Factors that influence new drug diffusion amongst EU primary care physicians

A systematic literature review

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List of abbreviations

ARBs	Angiotensin II receptor blockers
CME	Continuing medical education
CIs	Confidence intervals
EBP	Evidence-based practices
EU	European Union
GP	General practitioner
HCP	Health care practice
KNMP	Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
MeSH	Medical Subject Headings
PPQCs	Physicians-pharmacists quality circles
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyse
PSRs	Pharmaceutical sales representatives
PTAMs	Pharmacotheurapeutic audit meetings
UK	United Kingdom

Laymen's summary (High-school biology level)

Background

In the process of developing new drugs a number of obstacles are present, for instance acquiring patents or acquiring approval to sell the new drug. After passing these obstacles, a last challenge is to incorporate this new drug into a doctor's prescribing pattern or in different words for doctors to adopt the new drug. This study investigated the factors that are described in scientific literature that influence the adoption of new drugs by primary care doctors, focusing on European countries.

Methods

A conceptual model was created, by applying the Diffusion of Innovation theory to the drug market. A systematic literature review was performed, by searching the records of the PubMed database for articles published between 2005 and 2013 that addressed one of eleven questions formed on the basis of the conceptual model. In a second step articles that focused on European countries were selected.

Results

Our search resulted in 16 articles that studied nine different European countries. All but one study used numerical data to measure adoption of new drugs. Five mutual drug (classes) were identified; COX-2 inhibitors, esomeprazole, angiotensin II receptor blockers, rosuvastatin and tiotropium. The main investigated outcome was considerably different between studies, as well as their definition of a new drug, whilst some used no definition. All questions were addressed in at least one of the articles.

Conclusion

A limited amount of information was identified from studies that differed on a lot of key areas in their study design. As a result, our findings may translate not particularly well to other areas or even for Europe in general. That said six out of our eleven potential factors to influence the adoption of new drugs by European primary care doctors seemed to be established. First, when a doctor envisioned a new drug to have more relative benefit, he was more likely to adopt that drug. Second, charismatic colleague doctors influenced the opinion of a doctor about a new drug, thereby influencing adoption. Third, it was identified that within a doctor's practice nurses and secretaries had a positive influence on the time it takes to adopt a new drug. Fourth, patients and specifically request from patients changed drug prescribing behaviour of doctors, making it less based on scientific evidence. Fifth, contact with the pharmaceutical industry seemed to speed up adoption. Last, meetings between pharmacists and primary care doctors that were of high-quality and evaluated decisions from previous meetings, had a negative influence on new drug adoption, while making prescriptions more based on scientific evidence. These findings could help academics to increase the impact of their education towards primary care doctors.

Abstract

Background

Adoption of new drugs by physicians can be seen as a final hurdle for new drugs to reach patients. Previous studies have lacked to identify factors that are involved in the adoption of new drugs by general practitioners (GPs). Therefore, this study aimed to investigate the factors that influence the adoption of new drugs by primary care physicians, focusing on European Union (EU) member states.

Methods

A conceptual model was developed, by applying the Diffusion of Innovation theory specifically to the pharmaceutical market. This model yielded eleven potential factors to investigate. A systematic literature review was performed, by searching the records of the PubMed database for articles published between 2005 and 2013 that addressed one the eleven predetermined concepts. In a second step articles that focused on EU member states were selected.

Results

The search yielded 16 articles in total that focused on adoption amongst GPs in nine different EU member states. Five commonly studied drug (classes) were identified; COX-2 inhibitors, esomeprazole, angiotensin II receptor blockers, rosuvastatin and tiotropium. All but one study applied quantitative methods. Primary outcome measurements differed, as well as new drug definitions, whilst some studies lacked such a definition. All questions were addressed in one or more article.

Conclusions

Data was limited and studies differed substantially in methodology. As a result, identified relationships may have limited generalizability. Nonetheless, six out of eleven concepts seemed to influence drug adoption amongst EU GPs. First, more perceived relative advantage was linked with increase adoption speed. Second, opinion leaders, such as charismatic colleagues, seemed to influence adoption. Third, nurses and secretaries employed by practices, lowered time to adoption of GPs, as organisational leaders. Fourth, interacting with patients and specific patients' requests influenced adoption, whilst also resulting in is less evidence-based prescribing. Fifth, interaction with industry seemed to accelerate adoption of new medicines. Last, high-quality pharmacotheurapeutic audit meetings had a negative influence on adoption of new medicines, whilst improving evidence-based prescribing. Future efforts by academic detailers might benefit from these results by incorporating features from these high-quality meetings.

Table of contents

List of abbreviations 1
Laymen's summary (High-school biology level) 2
Abstract 3
Introduction 5
Conceptual model 6
Diffusion of Innovation theory 6
Sub-questions 10
Methods 11
Search strategy 11
Results 13
Search results 13
Main characteristics 14
Information on sub-questions 15
Discussion 21
Conclusion 24
Bibliography 25
Appendices 28

Introduction

Diffusion of drugs amongst prescribers is the last, but nevertheless crucial step in the drug development process (Landsman *et al*., 2014), since patients can not benefit from new medicines, if those medicines do not reach them (Morris *et al*., 2011). The process of diffusion of new medicines amongst prescribers is complex (Atun and Sheridan, 2007). For example, at the moment of market entry, physicians have little knowledge about a new drug, creating uncertainty (Florentinus, 2006). As a result, new drugs are often channelled towards patients that do not respond sufficiently to existing pharmacotherapy (Petri and Urquhart, 1991)(Hudson and Suissa, 2010). This "channelling" should be addressed whilst designing confirmatory clinