and the questioned benefit/risk profile of antidepressants did not cause patients to stop using SSRIs between 2000-2010 [9].

Finally, the settlement of numerous drug-law suits in the period 2008-2012, accounting for US$12.83 billion dollars, reached the news and exposed questionable industry practices [3, 66, 67]. Positively or negatively, these settlements demonstrated an acceptance of pharmaceutical wrongdoing to the public/patients. Since wrongdoing can damage trust, these settlements could indicate that pharmaceutical companies were resigned to changing their attitude and were now willing to assume public responsibility [41]. With these actions, pharmaceutical companies might have aimed to repair and reestablish a more competent, conscious and responsible reputation in society, and this as a part of restoring public trust based on their professional competence [18, 44, 68].

Discussion and recommendations

We analyzed the role of trust in the SSRI and suicidality controversy and the factors/events that might have eroded public trust in the pharmaceutical sector at the time. During this controversy, most stakeholders were blamed at distinct points in time. Public distrust fluctuated among stakeholders, and although it was temporal for doctors and regulatory authorities, distrust seemed more persistent concerning pharmaceutical companies.

Regulatory authorities can improve their risk management strategies by proactively collaborating and interacting with pharmaceutical companies, doctors or news media to objectively inform the public and address risks, instead of being passive or reactive. From a public perspective, a passive or reactive response from authorities may increase the

vulnerability of patients during controversies, and may portray an image of incompetency to the public and patients. Furthermore, a pro-active guidance of regulatory authorities may enhance the quality of media reporting [12, 13, 61]. Regulatory authorities should also learn how to react to media interventions by focusing on the authorities' (scientific) competence and become better communicators [12]. Future proposals should include and further stimulate transparent risk communication among stakeholders of the pharmaceutical sector as a part of risk management plans. This would motivate institutions to become more socially responsible and increase or reinforce better communication with society, especially during drug controversies.

During the analysis of the SSRI and suicidality controversy, we observed that the competence component of trust is paramount to maintain and restore public trust in pharmaceutical companies and regulatory authorities. Pharmaceutical companies and regulatory authorities should substantiate and reinforce public trust based on their competences. This is a part of public trust that they can build on. The public and patients negotiate or compensate their vulnerability by focusing on the competencies of these institutions. On the other hand, doctors appear to largely benefit from public trust based on the vulnerability of patients and the public that is elicited during illness or pharmaceutical therapy. However, patients and the public should also be capable of perceiving doctors' competence as a way to compensate for their vulnerability [38]. All in all, the SSRI and suicidality controversy illustrates the importance and the role of the vulnerability and the competence components of public trust. Focusing on vulnerability and competence individually, but preferably together, may contribute to the restoration of public trust in pharmaceutical companies, regulatory authorities and doctors, all as the principal stakeholders of the pharmaceutical sector.

Efforts to build trust should rely on the ethical, professional (competent) and societal commitment of institutions and individuals [41, 69]. Furthermore, reliance on regulations should become less prominent and is not the way to guarantee safety [45]. Besides, undue regulation is costly [70]. Since shared values can create trust or increase the trust levels within a specific environment [38], pharmaceutical companies, regulatory authorities and doctors ought to develop novel, more cooperative and stronger strategies to highlight their shared values and motivations. This could be an important initial step towards restoring public trust in the pharmaceutical sector.

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References

1. Take a stand. Nature. 2012 Jul 12;487(7406):139-40.
2. Bauchner H FPB. Restoring confidence in the pharmaceutical industry. JAMA. 2013;309(6):607-9.
3. Outterson K. Punishing Health Care Fraud — Is the GSK Settlement Sufficient? New England Journal of Medicine. 2012;367(12):1082-5.
4. Check E. Analysis highlights suicide risk of antidepressants. Nature. 2004 Aug 26;430(7003):954.
5. Fontanarosa Pb RDDCD. Postmarketing surveillance,Äîlack of vigilance, lack of trust. JAMA. 2004;292(21):2647-50.
6. Olsen AK, Whalen MD. Public perceptions of the pharmaceutical industry and drug safety: implications for the pharmacovigilance professional and the culture of safety. Drug Saf. 2009;32(10):805-10.
7. Wadman M. Spitzer sues drug giant for deceiving doctors. Nature. 2004 Jun 10;429(6992):589.
8. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, Belitser SV, Raaijmakers JAM, Pieters T. Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study. BMJ Open. 2011 January 1, 2011;1(2).
9. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, Belitser SV, Warmerdam J, de Valk V, et al. A 10-Year Analysis of the Effects of Media Coverage of Regulatory Warnings on Antidepressant Use in The Netherlands and UK. Plos One. 2012;7(9):e45515.
10. Slovic P. Perception of risk. Science. 1987 April 17, 1987;236(4799):280-5.
11. Renn O, Levine D. Credibility and trust in risk communication. Kasperson, Roger E. (Hrsg.): Communicating risks to the public : international perspectives. Dordrecht : Kluwer, 1991 (Technology, risk, and society, 4). - ISBN 0-7923-0601-5, S. 175-218. Stuttgart2010.
12. Lofstedt R, Bouder F, Wardman J, Chakraborty S. The changing nature of communication and regulation of risk in Europe. Journal of Risk Research. 2011;14(4):409-29.
13. Ide RW, Yarn DH. Public independent fact-finding: A trust-generating institution for an age of corporate illegitimacy and public mistrust. Vanderbilt Law Review. 2003 May;56(4):1113-80.
14. Leslie CR. Trust, distrust, and antitrust. Texas Law Review. 2004 Feb;82(3):515-680.
15. van der Schee E, Braun B, Calnan M, Schnee M, Groenewegen PP. Public trust in health care: A comparison of Germany, The Netherlands, and England and Wales. Health policy (Amsterdam, Netherlands). 2007;81(1):56-67.
16. Wright S. Trust and Trustworthiness. Philosophia. 2010 Sep;38(3):615-27.
17. Hall MA, Camacho F, Dugan E, Balkrishnan R. Trust in the medical profession: Conceptual and measurement issues. Health Services Research. 2002 Oct;37(5):1419-39.
18. Hall MA, Dugan E, Zheng BY, Mishra AK. Trust in physicians and medical institutions: What is it, can it be measured, and does it matter? Milbank Quarterly. 2001 2001;79(4):613-+.
19. Baier A. TRUST AND ANTITRUST. Ethics. 1986 Jan;96(2):231-60.

20. Church R. Trust, Burroughs Wellcome & Co. and the foundation of a modern pharmaceutical industry in Britain, 1880-1914. Business History. 2006 Jul;48(3):376-98.
21. Holton R. DECIDING TO TRUST, COMING TO BELIEVE. Australasian Journal of Philosophy. 1994 Mar;72(1):63-76.
22. Michalos AC. THE IMPACT OF TRUST ON BUSINESS, INTERNATIONAL SECURITY AND THE QUALITY OF LIFE. Journal of Business Ethics. 1990 Aug;9(8):619-38.
23. Mullarkey M, Duffy A, Timmins F. Trust between nursing management and staff in critical care: a literature review. Nurs Crit Care. 2011 Mar-Apr;16(2):85-91.
24. Muller T. Semantics of Trust. In: Degano PESGJ, editor. Formal Aspects of Security and Trust. Lecture Notes in Computer Science. 65612011. p. 141-56.
25. Welter F. All you need is trust? A critical review of the trust and entrepreneurship literature. International Small Business Journal. 2012 May;30(3):193-212.
26. Burke CS, Sims DE, Lazzara EH, Salas E. Trust in leadership: A multi-level review and integration. Leadership Quarterly. 2007 Dec;18(6):606-32.
27. Connell NA, Mannion R. Conceptualisations of trust in the organisational literature: some indicators from a complementary perspective. J Health Organ Manag. 2006;20(5):417-33.
28. Goold SD. Trust and the ethics of health care institutions. Hastings Center Report. 2001 Nov-Dec;31(6):26-33.
29. Hupcey JE, Miller J. Community dwelling adults' perception of interpersonal trust vs. trust in health care providers. J Clin Nurs. 2006 Sep;15(9):1132-9.
30. Hupcey JE, Penrod J, Morse JM, Mitcham C. An exploration and advancement of the concept of trust. Journal of Advanced Nursing. 2001 Oct;36(2):282-93.
31. Murphy JT. Building trust in economic space. Progress in Human Geography. 2006 Aug;30(4):427-50.
32. Smith C. Understanding trust and confidence: two paradigms and their significance for health and social care. J Appl Philos. 2005;22(3):299-316.
33. Wang YD, Emurian HH. An overview of online trust: Concepts, elements, and implications. Computers in Human Behavior. 2005 Jan;21(1):105-25.
34. Whitley R, McKenzie K. Social capital and psychiatry: Review of the literature. Harvard Review of Psychiatry. 2005 Mar-Apr;13(2):71-84.
35. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. American Journal of Psychiatry. 1990;147(2):207-10.
36. FDA. Psychopharmacological drugs advisory committee Rockville, Maryland: FDA; 1991 [cited 2013 March 15]. Available from: http://www.fda.gov/ohrms/dockets/ac/prozac/2443T1.pdf.
37. Casadesus-Masanell R. Trust in Agency. Journal of Economics & Management Strategy. 2004;13(3):375-404.
38. Dupras C, Williams-Jones B. The Expert and the Lay Public: Reflections on Influenza A (H1N1) and the Risk Society. American Journal of Public Health. 2012 Apr;102(4):591-5.
39. BBC. Panorama: The Secrets of Seroxat London: BBC; 2002 [cited 2012 1 February]. Documentary]. Available from: http://news.bbc.co.uk/panorama/hi/front_page/newsid_8425000/8425414.stm.

40. Hurley R. The Decision to Trust. Harvard Business Review. 2006:55-62.
41. Wood DJ. Corporate Social Performance Revisited. The Academy of Management Review. 1991;16(4):691-718.
42. Carter MA. Trust, power, and vulnerability: a discourse on helping in nursing. Nurs Clin North Am. 2009 Dec;44(4):393-405.
43. Hieronymi P. The reasons of trust. Australasian Journal of Philosophy. 2008 Jun;86(2):213-36.
44. Harrison S, Smith C. Trust and moral motivation: redundant resources in health and social care? Policy and Politics. 2004 Jul;32(3):371-86.
45. Cross FB. Law and trust. Georgetown Law Journal. 2005 Jun;93(5):1457-545.
46. Das TK, Teng BS. The risk-based view of trust: A conceptual framework. Journal of Business and Psychology. 2004 Fal;19(1):85-116.
47. Faulkner P. The epistemic role of trust. In: Falcone RBSKLSM, editor. Trust, Reputation, and Security: Theories and Practice. Lecture Notes in Artificial Intelligence. 26312003. p. 30-8.
48. Blair MM, Stout LA. Trust, trustworthiness, and the behavioral foundations of corporate law. University of Pennsylvania Law Review. 2001 Jun;149(6):1735-810.
49. Shulman S. Undermining Science: Suppression and Distortion in the Bush Administration. Press UoC, editor. Berkeley and Los Angeles, California: University of California Press; 2008. 224 p.
50. Harris G. Expert kept from speaking at antidepressant hearing New York, NY: NYTimes; 2004 [cited 2013 March 21]. Available from: http://www.nytimes.com/2004/04/16/politics/16DEPR.html?hp.
51. Thomas CW. Maintaining and restoring public trust in government agencies and their employees. Administration & Society. 1998 May;30(2):166-93.
52. FDA. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications Rockville, MD: Department of Health and Human Services; 2004 [cited 2011 20th January 2011]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm.
53. MHRA. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. London: Committee on Safety of Medicines, 2004.
54. EMA. European Medicines Agency finalises review of antidepressants in children and adolescents London: EMA; 2005 [cited 2011 4th February]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/12/news_detail_000882.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1.
55. FDA. Antidepressant Use in Children, Adolescents, and Adults Rockville, MD: Department of Health and Human Services; 2007 [cited 2011 7th February 2011]. Available from: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm.
56. Moynihan R, Bero L, Ross-Degnan D, Henry D, Lee K, Watkins J, et al. Coverage by the news media of the benefits and risks of medications. N Engl J Med. 2000 Jun 1;342(22):1645-50.

57. Wilson A, Bonevski B, Jones A, Henry D. Media reporting of health interventions: signs of improvement, but major problems persist. PLoS One. 2009;4(3):e4831.
58. Ries NM, Rachul C, Caulfield T. Newspaper reporting on legislative and policy interventions to address obesity: United States, Canada, and the United Kingdom. J Public Health Policy. 2011 Feb;32(1):73-90.
59. Archer DF. Medical decisions regarding hormone therapy for menopausal women are significantly influenced by the media. Pharmacoepidemiology and Drug Safety. 2007;16(1):28-31.
60. Williams D, Kelly A, Feely J. Influence of media and regulatory changes on prescribing of Cotrimoxazole and Trimethoprim in Ireland. Pharmacoepidemiol Drug Saf. 2000;9(4):313-7.
61. Slovic P. Perceived risk, trust, and democracy. Risk Analysis. 1993;13(6):675-82.
62. Brown P, Calnan M. Braving a faceless new world? Conceptualizing trust in the pharmaceutical industry and its products. Health:. 2010 December 15, 2010.
63. Entwistle V. Trust and shared decision-making: an emerging research agenda. Health Expectations. 2004 Dec;7(4):271-3.
64. Pescosolido BA, Tuch SA, Martin JK. The profession of medicine and the public: examining Americans' changing confidence in physician authority from the beginning of the 'health care crisis' to the era of health care reform. J Health Soc Behav. 2001 Mar;42(1):1-16.
65. Hillen MA, de Haes H, Smets EMA. Cancer patients' trust in their physician-a review. Psycho-Oncology. 2011 Mar;20(3):227-41.
66. NYTimes. Glaxo agrees to pay $3 billion in fraud settlement New York: NYTimes; 2012 [cited 2013 March 20]. Available from: http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html?pagewanted=all&_r=0.
67. BBC. GlaxoSmithKline agrees $3bn US settlement London: BBC; 2011 [cited 2012 March 7]. Available from: http://www.bbc.co.uk/news/business-15569656.
68. Misztal BA. Trust and cooperation: the democratic public sphere. Journal of Sociology. 2001 Dec;37(4):371-86.
69. Churchill LR. TRUST, AUTONOMY, AND ADVANCE DIRECTIVES. Journal of Religion & Health. 1989 Fal;28(3):175-83.
70. Bouvy JC, Koopmanschap MA, Shah RR, Schellekens H. The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. Clin Pharmacol Ther. 2012 Feb;91(2):281-8.

Appendix

Late 1980s
• The SSRIs entered the market as a new pharmacotherapy alternative to treat depression and other psychiatric disorders with benefits like fewer side effects and less risk of overdose when compared with former antidepressants, such as tricyclic (TCAs) or monoamine oxidase inhibitors (MAOIs).
1990
• Teicher et al. reported six cases of increased suicidal ideation during a course of fluoxetine (an SSRI).
1991
• The FDA concluded that there was no clear evidence between SSRI use and an increased suicidality risk.
2002
• GlaxoSmithKline (GSK) submitted extra clinical trial data to the FDA requesting six-month market exclusivity for paroxetine (an SSRI) for the treatment of pediatric depression. • The BBC reported that the data submitted by GSK was altered and that negative results which showed an increased suicidality risk with paroxetine were undisclosed. This data was not unknown to regulatory authorities since it was part of the registration dossiers. • Preliminary regulatory analyses confirmed an increased risk of suicidality in children and adolescents when using antidepressants.
2003-2004
• Several regulatory agencies issued a black-box warning for all SSRIs, banning their use in children and adolescents as a result of an increased suicidality risk.
2004
• The Attorney General of New York State sued GSK for “allegedly suppressing negative results” of antidepressant trials.
2007-2008
• The warnings were revised and the SSRI ban was extended to young adults (19 to 25-years-old).

2008

- A review demonstrated flaws in the scientific publishing system, wherein antidepressant studies with negative outcomes were discriminated for publication, thus providing an unbalanced benefit/risk profile of antidepressants for practitioners, scientists, and policy-makers.
- A meta-analysis on antidepressants' studies claimed that these medicines were as effective as placebo.
- The CHMP-EMA refuted the conclusion of the meta-analysis citing that it lacked a sufficient methodological/clinical basis to evaluate the benefits of antidepressants.

After 2009

- Several pharmaceutical companies have settled numerous civil law cases for unethical practices or data concealment amounting to US$12.83 billion.

2010

- GSK and AstraZeneca publicly decided not to continue their activities in drug discovery in the field of depression and anxiety since drug development for the central nervous system represented too many risks that were not proportional to possible revenues.
- Unfortunately, the industry decision to step out of this therapeutic field has left a significant gap for the future treatment of mental diseases, research opportunities and public health.

2012

- A re-analysis of published and unpublished studies demonstrated the efficacy of antidepressants compared to placebo and for reducing suicidality in youths, adults and elderly.

CHAPTER

7

Drug life cycles as a tool to analyze drug safety controversies

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Manuscript prepared for submission

Abstract

The occurrence of drug safety controversies has had a marked effect on public trust in the pharmaceutical industry and regulatory authorities. Approaches to analyze the dynamics of those controversies have been hampered by inadequate and limited analytical models and tools. In this paper, we postulate the use of Drug Life Cycles (DLC) as a heuristic tool to further elucidate the underlying dynamics of drug safety controversies for pharmaceutical policy analysis. We demonstrate that by combining different types of data (e.g., articles in newspapers and scientific journals, sales/prescription data, and contextual event-related data) in DLC studies, scenarios can be produced that can help policy analysts to assess and understand the effects of stakeholder's interventions on medication consumption, brand trust and other product reputation related issues during drug safety controversies.

Introduction

The serial occurrence of drug safety controversies has affected public trust in pharmaceutical companies and regulatory authorities and the credibility and sustainability of the drug development system [1-6]. Several proposals have been made to address this problem, such as strengthening the independence of regulatory authorities, creating a culture of transparency, or financial incentives for innovative products in high-need/high-risk disease areas [2, 4, 6, 7]. Both the cultural enthusiasm for the benefits of drugs and societal concerns about their risks are important in this respect. Most of these proposals, however, have failed to address the life cycle dynamics underlying the public perception and use of drugs, providing incomplete assessments about their governance and performance, as well as limited identification and clarification of the factors that may influence their performance. For instance, antidepressants have been focal points of public enthusiasm and at the same time the locus of public controversy that changed over time because these drugs have been associated with an increased (suicidality) risk [5, 6, 8-14]. A multidimensional model may integrate both aspects of life cycle dynamics (i.e., cultural enthusiasm and societal concerns) in the analysis of drugs. These types of analyses may yield new insights, which can contribute to a better understanding and governance of drug safety controversies. However, new proxy parameters and new forms of visualizations are first required.

Product life cycles (PLC) have been studied in marketing, business, environmental sciences and economics [15-19]. In environmental sciences, for instance, PLCs have been used to calculate life expectancy based on economic output vis-à-vis life cycle environmental impacts on health [19]. Using a method named life cycle attribute assessment (LCAA), life expectancy data (in years) coupled to gross national product (GNP) data were analyzed and adjusted to purchasing power parity to demonstrate that economic development had a positive impact on health benefits, while health damages caused by environmental pollution (due to production/economic development) were greatly compensated by these benefits. Thus, LCAA may support policy and decision makers in implementing environmental and health related decisions in the supply chain throughout PLCs [19].

In the same fashion as health, economic benefits, or risks can be evaluated in terms of PLC analysis, we hypothesize that drug life cycles (DLCs) could serve as a model to analyze drug safety controversies, to assess the effectiveness of regulatory interventions and to define and understand the role of stakeholders at different stages during controversies. The strength of DLC lies on its multidimensional perspective/nature to analyze controversies. Improved risk management approaches may reflect on the perceived competence of pharmaceutical companies and regulatory authorities to govern drug use and henceforth protect public safety.

Aim

The aim of the present article is to postulate a DLC model that is of added value to the analysis and governance of drug safety controversies from a multidimensional perspective.

PLCs and DLCs

Being the core of PLC analyses, a "product" can be defined as an act or tangible material that is the result of labor or effort [20]. PLC research demonstrated that non-durable goods (e.g., pharmaceuticals) are more applicable to study: they have shorter life periods, lower prices, more dynamic sales patterns and challenging market performances compared with durable industrial goods/products [21, 22].

Products have different aggregation levels: product-class, -form, and -brand [15, 21, 23-25]. For most drugs, these aggregation levels are exhibited in Figure 1. Product class represents drugs with similar function(s), such as the main therapeutic group (e.g., analgesics). Further subdivisions are represented according to their chemical/therapeutic/pharmacological properties (e.g., (mild) opiates, antipyretics, or antimigraine preparations) [26]. Product form refers to the available presentation or dosage form of medicines (e.g., capsule, tablet, cream, elixir, or injection). Finally, product brand is explicit and unique (e.g., Advil, Aspirin, or Tramal for analgesics) [15, 21, 23-25].

Originally, the PLC concept was established to describe the phases, dynamics, and evolution of a product during its lifetime. To this end, a unidimensional approach was used, which was depicting the sales of a product over time. In 1963 and 1967, Cox pioneered DLC research by describing the promotional strategy and market behavior of 754 different prescription drugs [15, 18]. With this unidimensional analysis of sales data, Cox demonstrated that DLCs can be studied either individually or as a group (e.g., codeine, or as analgesics-Figure 1) [18, 27].

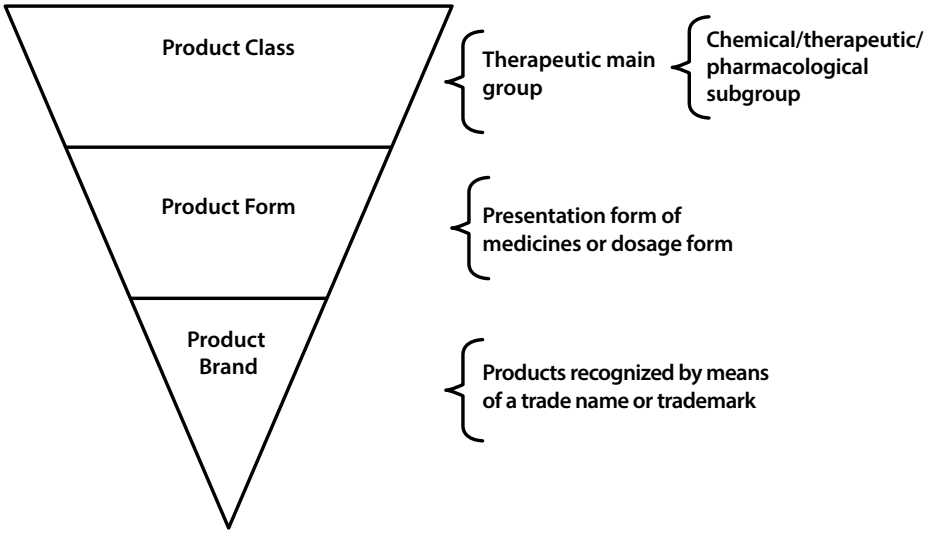

Figure 1. Product aggregation levels according to DLCs. As first, product class represents items with similar function (e.g., analgesics). Product class could be divided in subgroups indicating molecular level or pharmacological action (e.g., opiates, or antimigraine preparations). Product form indicates the presentation form (e.g., injection, tablet, capsule, or suppositories). Product brand refers to products in the market that use trademarks or trade names (e.g., Advil, Aspirin, etc.)

Phases of DLCs

A conventional DLC curve has an hyperbola shape (Figure 2A) and consists of four phases: introduction, growth, maturity and decline [16, 18, 21, 23, 24, 28, 29]. The introduction phase initiates when the drug is granted a market approval. Quite often, products may not evolve further than this stage; the competition is harsh between products and the initial sales average is relatively low [24]. During this phase, a combination of market push and demand pull is exerted [30].

The growth phase initiates when a drug is being increasingly prescribed. During this phase, the highest revenues are cashed [18]. As the product is earning acceptance, sales, production, advertising and distribution co-evolve [31]. In the 1960s, the growth phase was acknowledged when new drugs surpassed 5000 prescriptions in a month [15, 18].

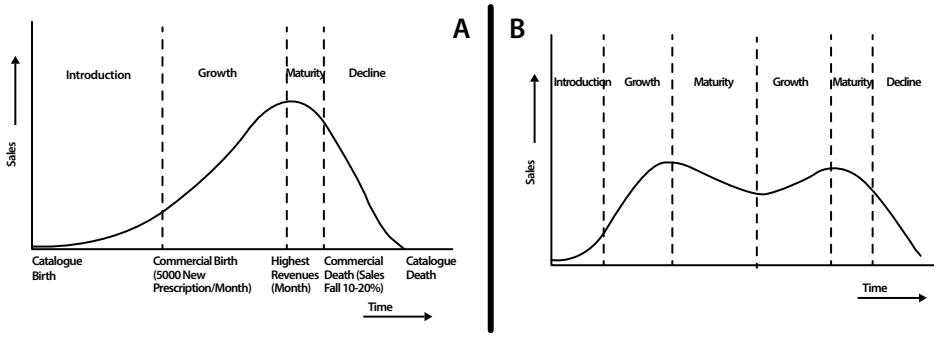

Figure 2. (A) Standard or classic PLC/DLC pattern (hyperbola): introduction, growth, maturity and decline. (B) Cycle-recycle curve: this curve comprehends a boost in the sales after the maturity phase, where the cycle of the drug is revitalized. A second growth-maturity phase will take place before market decline.

The maturity phase is defined as the lapse between the highest monthly revenue and the month where revenues drop by 20 or 10% (compared with the greatest monthly revenue) [18]. Cox reported in the 1960s that this phase may last 15 to 20 months [15, 18]. Nowadays, the maturity phase may vary from months to years, depending on factors such as drug replacement (effectiveness), marketing strategies, reimbursement, safety events, and/or market withdrawal. The maturity phase is said to provide good opportunities for product innovation and re-launch [30].

Finally, the decline phase delineates the period between the end of the maturity phase and commercial death. This phase is named after the downward sales trend that is influenced by technological advances, end-of-patent period, customer's shift in needs and preferences, and competition (improved benefit/risk profile) [21, 32].Trade activity, advertising and brand loyalty decline together with the sales.

DLC curves and types of data

Next to the hyperbola curve, 11 other different curves have been reported: cycle-recycle, cycle half-recycle, increasing and decreasing sales, high and low plateau, stable maturity,

growth maturity, innovative maturity, growth-decline plateau and rapid penetration [23, 29]. The most representative DLC curves are the hyperbola and the cycle-recycle curve (Figure 2 A and B, respectively) [15, 18, 23, 29, 33]. In the cycle-recycle curve, the impact of marketing/management (positioning) or R&D (innovation) approaches is observed, recreating a second growth and maturity phase that extends the DLC.

How have been DLCs used so far?

Mostly, sales data (in different formats) have been used to characterize the different DLC's phases (Table 1) [27, 34]. To our knowledge, no studies have brought together all the possible applications of DLCs that have been published so far. Hence, we will provide a full range of exemplary uni- and multidimensional DLC applications for the following purposes: i) to analyze migrational production patterns from domestic to foreign markets [35], ii) describe economic risk, market behavior and the consequences of timely market launch of pharmaceuticals [25], iii) investigate the regulatory evaluation and approval of biopharmaceuticals in terms of efficacy, safety and cost-effectiveness [36], or iv) evaluate the economic influence of regulatory decisions on society and pharmaceutical companies [37].

Table 1. Common types of data used in DLC/PLCs

Type of Data	Measurement Methods
Sales frequency	Daily, weekly, monthly, quarterly, annually, or continuously
Sales volume	Number of shares traded, number of goods sold, services rendered
Unit sales	Tablet, bottle, package, blister, box, number of tons, US dollars, Euro's (currency)
Per capita sales	Sales according to the number of people, per individual –the total sales is divided by the total population
Percentage change in sales from a base year	Units US dollars, Euro's – is the fraction of sales during a specified period
Advertising expenditure	US dollars, Euro's in time
Market share	Percentage or proportion of total available market or market segment – it can be calculated by revenues or unit sales

i. DLCs to analyze migrational production patterns from domestic to foreign (overseas) markets

Using aggregated export and non-trade sales data over the years, Parry demonstrated similarities amongst the DLC phases of 16 different prescription drugs [35]. These 16 drugs entered the international market through foreign production and distribution during the introduction phase. During the maturity phase, another 15 international markets were manufacturing these drugs; whilst during the growth phase their production was still inactive, demonstrating that production might move from innovative to international (mass) markets during the maturity phase. Although this application of a DLC demonstrated that the more "mature" a product is, the higher the probability that production will take place globally [35], Perry's study lacked a clear visualization of the DLC phases because sales data across the years was analyzed in an aggregated way.

ii. DLCs to describe economic risk, return on investments and the consequences of timely market launch of pharmaceuticals

Using annual sales data (in standard units), global turnovers and advertising/promotion spending over a decade (1983 - 1993 and 1987 - 1997), Bauer and Fischer's study revealed a direct association between the amount of revenues and the intensity of marketing activities for cardiovascular (CV) drugs [25]. Pioneer CV drugs (first-in-class) reached a reasonable market share 4-5 years after introduction, whereas late movers' (second- or third-in-class) market share was the same after 1-2 years. Late movers showed a sharper introduction phase, steeper and shorter maturity phase, and a more precipitous decline phase compared with early movers; the opportunities to increase profits were intensified in the late movers during the earlier phases [25]. Bauer and Fischer argued that prescribing behavior determined these either sharp or delayed growths because doctors perceived higher risks with early movers –their benefit/risk profile is unknown- and were more conservative in prescribing them. The benefit/risk profile of late movers was better comprehended and were therefore prescribed more often [25]. However, these inferences cannot be supported because detailed prescribing data were not used in this study. Also, this study did not describe the influence of controversies, regulatory or media interventions on prescribing behavior and their impact on either early or late movers.

iii. DLCs to investigate the regulatory evaluation and approval of biopharmaceuticals in terms of efficacy, safety and cost-effectiveness

Although limited in scope, DLCs have recently been used for the analysis of the behavior of pharmaceuticals within a regulatory context. In 2012, Ahmed et al. analyzed the relationship between the structural/biophysical variation and the risk/benefit profile of biosimilars as part of the DLC of biological products approved in Europe [36]. For this purpose, different types of elements were analyzed such as manufacturing processes, comparative analyses between originators and generics, and regulatory documents (i.e., registration dossiers, or evaluations of approved and rejected biopharmaceutical products published by the World Health Organization, US Food and Drug Administration (FDA), European Medicines Agency (EMA), or national regulatory agencies). The analysis of these documents was set up against time to create a qualitative DLC curve. Although this study lacked a structured and quantitative methodological framework, Ahmed et al. observed no significant clinical differences between their sample of approved biosimilars in the EU and their respective reference originator compounds. This regulatory analysis proved that biosimilars approved in the EU have comparable efficacy and safety profiles, compared with originators, but are cost-effective for health care systems and patients [36].

iv. DLCs to evaluate the economic influence of regulatory decisions on society and pharmaceutical companies

Philipson et al. analyzed the efficacy of FDA regulations prior and after the introduction of the Prescription Drug User Fee Act (PDUFA) in 1992[3] . Using sales data (in US dollars), the revenues produced by a certain drug prior and after inclusion of PDUFA were evaluated. The FDA review and withdrawal periods for new drug applications (NDAs) and biologic license

3 With the introduction of PDUFA, industrial application fees were established to fund the FDA. In return, the FDA was compelled to improve the review periods for NDAs or BLAs. PDUFA comprehends several phases: PDUFA I (1992-1997), PDUFA II (1997-2002), PDUFA III (2002-2007) and PDUFA IV (2007-present) [38. (FDA) FaDAUS. Prescription Drug User Fees 2009 [cited 2014 March 19]. Available from: http://www.fda.gov/oc/pdufa/default.htm.

applications (BLAs) were also included. After the PDUFA, the producers'- and social surplus[4] increased from US$ 7 to 11 billion and from US$14 to 31 billion, respectively. In the period 1992-1997, the sample of studied drugs (n=284) showed profits between US$25 and 39 million per drug. Although these 284 drugs were analyzed in an aggregated way, the study showed that PDUFA helped to decrease the FDA approval times with 6–7% and 3–4% during PDUFA I, and II, respectively. Subsequently, by valuing one life year at $100,000, this study concluded that a more rapid access to medicines may gain 140,000 to 310,000 saved life years [37].

Abovementioned sample of studies illustrates the manifold uses of DLCs. However, it also exposes the shortcomings of some of these uses, such as analyzing aggregated or insufficient quantitative data or non-longitudinal analyses. In the next section, we postulate the multidimensional use of DLCs as a tool for the study of drug safety controversies.

DLCs in safety controversies

Using a single type of data to analyze market patterns (unidimensional), DLCs have been used to assess the impact of safety controversies [39-41]. We propose that multidimensional DLC analyses can improve our understanding of the dynamics of drug safety controversies by analyzing different types of data all related to the same drug/controversy. These multidimensional analyses may support the characterization of factors, actors and consequences within controversies to explain how and why certain (regulatory) interventions are more effective than others. The added value of this multidimensional DLC model is that controversies are simultaneously analyzed from different/several perspectives using different types of data that are transposed/superimposed on or compared with the traditional sales or usage data to recreate real market dynamics. In Figure 3, the analytical framework of our postulated model is depicted. Importantly, data collection should be conducted on a structured and systematic manner as a prerequisite for reliable and reproducible results.

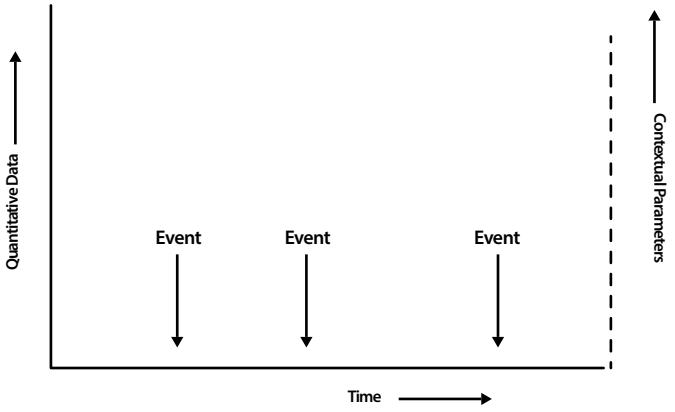

Figure 3. Structural representation of multidimensional DLC studies. The y-axis contents the analysis of quantitative data, such as sales/prescription data. The x-axis illustrates the timeline on the bottom, and the description of (singular) important events on top (e.g., market approval, or warnings). The z-axis plots additional contextual parameters or other type of data, such as amount of scientific or newspaper articles.

4 The combined social surplus is the result of the sum of both, the consumers' and producers' surplus.

In the proposed model, the y-axis consists of quantitative data, such as sales and/or prescription data that should be used to create (various) DLC curves. This quantitative data should be transposed/superimposed on or compared with other types of data that are placed on the x- and z-axis. The x-axis represents the time dimension on the bottom, whilst qualitative or contextual data (event-related, such as market approval date, media interventions, change of indication, lawsuits or regulatory warnings) could be illustrated on the top of this axis. Finally, the z-axis consists of contextual data with a quantitative nature, such as time to approval, number of approved molecules, capital investments, financial resources, twitter patterns, or publication patterns in the specialized/medical literature or in the media. For a DLC analysis of safety controversies, we deem the publication patterns dimension as important to construct DLCs because discussions and advances in the scientific arena are communicated through the specialized/medical literature. This source is influential for prescribing patterns and the development of guidelines and regulations, which in turn may affect the DLC curve. Similarly, media analyses is a relevant dimension to construct DLCs since the public understanding of risks is likely to be influenced/shaped by the media such as newspapers [42].

Using the methodology described above, we now integrate two different studies that have been conducted separately and place them on the y- and z-axis to analyze drug safety controversies as an example to demonstrate the added value of this multidimensional DLC approach. The context selected, as a drug safety controversy, was the presumed increased risk of suicidality in patients treated with one specific group of antidepressants: selective serotonin reuptake inhibitors (SSRIs). Because of this presumed suicidality risk, regulatory authorities issued warnings banning the use of SSRIs in children, adolescents, and young adults in the periods 2003-2004 and 2007-2008 [43-46]. Simultaneously, news media devoted significant attention to this controversy, portraying adverse news about the safety and efficacy of SSRIs and malpractices from pharmaceutical companies [47-49].

In an initial study, we analyzed the publication patterns in newspapers and scientific journals during the controversy and their influence on regulatory warnings [50]. A curve was constructed using articles from British and Dutch newspapers and scientific journals between 2000 and 2010. Articles were extracted from the databases, categorized by age group (i.e., pediatrics or adults) and analyzed for positive or negative messages. Scientific articles were mainly positive about the safety and efficacy of SSRIs. There was an association between the timing of the regulatory warnings and negative publications in newspapers. Negative publication patters were more prominent in pediatric populations compared with adults. There were also discrepancies in publication patterns between the Netherlands and the UK [50]. However, this analysis could not determine the impact of negative publications (regulatory warnings, newspapers or scientific publications) on SSRI use.

Adding an extra dimension to our DLC model, a longitudinal drug utilization study was performed on SSRI use. This second study aimed to ascertain whether there was an association between SSRI use and the results obtained from the publication patterns study. Using monthly SSRI sales data, several DLC curves were constructed (i.e., per individual molecule or aggregated as therapeutic group). This drug utilization study demonstrated that changes in SSRI use were associated with the timing of both periods of regulatory warnings and negative newspaper

articles. Both warning periods interrupted the growth phase of SSRIs that kept growing thereafter. This research demonstrated the usefulness of longitudinal studies using a DLC approach to assess the impact of controversies in real-life drug utilization patterns [51].

When placing the results from the study about SSRI use patterns on the y-axis against the results from the publication patterns study on the z-axis, we can observe similar dynamics in the DLC of SSRIs either as a group or per molecule, with small variations between the Netherlands and the UK (Figure 4 and 5, respectively). While the public, and herewith also SSRI users, and prescribers were exposed to a growing number of negative publications (in scientific journals and mainly in newspapers), SSRI use (as a group) kept

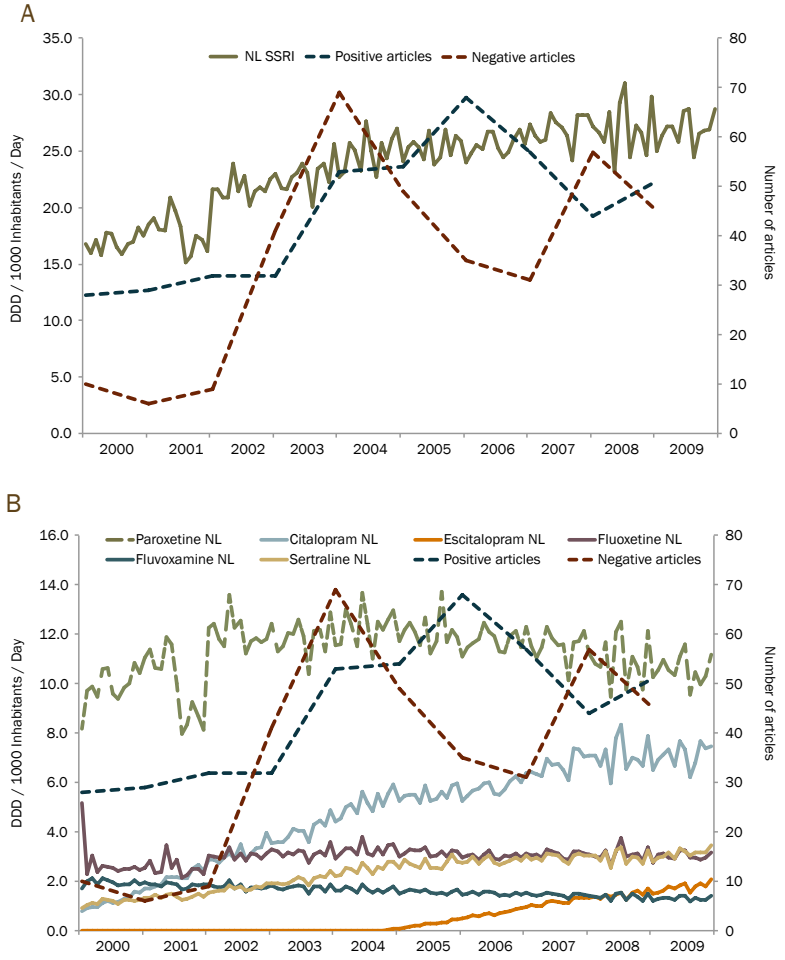

Figure 4. Multidimensional DLC model analyzing the SSRI and suicidality controversy. Figure A portrays overall SSRI use in NL, whereas Figure B portrays SSRI use per individual molecule. On the y-axis, SSRI use in NL is presented as DDD/1000 inhabitants/day. On the z-axis (3rd dimension), the number of articles (indexed in negative and positive) in newspapers and scientific journals is presented.

increasing in the NL and in the UK from 2000 to 2010 [51]. The effect of the controversy (warnings, and negative publicity) on overall SSRI use seemed negligible as their use nearly doubled during a decade and that, despite the fact that the public was confronted with the possibility of being at a plausible (suicidality) risk.

The growth phase of paroxetine (the most used SSRI) was substantially interrupted in 2002 in UK when the first controversial signs started to emerge (Figure 5b). In the NL, paroxetine gradually moved from the maturity to a decline phase after the first period of warnings and newspaper coverage in 2003-2004 (Figure 4b) [51]. In both countries, the market potential of paroxetine was significantly incapacitated under the influence of warnings and newspaper coverage. Conversely, market performance varied per individual molecule. As paroxetine use declined, other SSRIs (i.e., citalopram, escitalopram, sertraline and to a lesser extent fluoxetine) moved into a sharp growth (use) phase, revealing no clear maturity phase until 2010 (Figures 4b and 5b). But more importantly, the intended effect of the interventions from the different regulatory agencies (FDA, EMA, or the Dutch Medicines Evaluation Board-CBG/MEB) to promote a rational use of SSRIs was diluted by this general "shift" from paroxetine to another SSRI.

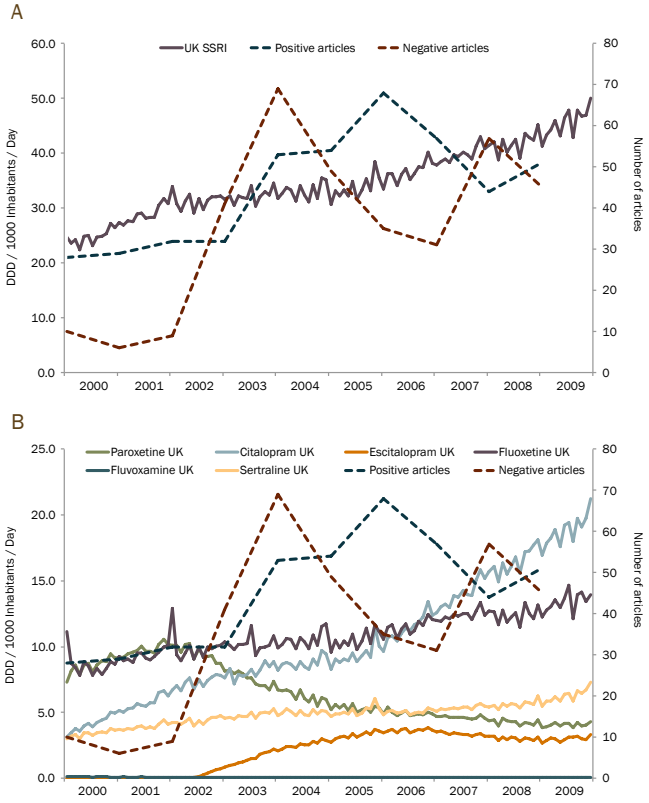

Figure 5. Multidimensional DLC model analyzing the SSRI and suicidality controversy. Figure A portrays overall SSRI use in the UK, whereas Figure B portrays SSRI use per individual molecule. On the y-axis, SSRI use in the UK is presented as DDD/1000 inhabitants/day. On the z-axis, the number of articles (indexed in negative and positive) in newspapers and scientific journals is presented.

Finally, a third dimension of qualitative nature was added to our multidimensional DLC model: public trust. In this study, the outcomes from the publication patterns study and the drug utilization study were analyzed in the context of the role of public trust during the SSRIs and suicidality controversy. With this step, we aimed to further enhance our understanding of the lack of impact of negative news on overall SSRI use [52].

To set the scene for this public-trust study, two important elements were required:

1) A detailed description of events that shaped the controversy (event-related data), and

2) A comprehensive definition of public trust for the pharmaceutical sector. Concerning the first element, event-related data were gathered manually by searching through several databases (i.e., Google, PubMed, Web of Science, Scopus, or LexisNexis), articles (newspapers and scientific), and books. Concerning the second element, public trust in the pharmaceutical sector was defined as:

- "The willingness to assume a position of vulnerability in relation to the provision of care and the management and use of medicines [52-61]; and as
- The reliance on the competence of companies, authorities, and healthcare providers to perform the tasks they are responsible for and expected to do" [52-54, 62-70].

This public-trust study demonstrated that all stakeholders (pharmaceutical companies, regulatory authorities, or doctors) were distrusted at different points during the controversy. Distrust lasted longer and was more pronounced in pharmaceutical companies compared with authorities or doctors [52]. We therefore concluded that the increasing SSRI use trend may be attributable to the fact that the public is less risk-avert than policy-makers and regulators are [52, 71, 72]. Prescribers seemed to have played a mediating role between the questioned benefit/risk profile of SSRIs, the associated sense of vulnerability of patients, and the competence of authorities in safeguarding the public and overseeing the pharmaceutical industry. Due to these multidimensional DLCs analyses with quantitative and qualitative data, the understanding of drug use and trust dynamics could be expanded within the stakeholders of the drug developing, evaluating, and prescribing system, as well as in drug users and the public. These trust dynamics indicate that, even during controversies, trust could be preserved if stakeholders emphasize and focus on their (scientific) competences. Proactive risk management and transparent communication approaches are important tools in achieving this aim, while reactive/passive approaches seem to be counter-productive [52]. Although multidimensional DLCs analyses are useful to improve our understanding of trust-dynamics and the role of stakeholders during drug safety controversies, more case studies are needed to validate the use of DLCs in other drug safety controversies and therapeutic areas.

Discussion and conclusion

Derived from PLCs, DLCs have been used to describe the lifetime phases (i.e., introduction, growth, maturity and decline), influencing factors, and market performance of

marketed drugs [18, 23]. Using mostly sales data, the usefulness of DLC has been demonstrated [16, 25, 35-37]. However, most DLC studies have been conducted using a singular type of data, resulting in unidimensional analyses susceptible to myopic interpretations. Here, we postulate a DLC model to analyze drug safety controversies in a multidimensional way. This DLC model could be constructed with several types of data in superimposed layers to produce multidimensional analyses with additional heuristic value representations.

Multiple attempts have been made to determine the impact of the SSRI and suicidality controversy on SSRI use and clinical outcomes. For instance, using SSRI prescription patterns, and linking their use to suicide rates, several studies have claimed a persistent decline in antidepressant use [39, 40, 73-77]. Most of these studies argued that the declining trend in antidepressant use might represent an increasing risk for untreated patients with depression or anxiety, while suicide rates seemed to increase [39, 73-76]. Two other studies analyzed the impact of media coverage on public perceptions and on SSRI use [78, 79]. Firstly, Martin et al. analyzed SSRI use in relation to the number of yellow-card (self-reporting adverse events by patients or other caregiver) reports in the UK. They demonstrated that after the period of adverse media coverage the number of yellow card reports about paroxetine seemed to increase while SSRI use decreased [78]. Secondly, Medawar et al. analyzed 1374 emails sent to the BBC after broadcasting "The Secrets of Seroxat" (Panorama-2002), a documentary about the safety of SSRIs, in particular paroxetine. This second study reported that most emails contained information about patients reporting withdrawal symptoms and experiences of distress concerning the reports about the questionable benefit/risk profile of antidepressants. These reports seemed to have been exacerbated after the transmission of the BBC-documentary [79].

Altogether, abovementioned studies enriched our knowledge about the controversy, its effect on SSRI use, and on society. However, although antidepressant use was analyzed together with other types of data, such as suicide rates, adverse events records, or public e-mails, these studies were unable to reveal a comprehensive insight into the dynamics of public trust during the SSRI and suicidality controversy and its influence on drug use. We observed that all these other data types had, eventually, a limited and transitory predictive/heuristic power concerning the real extent of the SSRI and suicidality controversy in society as they reported a drop in use. In contrast, our multidimensional DLC analysis not only demonstrated that the warnings had a negligible effect (as SSRI use kept increasing) but further enhanced our understanding of the potential explanation(s) for this observation because of the different types and combinations of data that were used to build the model (i.e., publications patterns, SSRI use and trust).

Multidimensional DLC analyses also have their limitations. Comprehensive and powerful predictive analyses are largely determined by the quality of the data (qualitative and quantitative). On the one hand, gathering qualitative data is a manual process that should be done exhaustively and thoroughly to draw a reliable event-related scenario. This step is bound to human error as important events could be omitted. Future research should focus on exploring possibilities to gather qualitative data automatically. On the other hand, while quantitative data could be automatically gathered (for the greatest part using databases

for instance for medical, prescribing or wholesale records), the completeness of this data can not always be guaranteed due to factors such as stockpiling, double-records or missing-records over time. Statistical approaches could be used to circumvent this disadvantage or limit its impact on the quality of the data and thereby of DLC analyses.

Conclusion

The construction of a DLC curve that makes use of differentiated data types may provide a more thorough understanding of the embedding process of pharmaceuticals in medicine and in society. Multidimensional DLC analyses may result in novel insights on how and why certain regulatory interventions may be more or less effective than others. The advantage of a multidimensional DLC analysis above a single/unidimensional DLC analysis is that the market behavior of pharmaceuticals can be displayed from different perspectives/dimensions and in a more comprehensive and realistic way. Whereas a single DLC analysis may reveal (or not) significant changes, multidimensional DLC analysis could further explain the reasons behind those changes, their consequences, and the role of stakeholders. Therefore, selecting the best/most predictive type of data (proxy parameters) to perform DLC studies is paramount to maximize the use of this proposed model. In essence, the functionality of these proxy parameters and thereby usefulness of multidimensional DLC analyses is largely determined by the quality and completeness of the data that is analyzed (i.e., publications patterns and antidepressant use), in combination with the selection of qualitative or contextual data (i.e., event-related data, regulatory warnings, and public trust). With the introduction and progression of new digital tools and databases, such as The Newsreader Project from the European Union (i.e., news or event-related data) [80], that increasingly allows the use of quantifiable information, the added value of a multidimensional DLCs analysis as a tool for decision making could be further explored.

References

1. Abraham J, Davis C. Drug Evaluation and the Permissive Principle: Continuities and Contradictions between Standards and Practices in Antidepressant Regulation. Social Studies of Science. 2009 Aug;39(4):569-98.
2. Edwards B, Olsen AK, Whalen MD, Gold MJ. Guiding principles of safety as a basis for developing a pharmaceutical safety culture. Curr Drug Saf. 2007 May;2(2):135-9.
3. Lofstedt R, Bouder F, Wardman J, Chakraborty S. The changing nature of communication and regulation of risk in Europe. Journal of Risk Research. 2011;14(4):409-29.
4. Olsen AK, Whalen MD. Public perceptions of the pharmaceutical industry and drug safety: implications for the pharmacovigilance professional and the culture of safety. Drug Saf. 2009;32(10):805-10.
5. Wilson Le BDSJM. Fungal meningitis from injection of contaminated steroids: A compounding problem. JAMA. 2012;308(23):2461-2.
6. Bauchner H FPB. Restoring confidence in the pharmaceutical industry. JAMA. 2013;309(6):607-9.
7. Ameer B. Novel trial design: a report from the 19th frontiers symposium of ACCP. J Clin Pharmacol. 2008 Jul;48(7):793-8.
8. Take a stand. Nature. 2012 Jul 12;487(7406):139-40.
9. Outterson K. Punishing Health Care Fraud — Is the GSK Settlement Sufficient? New England Journal of Medicine. 2012;367(12):1082-5.
10. BBC. GlaxoSmithKline agrees $3bn US settlement London: BBC; 2011 [cited 2014 March 19]. Available from: http://www.bbc.co.uk/news/business-15569656.
11. NYTimes. Glaxo agrees to pay $3 billion in fraud settlement New York: NYTimes; 2012 [cited 2014 March 19]. Available from: http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html?pagewanted=all&_r=0.
12. McLaughlin T. FDA took 684 days to warn meningitis-linked firm: files Boston, MA: Reuters; 2012 [cited 2013 January 15]. Available from: http://www.reuters.com/article/2012/11/21/us-usa-health-meningitis-fda-idUSBRE8AK0T520121121.
13. Outterson K. Regulating Compounding Pharmacies after NECC. New England Journal of Medicine. 2012;367(21):1969-72.
14. Pollack A, Tavernise S. Oversight Failures Documented in Meningitis Outbreak New York, NY: New York Times; 2012 [cited 2013 January 15]. Available from: http://www.nytimes.com/2012/11/22/health/documents-show-fdas-failures-in-meningitis-outbreak.html?_r=0.
15. Cox WEJ. Product Life Cycles and Promotional Strategy in the Ethical Drug Industry: University of Michigan; 1963.
16. Levitt T. Exploit the Product Life Cycle. Harvard Business Review. 1965;43(6):81-94.
17. Brockhoff K. A Test for the Product Life Cycle. Econometrica. 1967;35(3-4):472-84.
18. Cox WEJ. Product Life cycles as Marketing Models. The Journal Of Business. 1967;40(4):375-84.
19. Norris G. Social Impacts in Product Life Cycles: Towards Life Cycle Attribute Assessment. International Journal of Life Cycle Assessment. 2006;11(1):97-104.

20. Kotler P, Armstrong, G., Brown, L., and Adam,S. Marketing. 7th ed: Pearson Education Australia/Prentice Hall; 2006.
21. Day GS. The Product Life Cycle: Analysis and Applications Issues. Journal Of Marketing. 1981;45(4):60-7.
22. Buzzell R, and Cook, Victor. Product Life Cycles. Cambridge: Marketing Science Institute; 1969.
23. Rink DR. Product Life Cycle research: a Literature Overview. journal Of Business Research. 1979;7(3):219-42.
24. Polli R, Cook, V. Validity of the Product Life Cycle. The Journal Of Business. 1969;42(4):385-400.
25. Bauer HHF, M. . Product life cycle patterns for pharmaceuticals and their impact on R&D profitability of late mover products. International business review. 2000;9(6):703-25.
26. WHO. ATC/DDD Index 2011 Geneva: WHO; [cited 2014 March 19]. Available from: http://www.whocc.no/atc_ddd_index/.
27. Evans JR. Product Life Cycles in the Automobile, Food, and Proprietary Drug Industries: Evolution, Description, and Analysis. 18, editor. New York: Hofstra University Yearbook of Business; 1983. 283 p.
28. Thorelli HB. The Nature of Product Life Cycles for Industrial Goods Business. Journal Of Marketing. 1981;45(4):97.
29. Cao H, Folan P. Product life cycle: the evolution of a paradigm and literature review from 1950-2009. Production Planning & Control. 2012;23(8):641-62.
30. Hofer CW. Toward a Contingency Theory of Business Strategy. The Academy of Management Journal. 1975;18(4):784-810.
31. Staudt TA, Taylor, D.A., Bowersox, D.J. A Managerial Introduction to Marketing. 3rd ed. Englewood Cliffs, N.J.: Prentice-Hall; 1976.
32. Barksdale HC, Harris CE. Portfolio analysis and the product life cycle. Long Range Planning. 1982;15(6):74-83.
33. Hinkle J. Life Cycles. New York: Nielsen; 1966.
34. Clifford D. Managing The Product Life Cycle. European Business Journal. 1969 July
35. Parry TG. The Product Life cycle and International Production: U.K. Pharmaceuticals. The Journal of Industrial Economics. 1975;24(1):21-8.
36. Ahmed I, Kaspar B, Sharma U. Biosimilars: Impact of Biologic Product Life Cycle and European Experience on the Regulatory Trajectory in the United States. Clinical Therapeutics. 2012;34(2):400-19.
37. Philipson T, Berndt ER, Gottschalk AHB, Sun E. Cost-benefit analysis of the FDA: The case of the prescription drug user fee acts. Journal of Public Economics. 2008;92(5-6):1306-25.
38. (FDA) FaDAUS. Prescription Drug User Fees 2009 [cited 2014 March 19]. Available from: http://www.fda.gov/oc/pdufa/default.htm.
39. Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry. 2007 Jun;164(6):884-91.
40. Olfson M, Marcus SC, Druss BG. Effects of Food and Drug Administration warn-

ings on antidepressant use in a national sample. Arch Gen Psychiatry. 2008 Jan;65(1):94-101.
41. Stolk P. From New Molecules to Leads for Innovations. Utrecht: Utrecht University; 2008.
42. Rowe G, Frewer L, Sjoberg L. Newspaper reporting of hazards in the UK and Sweden. Public Understanding of Science. 2000 January 1, 2000;9(1):59-78.
43. EMA. European Medicines Agency finalises review of antidepressants in children and adolescents London: EMA; 2005 [cited 2014 March 19]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/12/news_detail_000882.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1.
44. FDA. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications Rockville, MD: Department of Health and Human Services; 2004 [cited 2014 March 19]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm.
45. FDA. Antidepressant Use in Children, Adolescents, and Adults Rockville, MD: Department of Health and Human Services; 2007 [cited 2014 March 19]. Available from: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm.
46. MHRA. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. London: Committee on Safety of Medicines, 2004.
47. BBC. Panorama: The Secrets of Seroxat London: BBC; 2002 [cited 2014 March 19]. Documentary]. Available from: http://news.bbc.co.uk/panorama/hi/front_page/newsid_8425000/8425414.stm.
48. BBC. GlaxoSmithKline agrees $3bn US settlement London: BBC; 2011 [cited 2012 March 7]. Available from: http://www.bbc.co.uk/news/business-15569656.
49. NYTimes. Glaxo agrees to pay $3 billion in fraud settlement New York: NYTimes; 2012 [cited 2013 March 20]. Available from: http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html?pagewanted=all&_r=0.
50. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, Belitser SV, Raaijmakers JAM, Pieters T. Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study. BMJ Open. 2011 January 1, 2011;1(2).
51. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, Belitser SV, Warmerdam J, de Valk V, et al. A 10-Year Analysis of the Effects of Media Coverage of Regulatory Warnings on Antidepressant Use in The Netherlands and UK. Plos One. 2012;7(9):e45515.
52. Hernandez JF, van Thiel GJMW, Mantel-Teeuwisse AK, Raaijmakers JAM, Pieters T. Restoring trust in the pharmaceutical sector on the basis of the SSRI case. Drug Discovery Today. 2013 (0).
53. Hall MA, Camacho F, Dugan E, Balkrishnan R. Trust in the medical profession: Conceptual and measurement issues. Health Services Research. 2002 Oct;37(5):1419-39.
54. Hall MA, Dugan E, Zheng BY, Mishra AK. Trust in physicians and medical institu-

tions: What is it, can it be measured, and does it matter? Milbank Quarterly. 2001 2001;79(4):613-+.
55. Baier A. TRUST AND ANTITRUST. Ethics. 1986 Jan;96(2):231-60.
56. Church R. Trust, Burroughs Wellcome & Co. and the foundation of a modern pharmaceutical industry in Britain, 1880-1914. Business History. 2006 Jul;48(3):376-98.
57. Holton R. DECIDING TO TRUST, COMING TO BELIEVE. Australasian Journal of Philosophy. 1994 Mar;72(1):63-76.
58. Michalos AC. THE IMPACT OF TRUST ON BUSINESS, INTERNATIONAL SECURITY AND THE QUALITY OF LIFE. Journal of Business Ethics. 1990 Aug;9(8):619-38.
59. Mullarkey M, Duffy A, Timmins F. Trust between nursing management and staff in critical care: a literature review. Nurs Crit Care. 2011 Mar-Apr;16(2):85-91.
60. Muller T. Semantics of Trust. In: Degano PESGJ, editor. Formal Aspects of Security and Trust. Lecture Notes in Computer Science. 65612011. p. 141-56.
61. Welter F. All you need is trust? A critical review of the trust and entrepreneurship literature. International Small Business Journal. 2012 May;30(3):193-212.
62. Burke CS, Sims DE, Lazzara EH, Salas E. Trust in leadership: A multi-level review and integration. Leadership Quarterly. 2007 Dec;18(6):606-32.
63. Connell NA, Mannion R. Conceptualisations of trust in the organisational literature: some indicators from a complementary perspective. J Health Organ Manag. 2006;20(5):417-33.
64. Goold SD. Trust and the ethics of health care institutions. Hastings Center Report. 2001 Nov-Dec;31(6):26-33.
65. Hupcey JE, Miller J. Community dwelling adults' perception of interpersonal trust vs. trust in health care providers. J Clin Nurs. 2006 Sep;15(9):1132-9.
66. Hupcey JE, Penrod J, Morse JM, Mitcham C. An exploration and advancement of the concept of trust. Journal of Advanced Nursing. 2001 Oct;36(2):282-93.
67. Murphy JT. Building trust in economic space. Progress in Human Geography. 2006 Aug;30(4):427-50.
68. Smith C. Understanding trust and confidence: two paradigms and their significance for health and social care. J Appl Philos. 2005;22(3):299-316.
69. Wang YD, Emurian HH. An overview of online trust: Concepts, elements, and implications. Computers in Human Behavior. 2005 Jan;21(1):105-25.
70. Whitley R, McKenzie K. Social capital and psychiatry: Review of the literature. Harvard Review of Psychiatry. 2005 Mar-Apr;13(2):71-84.
71. Slovic P. Perception of risk. Science. 1987 April 17, 1987;236(4799):280-5.
72. Slovic P. Perceived risk, trust, and democracy. Risk Analysis. 1993;13(6):675-82.
73. Busch SH, Barry CL. Pediatric antidepressant use after the black-box warning. Health Aff (Millwood). 2009 May-Jun;28(3):724-33.
74. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry. 2007 Sep;164(9):1356-63.
75. Gibbons RD, Brown CH, Mann JJ. SSRI prescribing rates and adolescent suicide: Is the black box hurting or helping? Psychiatric Times. 2007;24(12):33-7.
76. Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment after FDA

warnings. Arch Gen Psychiatry. 2009 Jun;66(6):633-9.
77. Ludwig J, Marcotte DE. Anti-depressants, suicide, and drug regulation. Journal of policy analysis and management : [the journal of the Association for Public Policy Analysis and Management]. 2005;24(2):249-72.
78. Martin RM, May M, Gunnell D. Did intense adverse media publicity impact on prescribing of paroxetine and the notification of suspected adverse drug reactions? Analysis of routine databases, 2001-2004. Br J Clin Pharmacol. 2006 Feb;61(2):224-8.
79. Medawar C, Herxheimer A, Bell A, Jofre S. Paroxetine, Panorama and user reporting of ADRs: Consumer intelligence matters in clinical practice and post-marketing drug surveillance. International Journal of Risk and Safety in Medicine. 2002;15(4/3):161-9.
80. EU. Newsreader project EU 2013 [cited 2014 14 October]. Available from: http://www.newsreader-project.eu/publications/papers/.

CHAPTER

8

General discussion

Introduction

Developing and marketing new medicines is risky business. The rate of success for marketing a new drug is very low (approximately 20%) and the costs are significantly high (approximately US$1 billion) [1]. As a result of the 2004 WHO Priority Medicines report [2], several stakeholders have proposed to rethink the drug regulatory system, shorten the drug development and evaluation process, or institutionalize public-private partnerships (PPP). In the Netherlands, in 2006, the government created TI Pharma (a PPP) in cooperation with the pharmaceutical industry and academia [3]. The Escher Project was an initiative within TI Pharma developed in 2007 to search for innovative solutions by "studying medicine development and the European regulatory system for medicines" [4]. In reference to the themes "scientific dialogue and stakeholder interaction" and "health technology assessment and evaluation of societal impact", this thesis presents the studies we have conducted to analyze drug safety controversies as a sum of events that may influence/(re-)shape drug regulation. Using drug life cycles (DLC) as a heuristic tool, we analyzed one drug safety controversy (SSRI and suicidality), the role of various stakeholders (i.e., pharmaceutical companies, regulatory authorities, and doctors) during this controversy, and the controversy's impact on public trust.

Why should we study drug safety controversies? Drug safety controversies have a marked impact on society since they influence public perception towards the institutes and stakeholders that develop, evaluate, market and prescribe medicines (i.e., pharmaceutical companies, regulatory authorities and doctors). Many have argued that public trust in these stakeholders has been compromised as a result of controversies [5-8]; however, no one has specified what they meant by "trust". Nor have they have tried to explain why trust is compromised during drug safety controversies using a well-defined (quantitative) analytical framework.

In **chapter 1,** we explained that studies about drug safety controversies have overlooked the life-cycle dynamics that underlie public perceptions, expectations and drug use in a longitudinal manner. Hitherto, analyses of drug safety controversies and stakeholders' roles in (re-)shaping trust have been anecdotal, incomplete or superficial due to insufficient qualitative and quantitative methodologies [7]. In this thesis, both aspects of life-cycle dynamics (public trust and drug use) have been integrated in well-structured combinations of qualitative and quantitative analyses using DLC.

Before analyzing the SSRI and suicidality controversy in the period 1999 - 2009 and the role of public trust using DLC, we encountered two significant hurdles. First, public trust in the pharmaceutical sector has not been defined in the literature. Although many authors have mentioned an erosion of public trust in the pharmaceutical sector [5-8], we cannot assume that they all refer to the same concept or perception. The second hurdle was the evidence for claims of an erosion of public trust. These two issues were addressed in chapters 2 and 3, respectively.

What does trust mean in the pharmaceutical sector?

To address the concept of trust, in chapter 2, we defined trust in pharmaceutical companies, regulatory authorities and doctors as:

1.The willingness to accept or assume a position of vulnerability in relation to the provision of care and the management and use of medicines, and

2. The reliance on or belief in the competence of pharmaceutical companies, regulatory authorities, and healthcare providers to perform the task they are responsible for and expected to do—developing, making and evaluating high quality pharmaceutical products for public use and providing adequate healthcare.

When a patient is ill and needs medical care, they are in a position of vulnerability. If the patient is untreated, their condition may worsen and become life-threatening. A patient's trust in their physician's ability to manage their illness is important. If a physician is incompetent, the patient's sense of risk and vulnerability is increased [9, 10].

We can assume that there are occasions when a patient's trust has been undermined because a healthcare stakeholder has demonstrated incompetent or unethical behavior, resulting in patients and the public having an unnecessary exposure to risk. However, in chapter 3, we observed that although there is a history of research on trust in doctors, research on trust in pharmaceutical companies and regulatory authorities was extraordinarily scarce. More importantly, we observed that most of these studies on trust (either in pharmaceutical companies, or regulatory authorities or in doctors) lacked a robust methodology to analyze trust.

Methodologies of studies measuring trust

The most salient methodological disadvantages of overall empirical studies about trust in studies we reviewed were:

- The lack of a definition of trust
- The absence of (a methodological) standardization, and
- The varying and sometimes quite low response rates or participation rates.

If participants or researchers do not define trust, then how can it be measured? Trust can be confused with a multitude of characteristics (synonyms), such as mutuality, empathy, reciprocity, respect, solidarity, confidence or fraternity; even behavior can reflect trust [11]. Having a conceptual definition of trust guarantees empirical precision and methodological robustness. It also helps to discern between the participants' objective/subjective responses in relation to attitudes about trust [12].

The use of various instruments and/or open-ended questionnaires was another methodological disadvantage identified in the trust studies we reviewed. In particular, the use of open-ended questions is controversial because it allows for personal interpretations

that can fluctuate depending on the type of participant (e.g., public or patient), personal needs, age, cultural background, or feelings [13]. Personal interpretations of trust may introduce bias in trust measurements by increasing the influence of a patient's subjectivity and thereby affecting the validity of the results [13].

All in all, these methodological disadvantages impede the comparison of studies and trust outcomes in a sophisticated analysis, such as a meta-analysis. Even more problematic was our finding that public trust was not the main topic of research or outcome in our sample of academic studies on trust in pharmaceutical companies, regulatory authorities and, to a lesser extent, in doctors. Therefore, we consider that the studies' quality and representativeness—in terms of measurements and outcomes—may not be reliable for drawing conclusions about the state of trust in pharmaceutical companies and regulators.

What is the state of trust?

Pharmaceutical companies and regulators

Most empirical studies of trust in pharmaceutical companies and regulatory authorities demonstrated low levels of trust. The reasons for distrust in these stakeholders were multiple perceptions of vulnerability and competency, such as:

- Profits prioritized over the needs of patients and the public
- Lack of transparency, integrity or honesty
- Lack of societal recognition (in particular of European regulatory authorities)
- Excessive regulation
- The increasing costs of health care and medicines
- A possible political agenda

On the other hand, the findings in the studies we reviewed also noted that pharmaceutical companies and regulatory authorities seemed to be trusted because they were considered to be adequately competent to develop, manufacture and oversee drugs.

Trust in doctors

We observed that according to the literature, most doctors were considered trustworthy. Those who prioritized their patients' needs and were honest, caring, respectful, supportive, communicative and technically skilled were highly trusted. Doctors who were less trusted displayed inappropriate or unethical behavior towards their patients such as being judgmental, discriminatory, condescending, dishonest or impatient [14-19].

Are doctors distrusted when they have connections to the pharmaceutical industry? While academic studies demonstrated that this type of relationship damages public trust, polls reported that the relationship is irrelevant as long as patients and the public receive better treatments. Nevertheless, we observed that having high levels of trust in doctors,

regardless of connections to the pharmaceutical industry, was beneficial for patients in term of diagnoses, therapies, adherence and outcomes [20-22].

Having reviewed studies on the public's trust in the pharmaceutical industry and physicians, we used DLC as a heuristic tool to analyze drug safety controversies, and the role of stakeholders and public trust. Our DLC model made use of several types of data (dimensions) in superimposed layers to produce multidimensional analyses in the context of the SSRI and suicidality controversy. These dimensions were:

1. Publication patterns in scientific journals and Dutch (NL) and British (UK) newspapers (**chapter 4**)
2. SSRI use patterns in the NL and the UK (**chapter 5**), and
3. Event-related data – including two important elements:
   a. A detailed description of the events that shaped the controversy (**chapter 1**), and
   b. A comprehensive definition of public trust for the pharmaceutical sector (**chapter 2**)

DLC as a heuristic tool to analyze drug safety controversies

Publication patterns in scientific journals and newspapers

In **chapter 4**, we presented the first dimension/parameter that was used to build our DLC model: an analysis of publication patterns in scientific journals compared to the long-term dynamics of "good" and "bad" news in UK and NL newspapers in the context of the SSRIs and suicidality controversy between 2000 and 2010.

Most scientific publications we reviewed reported on the positive therapeutic effect of SSRIs for depression, mainly in adults. During the regulatory warning periods (2003 and 2007), this trend became less positive, but then recovered thereafter. In contrast, newspaper articles during the same time were mainly negative about the use of SSRIs, and argued for an association between their use and an increased suicidality risk. So, the dissemination of scientific knowledge to the public by the newspapers was inconsistent with scientific sources. This negative reporting trend in newspapers was comparable in both the NL and UK despite the tabloid and sensationalist culture in the British media. Newspapers in both countries informed the public about the SSRI and suicidality controversy in a timely fashion.

What was the influence of publication patterns in scientific journals and newspapers and regulatory warnings on SSRI use?

When we added a second dimension/parameter to our DLC model (sales and prescription patterns of SSRIs - **chapter 5**), we observed that changes in SSRI use coincided with the regulatory warnings periods. No significant reductions were observed in SSRI use in NL and the UK despite the restrictions issued from the health authorities and/or an increasing number of (negative) articles. Instead, SSRI use showed a twofold increase over a 10-year period.

Regarding individual SSRI use, paroxetine use markedly dropped before the first warning period (pre-2003) in the UK. In the NL, paroxetine use decreased only for young

patients during this time period, whereas its use by the elderly continued to increase. Although paroxetine use in the NL decreased, the use of other SSRIs (i.e., citalopram, escitalopram or sertraline) increased, which compensated for the reductions in paroxetine use. This explains the constant increase in overall SSRI use that was observed in both countries (2000-2010) with paroxetine as the most used SSRI in the NL and fluoxetine in the UK.

What was the role of trust during the SSRI and suicidality controversy?

In **chapter 6**, we added the event-related dimension/parameter to our DLC model to analyze the role of trust during this controversy. Public trust in all stakeholders fluctuated, and although it was temporal for doctors and regulatory authorities, distrust appeared to be more persistent for pharmaceutical companies.

Regulatory authorities acted upon the increased suicidality risk due to SSRI use by holding public hearings, evaluating SSRI safety and efficacy, and issuing warnings to ban SSRI use in young people [23-28]. However, these actions only took place after the media started to report on SSRI risks and unethical practices within the industry, which reflected the passive/reactive role of the regulatory authorities that did not contribute to alleviation of the vulnerability of patients [7, 29, 30]. Political interests delayed the US FDA's release of SSRI trial results, which resulted in Congressional investigations, media attention, and ultimately revealed the regulatory authorities' incompetent behavior to the public [31, 32].

Negative media reports affected the pharmaceutical industry's reputation, creating suspicion and distrust. These reports exposed the industry's incompetent behavior since they were unable to guarantee the safety and efficacy of their products (in this case SSRIs). However, recent lawsuit settlements indicate that pharmaceutical companies are willing to assume public responsibility and change their actions to repair and reestablish their trusted reputation in society, as part of restoring public trust based on their professional competence [12, 33, 34].

In **chapter 6**, we demonstrated the role of vulnerability and competence in public trust through a practical analysis of the SSRI and suicidality controversy reported in chapters 4 and 5. The information presented in chapter 6 provides the empirical evidence to support our definition of public trust presented in chapter 2. More importantly, using the DLC as a heuristic tool to analyze drug safety controversies proved to be successful as shown by the results described in **chapter 7**.

What is the significance of the use of DLC as a heuristic tool to analyze controversies compared to other data analysis techniques?

The combined use of quantitative and qualitative data in our DLC model with a longitudinal approach, allowed us to demonstrate that multidimensional analyses provide a more comprehensive view of the dynamics of drug safety controversies when compared to short-term analyses. Short-term analyses only provided a snapshot of the potential implications of these controversies, mainly reporting a drop in SSRI use. In reality, patients continued to use antidepressants and to trust these stakeholders after hearing about the bad news about antidepressants and dishonest/unethical corporate behavior.

As for the role of trust and stakeholders (chapter 6), we showed that public trust could be preserved if the pharmaceutical industry, regulatory authorities and doctors emphasize and focus on their (scientific) competency, even during periods of controversy. Doctors played a mediating role between the pharmaceutical industry, regulatory authorities, and the public, counterbalancing the potential risks and the levels of distrust in these stakeholders [12, 35-37] during the SSRI and suicidality risk controversy. The face-to-face nature of the patient-doctor relationship could explain the trusted role of doctors as gatekeepers for the healthcare system and their role as a buffer between patients' vulnerability and the latent risks of interrupting SSRI therapy [35, 38, 39].

DLC and drug safety controversies: insightful management beyond prevention

Throughout this thesis, we demonstrated the significance of innovative and multidimensional studies on drug safety controversies to expand on their underlying dynamics, the role of stakeholders and efficacy of regulatory interventions.

Our multidimensional DLC model not only demonstrated that the warnings had a negligible effect on SSRI use which continued to rise, but the model further enhanced our understanding of the potential explanation(s) for this observation (e.g., while paroxetine use dropped, the use of other SSRIs increased, or the apparent mediating role of prescribers during the controversy). Also, the role of stakeholders was described. This evidence was achieved because of the various types and combinations of data that were used in our DLC model.

Limitations of DLC

Analyzing DLC's is a well-structured and robust methodological approach for measuring the impact of drug controversies like the SSRI and risk for suicidality. During the process, however, we observed that the DLC approach could also have limitations. The usefulness of DLC largely depends on the quality, quantity and nature of the data. Poor data collection results in an incomplete and partial analysis of a drug or controversy, and a low-quality assessment. For instance, the use of aggregated, insufficient quantitative, incomplete, or short-term data may compromise the representativeness of the model.

Careful attention should be given to the selection of both quantitative and qualitative types of data (predictive or explanatory value) to maximize the heuristic value of DLC. Adequate data collection is also a prerequisite for the construction of DLC. To discern between various dynamics related to multiple products and obtain reliable and reproducible analyses, data collection and DLC construction should include the following aspects:

- Structured and systematic data collection, preferably using multiple data sources (digital databases)
- Longitudinal data collection (preferably several years)
- Similar products/drugs on the market (do not limit data collection to the product/drug in question, but include similar products/drugs)

- Include qualitative data (event-related), such as market approval dates, media interventions, changes of indications, lawsuits or regulatory warnings

In our model, we used publication patterns as a source of quantitative data. The use of LexisNexis (a digital database provider of legal, government, business and high-tech information sources) is advantageous for this because it enables data collection in a systematic and longitudinal fashion. The selection of keywords to identify articles relevant to the research question and controversy is an important step to optimize the functionality and usefulness of digital databases. Other quantitative data that can be used are: sales or prescription data linked to frequency (daily, weekly, quarterly, annually or continuously), volume (number of shares traded, number of goods sold, services rendered) or units (tablet, bottle, package, blister, box, tons, or currency, among many others).

The role of trust and stakeholders

Trust plays an important role in the interface between drug development, evaluation and use. It enables cooperation, provides sufficient ground for innovation to flourish and facilitates knowledge dissemination amongst stakeholders and the public [40]. For the stakeholders of drug development, regulation and use, we observed that trust is built on two important components: vulnerability and competence. The actions of pharmaceutical companies, regulatory authorities or doctors that call into question the competence of these groups and exacerbate patients' vulnerability may certainly harm the public's trust. Having a hidden political agenda or excessive regulatory environments can suffocate the public's trust and may represent a risk to patients [41, 42] as shown in chapter 3. Regulatory authorities and the industry should create more cooperative and transparent environments motivated by trust rather than increasing the number of regulations, which may increase the costs of drugs [43] and hamper innovation.

European regulatory authorities should also increase their profile to be recognized in society and communicate with the public through various channels (chapter 3), since the public cannot trust what does not know. As public representatives, regulatory authorities should educate the public about their societal role. Enabling bilateral communication processes between the public and regulators could avoid or limit "information vacuums" or "media interventions", such as controversial documentaries, interviews or reportages that may exacerbate a certain situation. "Information vacuums" and unbalanced media interventions have been shown to distort the communication process between regulators and society and damage public trust [6, 44, 45]. Proactive risk management and transparent communication approaches on the part of the regulatory authorities are important tools for this purpose, while reactive/passive approaches seem to be counter-productive as reported in chapter 6 [46]. Future risk management proposals should promote transparent and bilateral risk communication (especially during controversies) among all stakeholders of the pharmaceutical sector. The mentality of "working in silos" should be abolished if trust is to be restored. In this respect, within the Escher Project, the role and importance of scientific advice was analyzed as part of the marketing authorization of new medicines in the EU. This research highlighted

that there is room for improvement in terms of the utilization of scientific advice by pharmaceutical companies, regardless their size (i.e., big pharma or small companies), and also about the scientific competence of regulators when providing guidance [47].

Pharmaceutical companies and regulatory authorities should substantiate and reinforce public trust based on their societal commitment and ethical and scientific competence [48, 49]; this is a part of the public's trust they can build on. We demonstrated in this thesis (chapters 2, 3, and 6) that the public and patients negotiate or compensate for their vulnerability by focusing on the competencies of these institutions and the same applies for doctors [46]. Shared values can create or increase trust levels [50]; therefore, pharmaceutical companies, regulatory authorities and doctors ought to develop novel, more cooperative and stronger strategies to highlight their competencies, shared values and motivations. This could be an important initial step towards restoring public trust in the pharmaceutical sector.

Future perspectives

A better understanding of the dynamics of drug safety controversies, and how public trust in pharmaceutical companies, regulatory authorities and doctors is mediated, is necessary to create a more sustainable, cooperative and innovative drug development and evaluation system. Further research should focus on ways to stimulate and strengthen the collaboration among these stakeholders, including the public, in light of possible future risk events. However, there is an urgent need for additional well-structured studies on public trust in these stakeholders. Future methodologically robust studies about public trust should address the following prerequisites:

1. Provide a pre-specified definition of public trust (not a random one)
2. Use pre-specified questionnaires with answer scales (instruments), based on a pre-specified definition
3. Set-up trust as the main research objective, not as a secondary aim
4. Measure the vulnerability and competence components in these instruments, as well as other secondary components, such as fidelity, honesty, etc.
5. Analyze the process of the dissemination of knowledge in other media channels (e.g., television, social media, radio, magazines, or Internet) during drug controversies.

Concerning point number 5, the systematic analysis of these sources may be methodologically challenging because the level and type of information may fluctuate in time, information may disappear and be unreliable (misinformation). With the introduction and improvement of new digital tools and databases such as The Newsreader Project from the European Union (i.e., news or event-related data) [51] that increasingly allow for the use of quantifiable information, the significance of multidimensional DLC analysis could be further explored as a tool for decision making. Furthermore, these types of databases represent an attractive analytical platform to conduct case studies and validate the use of DLC in other drug safety controversies and therapeutic areas.

If we understand how trust is mediated and we know the levels of public trust in these stakeholders, we can influence and anticipate situations that may be detrimental to trust. Active public involvement is an essential requirement to limit damages to trust and may repair it; this may strengthen coherence in the pharmaceutical sector. Patients can benefit from high trust levels in terms of treatment and outcomes; regulatory authorities can enjoy more public support when deciding on issues of public interests; and pharmaceutical companies can benefit in terms of public recognition, support, social coherence, and economic reward. Understanding and creating a culture of trust between the pharmaceutical industry and regulatory authorities is essential for innovation, collaboration, and drug safety, and can also help to lower the burden of excessive regulations that have a direct impact on health care costs.

Concluding remarks

Drug safety controversies have a profound impact on the image and reputation of pharmaceutical companies, regulatory authorities and doctors. More importantly, drug safety controversies have eroded public trust, also affecting the relationships among these stakeholders. As demonstrated in this thesis, the analysis of drug safety controversies is a challenging endeavor that demands a multidisciplinary and multidimensional approach. The analysis of DLC may provide the required structure to perform this task, including analyzing the influence of controversies on public trust. However, trust should be defined a priori and should include important components such as vulnerability and competence.

This thesis also demonstrated that trust is fundamental for the healthy functioning of the pharmaceutical sector, especially in the relationship between pharmaceutical companies and regulatory authorities, since the increasing number of regulations is not contributing to public trust and increases the cost of medicines. Instead, bilateral dialogue, such as scientific advice, and even more informal modalities, should be stimulated between these stakeholders, so as not to result in close relationships, but rather more efficient and transparent relationships that foster innovation and benefit society at large.

References

1. Miller G. Is Pharma Running Out of Brainy Ideas? Science. 2010 July 30, 2010;329(5991):502-4.
2. WHO. Priority Medicines for Europe and the World Geneva: WHO; 2004 [cited 2014 Augustus 15]. Available from: http://archives.who.int/prioritymeds/report/index.htm.
3. Pharma TI. Top Institute Pharma 2014 [cited 2014 August 18]. Available from: http://www.tipharma.com/about-our-institute/our-mission.html.
4. Pharma TI. The Escher Project 2014 [cited 2014 August 18]. Available from: http://escher-projects.org.
5. Lenzer J. Scandals have eroded US public's confidence in drug industry. BMJ. 2004 2004-07-29 00:00:00;329(7460):247.
6. Lofstedt R. Risk Management in Post-Trust Societies. London: Pelgrave Macmillan; 2005.
7. Lofstedt R, Bouder F, Wardman J, Chakraborty S. The changing nature of communication and regulation of risk in Europe. Journal of Risk Research. 2011;14(4):409-29.
8. Edwards B, Olsen AK, Whalen MD, Gold MJ. Guiding principles of safety as a basis for developing a pharmaceutical safety culture. Curr Drug Saf. 2007 May;2(2):135-9.
9. Hupcey JE, Miller J. Community dwelling adults' perception of interpersonal trust vs. trust in health care providers. J Clin Nurs. 2006 Sep;15(9):1132-9.
10. Hupcey JE, Penrod J, Morse JM, Mitcham C. An exploration and advancement of the concept of trust. Journal of Advanced Nursing. 2001 Oct;36(2):282-93.
11. Newton K. Trust, social capital, civil society, and democracy. International Political Science Review. 2001 Apr;22(2):201-14.
12. Hall MA, Dugan E, Zheng BY, Mishra AK. Trust in physicians and medical institutions: What is it, can it be measured, and does it matter? Milbank Quarterly. 2001 2001;79(4):613-+.
13. Whitley R, McKenzie K. Social capital and psychiatry: Review of the literature. Harvard Review of Psychiatry. 2005 Mar-Apr;13(2):71-84.
14. Benkert R, Peters R, Tate N, Dinardo E. Trust of nurse practitioners and physicians among African Americans with hypertension. J Am Acad Nurse Pract. 2008 May;20(5):273-80.
15. Chu-Weininger MY, Balkrishnan R. Consumer satisfaction with primary care provider choice and associated trust. BMC Health Serv Res. 2006;6:139.
16. Copeland VC, Scholle SH, Binko JA. Patient Satisfaction: African American Women's Views of the Patient-Doctor Relationship. Journal of Health and Social Policy. 2003;17(2):35-48.
17. Graham JL, Giordano TP, Grimes RM, Slomka J, Ross M, Hwang LY. Influence of trust on HIV diagnosis and care practices: A literature review. Journal of the International Association of Physicians in AIDS Care. 2010;9(6):346-52.
18. Pagan JA, Balasubramanian L, Pauly MV. Physicians' career satisfaction, quality of care and patients' trust: the role of community uninsurance. Health Econ Policy Law. 2007 Oct;2(Pt 4):347-62.
19. Torke AM, Corbie-Smith GM, Branch Jr WT. African American Patients' Perspectives on Medical Decision Making. Archives of Internal Medicine. 2004;164(5):525-30.

20. Bachinger SM, Kolk AM, Smets EM. Patients' trust in their physician--psychometric properties of the Dutch version of the "Wake Forest Physician Trust Scale". Patient Educ Couns. 2009 Jul;76(1):126-31.
21. Blackstock OJ, Addison DN, Brennan JS, Alao OA. Trust in primary care providers and antiretroviral adherence in an urban HIV clinic. J Health Care Poor Underserved. 2012 Feb;23(1):88-98.
22. Pedersen VH, Armes J, Ream E. Perceptions of prostate cancer in Black African and Black Caribbean men: A systematic review of the literature. Psycho-Oncology. 2012;21(5):457-68.
23. Tonks A. Withdrawal from paroxetine can be severe, warns FDA. BMJ. 2002 2002-02-02 00:00:00;324(7332):260.
24. FDA. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications Rockville, MD: Department of Health and Human Services; 2004 [cited 2011 20th January 2011]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm.
25. MHRA. Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. London: Committee on Safety of Medicines, 2004.
26. EMA. European Medicines Agency finalises review of antidepressants in children and adolescents London: EMA; 2005 [cited 2011 4th February]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/12/news_detail_000882.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1.
27. FDA. Antidepressant Use in Children, Adolescents, and Adults Rockville, MD: Department of Health and Human Services; 2007 [cited 2011 7th February 2011]. Available from: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm.
28. EMA. CHMP Assessment Report on Antidepressants. London: European Medicines Agency, 2008 30 May 2008. Report No.
29. Ide RW, Yarn DH. Public independent fact-finding: A trust-generating institution for an age of corporate illegitimacy and public mistrust. Vanderbilt Law Review. 2003 May;56(4):1113-+.
30. Slovic P. Perceived risk, trust, and democracy. Risk Analysis. 1993;13(6):675-82.
31. Shulman S. Undermining Science: Suppression and Distortion in the Bush Administration. Press UoC, editor. Berkeley and Los Angeles, California: University of California Press; 2008. 224 p.
32. Harris G. Expert Kept From Speaking at Antidepressant Hearing New York: New York Times; 2004 [cited 2015 January 3]. Available from: http://www.nytimes.com/2004/04/16/politics/16DEPR.html?hp.
33. Harrison S, Smith C. Trust and moral motivation: redundant resources in health and social care? Policy and Politics. 2004 Jul;32(3):371-86.
34. Misztal BA. Trust and cooperation: the democratic public sphere. Journal of Sociology. 2001 Dec;37(4):371-86.

35. Brown P, Calnan M. Braving a faceless new world? Conceptualizing trust in the pharmaceutical industry and its products. Health:. 2010 December 15, 2010.
36. Entwistle V. Trust and shared decision-making: an emerging research agenda. Health Expectations. 2004 Dec;7(4):271-3.
37. Hall MA, Camacho F, Dugan E, Balkrishnan R. Trust in the medical profession: Conceptual and measurement issues. Health Services Research. 2002 Oct;37(5):1419-39.
38. Pescosolido BA, Tuch SA, Martin JK. The profession of medicine and the public: examining Americans' changing confidence in physician authority from the beginning of the 'health care crisis' to the era of health care reform. J Health Soc Behav. 2001 Mar;42(1):1-16.
39. Hillen MA, de Haes H, Smets EMA. Cancer patients' trust in their physician-a review. Psycho-Oncology. 2011 Mar;20(3):227-41.
40. Fukuyama F. Social capital, civil society and development. Third World Quarterly. 2001;22(1):7-20.
41. Cross FB. Law and trust. Georgetown Law Journal. 2005 Jun;93(5):1457-545.
42. Putnam D. RELATIONAL ETHICS AND VIRTUE THEORY. Metaphilosophy. 1991 Jul;22(3):231-8.
43. Bouvy JC, Koopmanschap MA, Shah RR, Schellekens H. The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. Clin Pharmacol Ther. 2012 Feb;91(2):281-8.
44. Bouder F. Benefit/risk communication by the European Medicines Agency: a study of influential stakeholders' expectations and attitudes London: EMA; 2011 [cited 2013 15 February]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/05/WC500106865.pdf.
45. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, Belitser SV, Raaijmakers JAM, Pieters T. Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study. BMJ Open. 2011 January 1, 2011;1(2).
46. Hernandez JF, van Thiel GJMW, Mantel-Teeuwisse AK, Raaijmakers JAM, Pieters T. Restoring trust in the pharmaceutical sector on the basis of the SSRI case. Drug Discovery Today. 2013 (0).
47. Putzeist M. Marketing authorisation of new medicines in the EU: towards evidence-based improvement. PhD thesis; Utrecht University; 2013.
48. Churchill LR. TRUST, AUTONOMY, AND ADVANCE DIRECTIVES. Journal of Religion & Health. 1989 Fal;28(3):175-83.
49. Wood DJ. Corporate Social Performance Revisited. The Academy of Management Review. 1991;16(4):691-718.
50. Dupras C, Williams-Jones B. The Expert and the Lay Public: Reflections on Influenza A (H1N1) and the Risk Society. American Journal of Public Health. 2012 Apr;102(4):591-5.
51. EU. Newsreader project EU 2013 [cited 2014 14 October]. Available from: http://www.newsreader-project.eu/publications/papers/

SUMMARY

S

"Trust is the glue that holds an organization together and the grease that keeps an organization working smoothly. It simply makes things happen in organizational life"

Dan R. Ebener

Summary

In the process of drug development and marketing, safeguards are implemented to assure a positive risk-benefit balance for marketed drugs. Before drugs are released to the market, they are extensively tested in well-selected populations under strictly controlled circumstances. After marketing authorization, the drug is made available and used in 'real world conditions', which are known to deviate from the trial setting. During the drug life cycle (DLC), many factors influence drug uptake and use in the market place. In some undesirable circumstances, a drug sparks societal debate due to unexpected or unforeseen safety concerns. Examples of these drug safety controversies are the thalidomide disaster (when babies were born with malformations due to the use of thalidomide during pregnancy in the late 1950s and early 1960s), the market withdrawal of rosiglitazone and rofecoxib due to an increased risk of myocardial infarction, or the black-box warning issued for antidepressants as a result of an increased suicidality risk in children and adolescents.

The consequences of drug safety controversies can be manifold, varying from market withdrawal, intensified regulation, lawsuits, or increased media attention. Many have argued that drug safety controversies damage public trust in the pharmaceutical sector. In **chapter 1**, we noted that several proposals have been made to address drug controversies and minimize society's exposure to drug-related risks. However, our knowledge about drug safety controversies and their impact on public trust is limited because the available evidence is either anecdotal, scarce, or lacks analytic rigor. Furthermore, the life cycle dynamics of public perception and drug use have been neglected in drug controversy analyses. These shortcomings emphasize the need for innovative studies on drug safety controversies using a sound analytical framework that includes the life cycle dynamics of public perception and drug use. Unfortunately drug-related risks inherent to the daily practice of prescribing and using medicines can develop into controversies. Adequate and timely management of societal debate on pharmaceuticals is important for avoiding unnecessary harm to patients and the pharmaceutical sector. In this thesis, we add to the knowledge of factors influencing drug controversies and the consequences on societal trust in the pharmaceutical sector. As part of the TI Pharma Escher Project, this thesis presents empirical studies on one particular drug safety controversy – the selective serotonin reuptake inhibitors (SSRI) and suicidality risk controversy. We have elucidated the dynamics of this controversy, its impact on public trust, and the role of stakeholders. Drug life cycles (DLCs) were used as a heuristic tool to analyze the controversy. Knowledge about controversies, their dynamics and stakeholder roles can be used to improve the management of future controversies (as part of risk management) and anticipate events or actions that can worsen a controversy or prove detrimental to trust in the pharmaceutical industry.

Before analyzing the SSRI and suicidality controversy, we identified two relevant hurdles: i) public trust in the pharmaceutical sector has not been previously defined in the literature, and ii) claims about distrust in the pharmaceutical industry often refer to evidence that has not been thoroughly evaluated. These hurdles were addressed in **chapter 2 and 3,** respectively.

In **chapter 2,** we analyzed the nature of definitions of trust in other fields/disciplines and then defined trust in pharmaceutical companies, regulatory authorities and doctors. For this purpose, a meta-narrative review of the literature was performed to identify articles that define trust from 1980 to 2013. Three databases (PubMed, Scopus, and Web of Science) and cross-referencing were used to find articles. Ninety-five articles were included from which two components of trust were distinguished: vulnerability and competence. These components were combined into a definition of trust in the pharmaceutical sector as:

1. The willingness to accept or assume a position of vulnerability in relation to the provision of care and the management and use of medicines, and

2. The reliance on or belief in the competence of pharmaceutical companies, regulatory authorities, and healthcare providers to perform the task they are responsible for and expected to do - developing, manufacturing and evaluating high quality pharmaceutical products for public use and providing adequate healthcare.

Patients are in a position of vulnerability due to their illness and need for medical care. Therefore, reliance on their physician's competence and the scientific expertise of pharmaceutical companies and regulators are important prerequisites for addressing a patient's vulnerability. Incompetent pharmaceutical companies, regulators or doctors may increase a patient's sense of risk and thereby, their level of vulnerability. As a result, a patient's trust may erode when their safety is compromised.

In **chapter 3**, the evidence for claims of an erosion of trust in pharmaceutical companies, regulatory authorities and doctors was analyzed. In particular, we conducted a methodological assessment of empirical studies to look at what has been measured and how it has been measured. A systematic review of the (academic) literature was performed up to 2012 to identify empirical studies that measured trust. The databases used were PubMed, Web of Science, and Scopus. In addition, we performed a review of non-academic public polls and surveys identified through Google and cross-referencing. We identified 47 academic and empirical articles measuring trust in pharmaceutical companies (8), regulatory authorities (3), and doctors (36), as well as non-academic public polls/surveys (16).

Surprisingly, we observed that although there is evidence of studies on trust in doctors (n=36), there has been little investigation of trust in the pharmaceutical industry (n=8) and regulatory authorities (n=3). More importantly, we observed that most studies (academic and non-academic) lacked a robust methodology to analyze trust. The most salient limitations were:

- The lack of a definition for trust
- The absence of (a methodological) standardization, and
- The varying and sometimes quite low response or participation rates

If trust is not defined in advance by a researcher, then how can it be measured? A clear definition is essential since trust can be confused with other characteristics such as mutuality, empathy, reciprocity, solidarity or confidence. Scale-based questionnaires

are useful instruments to measure trust. However, we observed in our sample of studies that there was little to no homogeneity in the use of these instruments: Trust in Physician Scale (n=7), Wake Forrest/Hall's Trust in Physician Scale (n=6), and the Public Trust in Healthcare Questionnaire (n=2). In addition, 25% of articles did not report the use of an instrument at all (n=12). Seven studies allowed the use of open-ended questionnaires, which are controversial because bias might be introduced in trust measurements; these instruments allowed for personal interpretations that may fluctuate according to the participant. Finally, studies that analyzed trust in pharmaceutical companies and regulatory authorities did not measure trust as a primary outcome or main topic of the research.

We observed that the public had low levels of trust in pharmaceutical companies and regulatory authorities. The reasons for distrust were that profits have been prioritized over patient safety and there has been a lack of transparency, honesty, integrity, and societal recognition (in particular for European regulatory agencies). The public has also noted excessive regulation, increasing health care costs, and a hidden (political) agenda on the part of the pharmaceutical industry and regulatory authorities. However, the public did trust the pharmaceutical companies for their scientific competence and experience in manufacturing and regulatory authorities for evaluating drugs.

Doctors who prioritized their patients' needs and who were caring, honest, respectful and seen as competent were more trusted by the public than those who displayed unethical, inappropriate, judgmental, condescending or discriminatory behavior towards their patients. In addition, the public appeared to give little importance to doctors having relationships with the pharmaceutical industry as long as the public and patients received better treatments.

After having defined trust and reviewed the body of evidence concerning trust measurements, we moved to analyze the SSRI and suicidality controversy using DLCs. As part of the construction of our DLC model, we used several types of data (dimensions) in superimposed layers to produce multidimensional analyses. These dimensions were:

1. Publication patterns in scientific journals and Dutch (NL) and British (UK) newspapers (**chapter 4**)
2. SSRI use patterns in the NL and the UK (**chapter 5**), and
3. Event-related data – including two important elements:
    a. A detailed description of the events that shaped the controversy, and
    b. The comprehensive definition of public trust for the pharmaceutical sector as proposed in **chapter 2**

In **chapter 4**, we presented an analysis of the publication patterns in scientific journals vis-à-vis newspapers articles in the NL and the UK for the SSRI and suicidality controversy between the years 2000 and 2010. We conducted a systematic review of the literature (Embase) and NL and UK newspaper articles (LexisNexis) on this controversy. Articles were categorized by "effect" (related to the treatment effect of antidepressants), "type of

article", and "age group". The articles' positive–to–negative effect ratio was determined. In total, 1,141 articles were categorized: 352 scientific articles, 224 Dutch newspaper articles and 565 British newspaper articles. There were more scientific and newspaper articles reporting a positive effect about the efficacy or safety of antidepressants (39%) than those reporting a neutral (30%) or a negative effect (31%; P<0.001). We observed a positive publication trend in scientific journals (ratio=8.5) and the majority of scientific articles were about research (60%). Most scientific articles with a negative trend discussed the safety of antidepressants in children. Newspaper articles in both in the NL and UK were generally negative about the efficacy and safety of antidepressants (ratios=0.69 and 0.94, respectively). The negative reporting trend increased during regulatory warnings periods (2003-2004/2007-2008) and in general were opinion articles in both scientific journals and newspapers. From these results, we concluded that knowledge dissemination to the public was inconsistent with the scientific evidence since only the studies that reported the negative side of antidepressants received significant media attention. Nevertheless, the public was informed about the SSRI and suicidality controversy in a timely fashion.

In **chapter 5**, we added a second dimension (sales and prescription patterns of SSRIs) to our DLC model to ascertain if the regulatory warnings or media portrayals of antidepressants influenced SSRI use in the NL and UK from 2000 to 2010. IMS Health provided monthly SSRIs sales data for the NL and the UK, which we presented as DDDs/1000 inhabitants/day (calculated using the standard counts sold, dosage strength and monthly population estimates per country). We studied SSRI-use trends using time-series segmented regression analyses. Next, the timing of SSRI-use trend changes (segments) was compared with both periods of media coverage of warnings. The National Health Care Institute (Zorginstituut Nederland - GIP-database) provided annual Dutch SSRI prescription data, which were analyzed by age groups (pediatrics 0-14 years old, adolescents 15-19 years old, young adults 20-24 years old, adults 25-64 years old, and elderly 65 years and older).

From this study, we observed that although changes in SSRI use coincided with the regulatory warnings periods, no significant reductions were observed in SSRI use despite the warnings. SSRI use increased in the NL from 16.7 DDDs/1000 inhabitants/day in January 2000 to 27.9 DDDs/1000 inhabitants/day in July 2010. In the UK, SSRI use doubled from 24.7 DDDs/1000 inhabitants/day in January 2000 to 50.1 DDDs/1000 inhabitants/day in December 2009. From the individual SSRIs, paroxetine was the only drug molecule that showed a pronounced decrease in use, mainly in children, adolescents and young adults. Despite this trend, paroxetine remained the most used SSRI in the NL, while in UK it was fluoxetine. In conclusion, this study demonstrated that the effect of the regulatory warnings and increased negative newspaper coverage was negligible on SSRI use.

The communication of the black-box warnings, negative media coverage about SSRIs and public polls all indicated an erosion of trust in the pharmaceutical industry and regulatory authorities. However, SSRI use continued to increase in the NL and the UK. These contradictory dynamics of distrust and increasing SSRI use raised questions about the role of public trust in pharmaceutical stakeholders. Therefore, in **chapter 6**, we analyzed the role of trust during the SSRI and suicidality controversy by adding an event-related

dimension to our DLC model. We systematically made a chronological reconstruction of the events and stakeholder interventions that shaped the SSRI and suicidality controversy. This event-related data was analyzed in the context of the definition of trust that was provided in **chapter 2**.

From this study, we learned that public trust in all stakeholders fluctuated at various stages during the controversy. We observed events that may have damaged trust in pharmaceutical and regulatory stakeholders. For instance, assuming a passive/reactive role during the controversy, receiving increasingly negative media attention, and being involved in lawsuits were the most relevant actions that contributed to a loss of trust in pharmaceutical companies and regulatory authorities during this controversy. The public perceived these actions as incompetent and unethical behavior, thus increasing their sense of risk and vulnerability. Furthermore, the results from multiple public polls (chapter 3) also indicated distrust in pharmaceutical companies and regulatory authorities during the SSRI controversy.

In **chapter 3**, we noted that doctors were more trusted than pharmaceutical companies and regulatory authorities based on patient vulnerability during illness or pharmaceutical therapy. Therefore, the increasing trend in SSRI use may have reflected high levels of public and patient trust in their prescribers that counterbalanced distrust in the pharmaceutical industry, regulatory authorities and the products for which they were responsible. Doctors may have had a mediating role between the controversy surrounding the pharmaceutical companies, authorities and the questioned risk/benefit profile of antidepressants.

In **chapter 7**, we presented the use of DLCs as a heuristic tool to analyze drug safety controversies. Combining quantitative and qualitative data in a longitudinal set-up, our DLC model demonstrated that multidimensional analyses provide a more comprehensive view of the dynamics of controversies vis-à-vis short-term analyses. Short-term analyses only provide a snapshot of the implications and repercussions of drug safety controversies and regulatory interventions. Furthermore, DLC analyses were useful for describing stakeholders' roles during the SSRI and suicidality controversy. However important, careful attention should be given to the selection and quality of data and databases. Incomplete data may result in partial, erroneous or superficial assessments of drug safety controversies.

In **chapter 8**, we discussed the key findings of this thesis. A clear and homogeneous definition of trust is important for future studies measuring trust. In this thesis, therefore, we proposed a definition of trust that has current value for the public and significance for pharmaceutical companies, regulatory authorities and doctors. Furthermore, we discussed and emphasized the need for more and better-structured empirical studies measuring trust in these stakeholders because the available evidence is insufficient to draw a decisive conclusion concerning the levels of public trust in pharmaceutical companies and regulatory authorities. Empirical studies on public trust in doctors could also benefit from homogeneous and robust methodologies to enable comparison between studies and other stakeholders (e.g., industry or authorities).

We discussed the use of DLCs as a tool to analyze controversies since it makes use of quantitative and qualitative data in a single model. However, the selection of quantitative

and qualitative data should be done carefully to maximize the heuristic value of DLCs. We have also provided specific guidance to important methodological aspects that should be considered when using DLCs. These innovative and well-structured analyses can contribute to explaining why some interventions are more effective than others and the role of multiple stakeholders during controversies. In this context, we argue that stakeholders that assume a proactive role during controversies are more helpful in safeguarding trust than those who are passive or reactive. Active public involvement also appears to be beneficial to public trust and all stakeholders of the pharmaceutical sector should advocate for this.

Trust is fundamental for the healthy functioning of the pharmaceutical sector because it promotes innovation, cooperation, and solidarity, among many other qualities. Since the costs of developing medicines continues to increase day by day alongside increasing regulations, trust can be helpful to mediate this situation and may diminish the burden of excessive regulation. Trust can also serve as the foundation for strong and stable relationships with the public based on bilateral dialogue between the industry and regulatory authorities.

SAMENVATTING

S

"A relationship without trust is like having a phone with no service. And what do you do with a phone without service? You play games"

Anonymous

Samenvatting

Voordat een nieuw geneesmiddel op de markt komt, wordt het grondig onderzocht. Is het geneesmiddel wel veilig en effectief? Onderzoek naar nieuwe geneesmiddelen gebeurt met geselecteerde patiëntengroepen en onder zeer strenge condities. Pas nadat geneesmiddelen op de markt zijn toegelaten, worden ze in de dagelijkse praktijk gebruikt. Dat deze significant afwijken van de klinische onderzoek condities is bekend. De onvoorziene of onverwachte bijwerkingen die kunnen optreden na introductie op de markt zijn regelmatig aanleiding geweest voor maatschappelijk debat. Een voorbeeld is het 'Softenon schandaal' dat ontstond toen eind jaren 50 en begin jaren 60 meerdere baby's werden geboren zonder bovenarm of –been vanwege het gebruik van het geneesmiddel thalidomide (Softenon) tijdens zwangerschap. Van de medicijnen rosiglitazon en rofecoxib werd de handelsvergunning ingetrokken toen bleek dat ze een significant verhoogde kans gaven op een hartaandoening. En alle selectieve serotonine heropnameremmers (hierna: selective serotonine reuptake inhibitors / SSRI) kregen zogenoemde "black-box" bijsluiterwaarschuwingen, die het gebruik bij kinderen en jongeren afraden vanwege een toenemende kans op suïcidaliteit.

De gevolgen van de controversen gerelateerd aan de veiligheid van geneesmiddelen zijn veelvoudig; van het intrekken van een handelsvergunning en toename van (strenge) regelgeving tot media-aandacht en rechtszaken. Velen menen dat deze controversen schadelijk zijn voor het publieke vertrouwen in de farmaceutische sector. In **hoofdstuk 1** laten we zien dat inzicht in geneesmiddelcontroversen, en het effect daarvan op de publieke opinie, vrij beperkt is De bestaande studies berusten onvoldoende op wetenschappelijke feiten of zijn oppervlakkig van structuur of aanpak. Bovendien wordt de relatie tussen de publieke perceptie en het geneesmiddelgebruik buiten beschouwing gelaten. Er is een maatschappelijk en wetenschappelijke vraag naar innovatieve studies die de relatie tussen de publieke perceptie en geneesmiddelgebruik onder de loep nemen. Geneesmiddel gerelateerde risico's zijn inherent aan hun gebruik. Met de juiste katalysatoren (bijvoorbeeld bepaalde acties en reacties van stakeholders of de media) kunnen gerapporteerde veiligheidsrisico's van geneesmiddelen altijd uitgroeien tot een controverse. Het adequaat monitoren van het publieke debat over geneesmiddelen is belangrijk voor alle stakeholders.

Als onderdeel van het TI Pharma Escher Project biedt dit proefschrift een reeks empirische studies omtrent één controverse in het bijzonder: het verhoogde risico op suïcidaliteit als gevolgd van het gebruik van SSRIs. We hebben de maatschappelijke dynamiek van deze jarenlange controverse, de impact op het publieke vertrouwen en de rol van verschillende stakeholders ontrafeld. Hiervoor hebben we de levenscycli van geneesmiddelen (voortaan Drug Life Cycle – DLC genoemd) gebruikt als een heuristisch instrument.

Voordat de eerste aanzet werd gedaan om de SSRI en suïcidaliteit controverse te bestuderen, stuitten we op twee belangrijke omissies: I) er bestaat geen definitie van publiek vertrouwen in de farmaceutische sector, en II) de claims over een gebrek aan vertrouwen in de farmaceutische sector refereerden aan bewijstukken die niet eerder grondig waren geëvalueerd. Deze twee beperkingen worden respectievelijk bestudeerd in **hoofdstuk 2 en 3.**

In **hoofdstuk 2** hebben we diverse definities van vertrouwen in andere disciplines geanalyseerd. Op basis hiervan hebben we een algemene definitie van vertrouwen voorgesteld die gebruikt kan worden voor de farmaceutische industrie, regulerende autoriteiten en artsen. Om te komen tot deze definitie werd een meta-analyse van de literatuur uitgevoerd. We zochten naar artikelen waarin het begrip vertrouwen tussen 1980 en 2013 werd gedefinieerd. Hiervoor gebruikten we drie verschillende databases en cross-citaties (PubMed, Scopus, en Web of Science). Uit de totaal 95 artikelen die we analyseerden, komen 2 belangrijke componenten van vertrouwen naar voren: kwetsbaarheid en deskundigheid. Rekening houdend met beide componenten kwamen we tot de volgende definitie van het begrip vertrouwen in de farmaceutische sector:

1. De bereidwilligheid zich kwetsbaar op te stellen (houding of situatie) bij het leveren/aanbieden van medisch en/of farmaceutische zorg en

2. De betrouwbaarheid of geloofwaardigheid in de deskundigheid van de farmaceutische industrie, regulerende autoriteiten, en artsen om de maatschappelijke taak uit te kunnen voeren waarvoor ze verantwoordelijk zijn gesteld. Te weten het ontwikkelen, maken en evalueren van geneesmiddelen van hoogwaardige kwaliteit en het verlenen van adequate gezondheidszorg.

Patiënten zijn per definitie een kwetsbare bevolkingsgroep vanwege hun conditie (ziekte) en vooral vanwege hun behoefte aan medische en/of farmaceutisch zorg. Daarom is het van belang dat patiënten kunnen vertrouwen op de deskundigheid van artsen. Dit geldt ook voor de wetenschappelijke expertise van de farmaceutische industrie en de regulerende autoriteiten om geneesmiddelen van kwaliteit te maken en ze grondig te evalueren. Hierdoor zal de kwetsbaarheid (conditie) van patiënten worden verminderd. Incompetent gedrag van artsen, regulerende autoriteiten en de industrie kan patiënten in onveilige situaties brengen waardoor wantrouwen kan ontstaan, die in het publieke debat door de verschillende stakeholders functioneel ingezet wordt en kan worden.

In **hoofdstuk 3** hebben we een mix van academische en non-academische empirische studies geanalyseerd die het vertrouwen in de farmaceutische industrie, regulerende autoriteiten en artsen hebben gemeten. We hebben een methodologische evaluatie van deze studies uitgevoerd om er achter te komen wat deze studies hebben gemeten en hoe ze dat hebben gemeten. Dit deden we door middel van een systematische review van de literatuur tot en met 2012. De gebruikte databases waren: PubMed, Web of Science en Scopus. Verder hebben we publieke polls geanalyseerd die via Google en cross-referencing werden geïdentificeerd. We analyseerden 47 wetenschappelijke studies naar vertrouwen in de farmaceutische industrie (8), regulerende autoriteiten (3) en artsen (36). Tevens werden zestien polls geanalyseerd.

Opmerkelijk is de conclusie dat er weliswaar voldoende onderzoek bestaat waarin het vertrouwen in artsen wordt getoetst (36), maar dat er een gebrek is aan studies waarin het vertrouwen wordt gemeten in de farmaceutische industrie (n=8) en regulerende autoriteiten (n=3). De methodologie van de meeste studies is matig te noemen. De opvallendste methodologische tekortkomingen zijn:

- Ontbreken van een expliciete en gedeelde definitie van vertrouwen
- Gebrek aan (methodologische) standaardisatie
- Een variabele en/of lage respons of deelname

Voor studies die vertrouwen willen meten, is het essentieel vooraf het begrip vertrouwen te definiëren. Dit kan verwarring met andere relationele kenmerken tussen deelnemers, zoals wederkerigheid, empathie of solidariteit, voorkomen. Questionnaires die gebruik maken van schalen zijn bruikbare instrumenten om vertrouwen te meten. Helaas konden we weinig tot geen homogeniteit onderscheiden tussen het gebruik van deze instrumenten: Trust in Physician Scale (n=7), Wake Forrest/Hall's Trust in Physician Scale (n=6), the Public Trust in Healthcare Questionnaire (n=2), en 25% van alle studies meldde geen instrument (n=12). Zeven andere studies hebben vragenlijsten met 'open vragen' gebruikt om vertrouwen te meten. Door ruimte te laten voor eigen interpretaties, beïnvloed door variabelen als achtergrond, opleidingsniveau, ras, geslacht of leeftijd, kan verwarring ontstaan. We kunnen tevens concluderen dat de studies naar vertrouwen in de farmaceutische industrie en regulerende autoriteiten vertrouwen niet hebben gemeten als primaire uitkomst van de studie of als hoofdonderwerp voor onderzoek.

Het publieke vertrouwen in de farmaceutische industrie en regulerende autoriteiten is volgens bovengenoemde studies laag. De reden: winst krijgt meer prioriteit dan patiëntveiligheid, gebrek aan transparantie, eerlijkheid, integriteit, en een geringe maatschappelijke erkenning (vooral in het geval van Europese regulerende autoriteiten). Ook de overmatige regulatie, de toegenomen kosten voor de gezondheidszorg en een verborgen of dubbele agenda zorgen voor wantrouwen. Opvallend is het gerapporteerde publieke vertrouwen in de wetenschappelijke expertise van de farmaceutische industrie en de regulerende autoriteiten om geneesmiddelen te maken en te evalueren.

Artsen die zorgzaam, eerlijk en respectvol waren, en die de behoeften van de patiënten voorop stellen, werden gezien als competent en kregen meer vertrouwen van het publiek dan artsen die onethisch, ongepast, veroordelend, neerbuigend of discriminerend gedrag uitten jegens hun patiënten. Zo lang artsen hun relaties met de farmaceutische industrie aanwenden voor betere behandelingen en geneesmiddelen, had dit geen effect op het publieke vertrouwen in de beroepsgroep.

Na het vaststellen van een definitie van vertrouwen in de farmaceutische sector en de meta-analyse van zogenaamde 'trust-barometer' studies , beschrijven we de analyse van de SSRI en suïcidaliteit controverse aan de hand van een multidimensionale DLC benadering. De datadimensies die werden gebruikt zijn:

1. Publicatiepatronen in wetenschappelijke tijdschriften én in Nederlandse en Britse kranten (**hoofdstuk 4**)
2. Gebruikspatronen van SSRI in Nederland en het Verenigd Koninkrijk (**hoofdstuk 5**), en
3. Gebeurtenis-gerelateerd data – verdeeld in twee elementen:
   a. Een gedetailleerde beschrijving van alle gebeurtenissen die de controverse hebben beïnvloed, en

b. De definitie van het publieke vertrouwen in de farmaceutische sector zoals gepresenteerd in **hoofdstuk 2**

In h**oofdstuk 4** hebben we een analyse van publicatiepatronen in wetenschappelijke tijdschriften versus krantenartikelen tussen 2000 en 2010 in NL en UK uitgevoerd. Een systematische analyse van de literatuur werd uitgevoerd (Embase voor wetenschappelijke- en LexisNexis voor krantenartikelen). Artikelen werden geïndexeerd in 3 verschillende categorieën: "effect" (gerelateerd aan de therapeutische effect van SSRIs), "artikelsoort" en "leeftijdsgroep". De ratio van positieve t.o.v. negatieve artikelen werd gecalculeerd. Er werden 1141 artikelen in totaal geïndexeerd: 352 wetenschappelijk artikelen, 224 NL en 565 UK krantenartikelen. Er waren meer positieve wetenschappelijke artikelen over de effectiviteit en veiligheid van SSRIs (39%) dan neutrale (30%) of negatieve artikelen (31%; P<0.001). We constateerden een positieve vooroordeel (bias) in wetenschappelijke publicaties (ratio=8.5). Meer dan de helft van alle wetenschappelijke publicaties (60%) waren onderzoekstudies. Wetenschappelijke artikelen die de negatieve kant van antidepressiva bespraken, zoomden vooral in op de veiligheid van deze middelen bij het gebruik door kinderen.

Nederlandse en Britse krantenartikelen waren over het algemeen negatief over de veiligheid en effectiviteit van antidepressiva (ratio's=0.69 NL en 0.94 UK). De negatieve trend in wetenschappelijke publicaties nam tijdens de veiligheidswaarschuwingen toe (tussen 2003-2004 en 2007-2008). Opiniestukken waren grotendeels verantwoordelijk voor deze negatieve publicatietrend. We concludeerden dat het publiek in Nederland en Engeland op tijd geïnformeerd werd over de mogelijke associatie tussen SSRI gebruik en suïcidaliteit. De verwachting was een duidelijk effect te zien van negatief nieuws op het antidepressivagebruik in beide landen.

In **hoofdstuk 5** hebben we een extra dimensie (verkoops- en voorschrijfpatronen van SSRI) aan ons DLC model toegevoegd. In deze studie hebben we gekeken of SSRI gebruik in NL en in UK tussen 2000 tot en met 2010 werd beïnvloed door de negatieve (media) aandacht en/of door de veiligheidswaarschuwingen die door verschillende regulerende autoriteiten werden gemaakt. IMS Health leverde verkoopcijfers van SSRI in NL en in UK per maand. Verkoopcijfers werden gedefinieerd in dagelijks doses (DDDs) per 1000 inwoners per dag (DDD/1000 inwoners/dag) gepresenteerd (DDDs werden gecalculeerd m.b.v. standaard aantallen verkocht, sterkte van de doses en maandelijks bevolkingsaantallen per land). SSRI gebruikstrends werden d.m.v. time-series (segmentaties) regressie analysen bestudeerd. Vervolgens werd de timing van veranderingen in SSRI gebruikstrends vergeleken met beide perioden van toenemende negatieve media aandacht en/of veiligheidswaarschuwingen. Tevens leverde het Zorginstituut Nederland (GIP database) jaarlijkse SSRI voorschrijfgegevens. Deze data hebben we geïndexeerd en geanalyseerd per leeftijdsgroep (pediatrisch 0-14 jaar, adolescenten 15-19 jaar, jong volwassenen 20-24 jaar, volwassenen 25-64 jaar en ouderen boven 65 jaar oud).

In deze studie hebben we een verband gesignaleerd tussen SSRI gebruikstrends en de perioden van veiligheidswaarschuwingen en media- aandacht. Significante dalingen in overall SSRI gebruik werden echter niet geobserveerd. In tegenstelling nam SSRI gebruik van 16.7 DDDs/1000 inwoners/dag in januari 2000 naar 27.9 DDDs/1000 inwoners/dag

in juli 2010 toe in NL. SSRI gebruik in UK verdubbeld van 24.7 DDDs/1000 inwoners/dag in januari 2000 naar 50.1 DDDs/1000 inwoners/dag in december 2009. Uit deze studie concludeerden we dat de veiligheidswaarschuwingen en de negatieve publiciteit over antidepressiva nauwelijks effect hadden op het voorschrijven van SSRIs aan volwassenen. Bij kinderen was een bescheiden tijdelijk effect overal waarneembaar.

De toenemende negatieve berichtgeving over de veiligheid van SSRI en de waarschuwingen van de autoriteiten gingen samen met een daling in het gerapporteerde vertrouwen in de farmaceutische industrie en regulerende autoriteiten aan. Des te opvallender is het dat het gebruik van SSRI's in Nederland en Engeland niet afnam. De tegenstrijdige dynamieken van wantrouwen en toenemende SSRI gebruik wekte vragen op over de rol van vertrouwen in de stakeholders van de farmaceutische sector tijdens deze controverse. Daarom analyseerden we in hoofdstuk 6 de rol van vertrouwen tijdens de SSRI en suïcidaliteit controverse. Hiertoe voegden we een extra (gebeurtenis-gerelateerde) dimensie aan ons DLC toe. Dit werd op basis van een systematisch en chronologisch reconstructie van alle gebeurtenissen gedaan die invloed op de SSRI en suïcidaliteit controverse hebben gehad. Deze gebeurtenis-gerelateerd data werd in het kader van onze definitie van vertrouwen in hoofdstuk 2 gepresenteerd.

Uit deze studie hebben we gezien dat het publieke vertrouwen in alle stakeholders fluctueerde van tijd tot tijd. Verschillende gebeurtenissen hebben plaatsgevonden waardoor vertrouwen eventueel werd beschadigd. Het spelen van een passieve of reactieve rol, telkens het object van negatieve publiciteit zijn, en betrokkenheid bij rechtszaken, zijn voorbeelden van gebeurtenissen die het vertrouwen in de farmaceutische industrie en regulerende autoriteiten ondermijnen. Deze gebeurtenissen kwamen bij het publiek als incompetent, onethisch en onhandig over. Als gevolg hiervan werd het risicogevoel vergroot, samen met de kwetsbaarheid van bepaalde groepen (bijvoorbeeld van antidepressiva gebruikers).

In **hoofdstuk 7** hebben we de toepassing van DLC als een heuristisch instrument gepresenteerd om controversen rondom geneesmiddelveiligheid te analyseren. Door de combinatie van kwalitatieve en kwantitatieve data, op een longitudinale wijze, hebben we aangetoond dat multidimensionale analyses meer inzicht verschaffen in de dynamiek van geneesmiddelcontroversen. Verder hebben we aangetoond dat DLC een valide instrument is om de rol van verschillende stakeholders tijdens de SSRI en suïcidaliteit controverse te kunnen beschrijven. Om het maximale analytische vermogen uit DLC te kunnen halen, moet extra aandacht worden besteed aan de selectie van kwalitatieve en kwantitatieve data en databases. Incomplete data kan leiden tot gedeeltelijk, foutieve of oppervlakkig analyses van geneesmiddelcontroversen.

In **hoofdstuk 8** worden de belangrijkste bevindingen van dit proefschrift bediscussieerd. Toekomstige studies over vertrouwen in stakeholders van de farmaceutische sector horen een duidelijke en homogene definitie van vertrouwen te hanteren. Daarom stellen we in dit proefschrift een hedendaags definitie van vertrouwen voor die relevant is voor de farmaceutische industrie, de regulerende autoriteiten en artsen. We benadrukken de wetenschappelijke behoefte aan goed gestructureerde en methodologisch verantwoor-

de studies die vertrouwen in deze stakeholders meten. Tot nu toe leveren bestaande studies onvoldoende gegevens om uitspraken te kunnen doen over het niveau van het publieke vertrouwen in de farmaceutische industrie en de regulerende autoriteiten. We pleiten dan ook voor standaardisatie van methodieken in empirische studies naar vertrouwen in de farmaceutische sector om vergelijkingen tussen meerdere studies (en ook tussen verschillende stakeholders) te kunnen bevorderen. Het gebruik van innovatieve DLC studies kan hierin een belangrijke rol spelen.

Vertrouwen is fundamenteel voor het gezond functioneren van het farmaceutische sector. Vertrouwen bevordert innovatie, samenwerking en solidariteit. Door de toenemende ontwikkelingskosten van geneesmiddelen en de exponentiele groei aan regelgeving kan vertrouwen een bemiddelende rol gaan spelen waardoor de regeldruk afneemt en de kosten kunnen worden verlaagd. Tevens kan vertrouwen als de fundament fungeren om sterkere en stabielere relaties met het publiek op te bouwen die berust op een bilaterale dialoog tussen de farmaceutische industrie en regulerende autoriteiten.

RESUMEN

R

"Trust is like an eraser, it gets smaller and smaller after every mistake"

Anonymous

Resumen

Los productos farmacéuticos o medicamentos deben ser sometido a pruebas rigurosas antes de que su uso en la sociedad sea permitido. ¿Acaso esto quiere decir que todos los medicamentos son seguros y efectivos? La investigación de nuevos medicamentos es conducida en poblaciones meticulosamente seleccionadas y bajo circunstancias estrictamente controladas. Únicamente después de que estos medicamentos reciben una aprobación para ser comercializados es que pueden ser prescritos por profesionales de la salud. Sin embargo, las condiciones de uso de medicamentos durante la investigación clínica y la vida real son, aunque conocidas, extremamente diferentes. Los inesperados efectos secundarios que pueden llegar a ocurrir después de que un nuevo medicamento es masivamente usado en la sociedad han sido tema de debate público. Ejemplos de debates son: "la catástrofe de la talidomida" que ocurrió a finales de los años 50 y principios de los años 60 y fue provocada por el efecto teratógeno del fármaco causando que muchos bebés nacieran sin brazos o piernas. El uso de los medicamentos "rosiglitazona" y "rofecoxib" fue sancionado cuando se conoció que podían causar riesgos cardiovasculares (insuficiencia cardiaca o arritmias causadas por cardiotoxicidad). Y finalmente, la restricción impuesta a antidepresivos, en particular los inhibidores selectivos de la recaptación de serotonina (ISRS), prohibiendo su uso en niños y adolescentes debido a un supuesto riesgo de suicidio.

Varias pueden ser las consecuencias provenientes de controversias relacionadas con la seguridad de medicamentos, como la suspensión o cancelación de la licencia de mercadeo, incrementos en la regulación, atención de los medios de comunicación, o demandas judiciales. Muchos han asegurado que estas controversias tienen un efecto perjudicial en la confianza del público en el sector farmacéutico. En **capítulo 1** mencionamos que nuestro conocimiento acerca controversias relacionadas con la seguridad de medicamentos, al igual que su efecto en la opinión publica, es extraordinariamente limitado. Los pocos estudios que existen sobre este tema son basados en insuficientes hechos científicos, son superficiales, o poseen una estructura metodológica de poca calidad. Además, la relación entre la percepción del público y el uso de medicamentos no ha sido tomado en cuenta. Estas deficiencias indican la necesidad social y científica de estudios innovadores que analicen la relación entre la percepción pública y el uso de medicamentos. Los riesgos de medicamentos son inherentes a su uso. Y con los catalizadores mas convenientes (por ejemplo algunas acciones o reacciones de los medios de comunicación u otras protagonistas del sector farmacéutico) cada uno de estos riesgos de medicamentos tiene un gran potencial para poder desarrollarse hasta convertirse en una gran controversia. Por esta razón es importante que los protagonistas del sector farmacéutico monitoreen adecuadamente el debate publico acerca medicamentos.

Siendo parte de el consorcio Top Instituto Pharma (TIPharma) y del proyecto Escher, esta tesis doctoral presenta una serie de estudios empíricos acerca una controversia en particular: el supuesto riesgo de suicidio a consecuencia del uso de ISRS. Hemos logrado descifrar la dinámica social de esta controversia, su impacto en la confianza del público y hemos descrito el papel de varias partes interesadas o protagonistas. Este objetivo fue

conseguido gracias al uso del Ciclo de Vida de Medicamentos (CVM) como un instrumento heurístico.

Antes de comenzar con nuestro análisis de la controversia acerca del riesgo de suicidio durante el uso de ISRS nos encontramos con dos omisiones: I) confianza pública no ha sido definida en el sector farmacéutico, y II) los reclamos de desconfianza del público en el sector farmacéutico remiten hacia evidencia que aun no ha sido evaluada. Estas dos limitaciones son estudiadas en los **capítulos 2 y 3**.

En **capitulo 2** analizamos diferentes definiciones de confianza en varias disciplinas y deducimos una definición de confianza que es aplicable a los interesados del sector farmacéutico (estos son la industria farmacéutica, agencias reguladoras y doctores). El método usado en este estudio fue un meta-análisis de la literatura. Buscamos artículos que definieran confianza en el periodo desde 1980 hasta 2013 en tres bases de datos (PubMed, Scopus y Web of Science) y referencias cruzadas. Entre los 95 artículos que fueron seleccionados y analizados encontramos dos prominentes componentes de confianza: vulnerabilidad y pericia. En base a estos dos componentes proponemos la siguiente definición de confianza para el sector farmacéutico:

1. La disposición de mostrarse vulnerable ante una determinada situación, persona o instituto al momento de recibir ayuda médica o farmacéutica, y

2. La expectativa en la pericia de la industria farmacéutica, agencias reguladoras y/o doctores para cumplir con la tarea la cual son responsables en la sociedad. Esta es el desarrollar, producir y evaluar productos farmacéuticos de alta calidad y el préstamo de cuidado de la salud de nivel aceptable.

Los pacientes son, por definición, un grupo frágil debido a su condición física y salud (enfermedad) y sobretodo por su necesidad de recibir cuidados médicos y/o farmacéuticos. Por esta misma razón es tan importante que los pacientes puedan depositar su confianza en la pericia de médicos. Confianza en la pericia de la industria farmacéutica y las agencias reguladoras de medicamentos es también muy importante como institutos responsables de la producción y evaluación de productos farmacéuticos. La pericia de estas instituciones fomentara confianza en el público, la cual ayudara a disminuir o sobrellevar la vulnerabilidad de pacientes. Acciones incompetentes por parte de estos actores del sector farmacéutico podrán generar desconfianza, la cual puede llegar a ser manipulada por otros actores involucrados.

En el **capitulo 3** de esta tesis analizamos un grupo de estudios académicos y no-académicos en los cuales en el tema de estudio fue confianza en la industria farmacéutica, en las autoridades reguladoras de medicamentos y en médicos. Concretamente, en este capitulo evaluamos la metodología de todos estos análisis para discernir que parámetros fueron estudiados y como lo hicieron. Para este fin desempeñamos una revisión sistemática de la literatura hasta el año 2012 y usamos PubMed, Web of Science y Scopus como bases de datos. Por otro lado también analizamos encuestas públicas las cuales identificamos por medio de búsquedas en Google y referencias cruzadas. En total evaluamos 47 artículos científicos que estudiaron confianza en la industria farmacéutica

(8 piezas), en las agencias reguladoras de medicamentos (3 piezas), y en médicos (36 piezas). Además evaluamos diez y seis encuestas no-académicas.

En base a este estudio concluimos que confianza ha sido razonablemente estudiada en la profesión médica (36). Lo mismo no pudimos concluir acerca la industria farmacéutica (8) o las agencias reguladoras de medicamentos (3), donde la cantidad de estudios es escaza. Además, pudimos observar que la gran mayoría de los estudios poseen deficiencias metodológicas. Las mas notables deficiencias son:

- La ausencia de una definición explícita de confianza
- La ausencia de estandarización (metodológica)
- Variable o bajos niveles de participación

Estudios que midan confianza deben proveer una definición de confianza (como termino) y/o especificar lo que los estudiadores entienden por este termino. De esta manera se pueden prevenir dudas o confusiones con otras cualidades relacionales tales como empatía, solidaridad, reciprocidad, o mutualidad. Cuestionarios a base de escalas son instrumentos útiles para poder medir confianza. Desafortunadamente no pudimos observar gran homogeneidad entre los artículos con respecto al uso de estos instrumentos: Trust in Physician Scale (7 artículos), Wake Forrest/Hall's Trust in Physician Scale (6 artículos), the Public Trust in Healthcare Questionnaire (2 artículos), y 25% de los estudios no menciono el uso de un instrumento (12 artículos). Otros siete estudios mencionaron el uso de cuestionarios con "preguntas abiertas". El uso de esta clase de cuestionarios es controversial ya que generan espacio para interpretaciones personales las cuales son influenciadas por variables como educación, sexo, raza, o edad. Además pudimos observar que los estudios de confianza en la industria farmacéutica y las agencias reguladoras no analizaron confianza como parámetro primario de investigación.

En cuanto a los niveles de confianza observamos que el público señalo desconfianza o poca confianza en la industria farmacéutica y en las agencias reguladoras de medicamentos. Las razones de desconfianza fueron: las ganancias tienen mas prioridad que la seguridad de los pacientes, falta de transparencia, honestidad, integridad y bajo reconocimiento por parte del público (especialmente refiriéndose a las agencias Europeas de regulación de medicamentos). El exceso de regulación, los incrementos en los costos de la sanidad pública y una agenda doble también fueron razones por las cuales el público argumento su desconfianza en estas instituciones. El público notablemente aseguro tener confianza en la industria farmacéutica y agencias reguladoras al tratarse de la pericia de estas instituciones para desarrollar, producir y evaluar productos farmacéuticos.

Médicos eran vistos por el público como competentes y con pericia al demostrar características como el ser cuidadosos, honestos, respetuosos y que priorizaban las necesidades de pacientes. Estos médicos recibían mayores niveles de confianza en comparación con médicos que se comportaban de manera inmoral, impropia, condenadora, presuntuosa, arrogante o que discriminaban a pacientes. La confianza del público en médicos no parece ser afectada si estos tienen relaciones profesionales con la industria farmacéutica con tal de que estas relaciones resulten en mejores terapias para la sociedad.

Después de haber dado una definición de confianza para el sector farmacéutico y de haber analizado la evidencia de estudios empíricos midiendo los niveles de confianza, pasamos a investigar la controversia del uso de los ISRS y el supuesto riesgo de suicidio. Este análisis fue conducido en base al uso multidimensional del CVM como instrumento explorador. A continuación vamos a enumerar las dimensiones de data que usamos en este análisis:

1. Patrones de publicaciones en revistas especializadas/científicas y en periódicos Holandeses e Ingleses (**capitulo 4**)
2. Patrones de uso de ISRS en los Países Bajos y en Reino Unido (**capitulo 5**), y
3. Datos relacionados con sucesiones de eventos – divididos en dos elementos:

   a. Una meticulosa y cronológica reconstrucción de todos los eventos que delinearon la presente controversia, y

   b. La definición de confianza pública en el sector farmacéutico, la cual fue presentada en el segundo capitulo de esta tesis

En el **capitulo 4** presentamos un análisis de los patrones de publicaciones en revistas especializadas/científicas y en periódicos de los Países Bajos y del Reino Unido entre los años 2000 y 2010. Para este fin hicimos una revisión sistemática de la literatura científica a través de Embase (base de datos) y de artículos de periódicos a través de LexisNexis (base de datos). Los artículos que fueron seleccionados de estas bases de datos fueron indexados en tres categorías: "efecto" (que es relacionado con el efecto terapéutico de los ISRS), "tipo de articulo" y "grupos de edad determinada". El ratio fue calculado entre los artículos que fueron indexados como positivos o negativos. En total indexamos 1141 artículos, los cuales eran: 352 científicos, 224 de periódicos Holandeses y 565 de periódicos Ingleses. En esta investigación pudimos observar que el tono de los artículos científicos sobre la seguridad y la efectividad de los ISRS era positivo en su gran mayoría (39%), comparado con artículos con tono neutral (30%) o negativo (31%; $P<0.001$). Además pudimos discernir una parcialidad con tendencia positiva en las publicaciones científicas (ratio=8.5). Mas de la mitad de las publicaciones científicas (60%) referían a estudios sobre la investigación de estos medicamentos en pacientes. Y los artículos científicos que discutían el lado negativo de estos medicamentos mas que todo discutían este problema en niños.

Los artículos de periódicos Holandeses y del Reino Unido comunicaban primordialmente un tono negativo en cuanto a la efectividad y seguridad de los antidepresivos (ratios: 0.69 en los Países Bajos y 0.94 en el Reino Unido). En las revistas científicas observamos que la tendencia de publicaciones negativas aumento en el periodo en que las alertas provenientes de las agencias reguladoras fueron pronunciadas (en los periodos de 2003-2004 y 2007-2008). Particularmente pudimos identificar que esta tendencia negativa u oleada de "malas" noticias fue causada por artículos de opinión, y no de investigación. De este estudio concluimos que el público Holandés y del Reino Unido fue informado a tiempo sobre la controversia de el uso de ISRS y el riesgo de suicidio. De este estudio se genero una nueva expectativa: la publicidad negativa acerca los ISRS podría generar un efecto en el uso de estos medicamentos en ambos países.

En el **capitulo 5** de esta tesis agregamos una dimensión adicional a nuestro modelo de CVM para el estudio de controversias. Esta dimensión son las ventas y prescripciones de ISRS. En este capitulo particularmente analizamos si la oleada de "malas" noticias y las alertas de las agencias reguladoras tuvieron una influencia en el uso de ISRS en los Países Bajos y el Reino Unido entre los años 2000 y 2010. Para este fin, IMS Health amablemente contribuyo proveyendo datos de ventas mensuales de ISRS en estos países. Las cantidades de ventas las presentamos como dosis diaria definida (DDD) por 1000 habitantes por día (DDD/1000 habitantes/día). Los DDD fueron calculados por medio de las cantidades vendidas, la intensidad de las dosis vendidas y la cantidad de habitantes (mensual) de cada país. Las tendencias de uso de ISRS fueron estudiadas por medio de un análisis de series temporales, el cual crea segmentos y examina los cambios por medio de regresiones. Adicionalmente analizamos si los cambios en uso de ISRS fueron sincronizados con los periodos de alertas de las agencias reguladoras o cuando aumento la publicidad negativa. Por otra parte, el instituto de la salud de los Países Bajos (bajo el proyecto de información de medicamentos – GIP) amablemente proveyó datos anuales de prescripciones de ISRS los cuales indexamos y analizamos en diferentes grupos de edad (pediatría 0-14 años, adolescentes 15-19 años, jóvenes adultos 20-24 años, adultos 25-64 años y ancianos 65 años y mayores).

En este estudio observamos una relación no causal entre cambios en los patrones de uso de ISRS y los periodos de las alertas y la oleada de "malas" noticias en periódicos. No pudimos observar significantes reducciones en el uso de ISRS. Al contrario, el uso de ISRS incremento de 16.7 DDD/1000 habitantes/día (Enero 2000) a 27.9 DDD/1000 habitantes/día (Julio 2010) en los Países Bajos. El uso de ISRS se duplicó en el Reino Unido de 27.4 DDD/1000 habitantes/día (Enero 2000) a 50.1 DDD/1000 habitantes/día (Diciembre 2009). En base a estas observaciones concluimos que las alertas emitidas por las agencias reguladoras de medicamentos y la oleada de "malas" noticias en periódicos tuvieron un impacto limitado con respecto al uso de ISRS en los Países Bajos y el Reino Unido.

La oleada de "malas" noticias acerca la seguridad de los ISRS y las alertas emitidas por las autoridades coincidieron con reportes de un incremento de desconfianza del público en la industria farmacéutica y las agencias reguladoras de medicamentos. Pero aún fue mas llamativo el hecho de que el uso de ISRS en los Países Bajos y el Reino Unido no disminuyó. Estas dinámicas conflictivas de menos confianza y un aumento en el uso ISRS generan interrogativas acerca el rol de confianza (como entidad psicológica) en los actores del sector farmacéutico durante esta controversia en particular. Por esta misma razón decidimos, en capitulo 6, estudiar el rol de confianza durante la controversia alrededor el uso de ISRS y el riesgo de suicidio. En este estudio agregamos una dimensión de mas a nuestro modelo de CVM para estudiar controversias. Esta dimensión se basa en una reconstrucción sistemática y cronológica de los eventos que moldearon e influyeron la controversia en dicho. Los datos, relacionados a los eventos, fueron presentados en el contexto de la definición de confianza que presentamos en el segundo capitulo de esta tesis.

Por medio de este análisis observamos fluctuaciones temporales de la confianza del público en todos los actores del sector farmacéutico. Varios fueron los hechos por los

cuales la confianza del público en la industria farmacéutica y agencias reguladoras fue perjudicada durante esta controversia como por ejemplo: el jugar o asumir un rol pasivo o reactivo, ser el objeto de publicidad negativa, o estar involucrado en procesos judiciales. En particular estos eventos fueron vistos en los ojos del público como acciones incompetentes, desmañadas, y faltas de ética. Como consecuencia a estas acciones, la percepción del público de estar en riesgo fue aumentada, junto con los niveles de vulnerabilidad de algunos grupos (como por ejemplo pacientes que usan antidepresivos).

En el **capitulo 7** presentamos el uso de CVM como un instrumento heurístico para analizar controversias relacionadas con la seguridad de medicamentos. Es por la combinación de datos de naturaleza cuantitativa y cualitativa, y por su análisis de forma longitudinal, que pudimos demonstrar el valor adicional de estudios multidimensionales que proporcionan una perspicacia mas profunda de las dinámicas de controversias de medicamentos. Además pudimos demonstrar que los CVM, como instrumento, son capaces de generar información suficiente para explicar el rol de diferentes involucrados y actores durante controversias. Sin embargo, extrema atención debe ser prestada a la selección de bases de datos y a los parámetros de carácter cualitativo y cuantitativo para poder utilizar al máximo la potencia analítica de estudios que usan CVM. Datos incompletos pueden resultar en análisis parciales, superficiales o erróneos de controversias de medicamentos.

En el **capitulo 8** discutimos los resultados mas importantes de la presente tesis. Futuros estudios de confianza en los principales actores del sector farmacéutico deben proveer de antemano una definición clara y homogénea de confianza. Por esta razón proponemos en esta tesis una definición de confianza que es actual al igual que relevante para la industria farmacéutica, las agencias reguladoras de medicamentos y médicos. Además enfatizamos la necesidad pública y científica para tener (mas) estudios que midan confianza en el sector farmacéutico de una manera mas estructurada y con mejores metodologías. Hasta hoy en día, los estudios que analizan confianza generan insuficiente evidencia como para hacer inferencias decisivas con respecto a los niveles de confianza del público en la industria farmacéutica o las agencias reguladoras de medicamentos. En esta tesis abogamos por una estandarización de metodologías en estudios empíricos que midan los niveles de confianza en el sector farmacéutico para poder hacer comparaciones entre estudios y entre diferente actores. Aquí puede el uso de CVM jugar un rol decisivo.

Confianza es fundamental para que el sector farmacéutico pueda funcionar saludablemente. Confianza promueve y estimula innovación, cooperación y solidaridad. Debido a los crecientes costos relacionados con el desarrollo de medicamentos y los constantes incrementos en el numero de regulaciones, confianza posee el suficiente potencial para lograr disminuir la necesidad de crear mas regulaciones y de por si los costos inherentes al desarrollo de medicamentos. Basadas en dialogo bilateral, confianza puede además funcionar como el fundamento fuerte para construir relaciones estables entre el público, la industria farmacéutica y las agencias reguladoras de medicamentos.

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"Gratitude is associated with higher levels of social support and lower levels of stress and depression"

- Wood A.M. et al. Journal of Research in Personality. 2008; 42:854–871

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Se acabo!!! Yes, it is done. He,he...eindelijk, het is af!!!

There is a saying in Spanish that goes: “no hay mal que dure cien años, ni cuerpo que lo resista.” The English translation would be something like: “there is no illness that would endure one hundred years, nor a body that would withstand it.” This saying summarizes in few words my experience of doing a PhD. It is not an easy job, nor a fast one, but you have to finish it before it finishes you. Of course, reaching the finish line was not a job that I achieved by myself. There was a team surrounding and supporting me throughout the whole road. To all of them, I want to demonstrate my immense gratitude for their help in the following paragraphs.

Dear God, I want to thank you for everything that you have given me in my life. I truly feel blessed for all those miracles that I don’t deserve such as my loving kids and my wonderful and beloved wife, a healthy life and the possibility to study. Thank you that, regardless of everything, you put the right people next to me and you put me in the right place to achieve the goal of becoming a doctor.

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LIST OF PUBLICATIONS

List of publications

Publication trends in newspapers and scientific journals for SSRIs and suicidality: a systematic longitudinal study.

Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJ, Belitser SV, Raaijmakers JA, Pieters T.

BMJ Open. 2011 Dec 6;1(2):e000290.

A 10-year analysis of the effects of media coverage of regulatory warnings on antidepressant use in The Netherlands and UK.

Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJ, Belitser SV, Warmerdam J, de Valk V, Raaijmakers JA, Pieters T.

PLoS One. 2012;7(9):e45515.

Restoring trust in the pharmaceutical sector on the basis of the SSRI case.

Hernandez JF, van Thiel GJ, Mantel-Teeuwisse AK, Raaijmakers JA, Pieters T.

Drug Discov Today. 2014 May;19(5):523-7.

Unrelated to this thesis:

Gebruik antidepressiva opmerkelijk resistent tegen negatief nieuws

Hernandez JF.

MFM editie 1, Maart 2013 (Article in Dutch)

ABOUT THE AUTHOR

"Everybody is a genius. But if you judge a fish by its ability to climb a tree, it will live its whole life believing that it is stupid"

Anonymous

About the author

Juan Francisco Hernandez was born on the 28th of August 1977 in Bogotá, Colombia. He graduated from the San Luis high school in 1994. He studied pharmaceutical chemistry and obtained his bachelor in pharmacy in 2001 at the Corporación Tecnológica de Bogotá. From 1999 to 2001, he worked, first as a pharmacist trainee, then as a full pharmacist, in a wholesale distribution center in Bogotá. In 2002, Francisco moved to the Netherlands. In 2003, he obtained his certificate for Dutch as second language (Nederlands als Tweede Taal - higher level). Between 2003 and 2006, he also studied organic chemistry (BSc) at the Avans University of Applied Sciences in Breda, the Netherlands. After this, Francisco started a master study (Drug Innovation) at Utrecht University, from which he graduated from in 2009. From 2009, he worked full time as a PhD-student at the Department of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute of Pharmaceutical Sciences, Faculty of Science of Utrecht University. The results from this work are presented in this thesis. Since 2013, he has worked for Excerpta Medica as an Associate Medical Communications Manager. Francisco lives in Hendrik Ido Ambacht, the Netherlands.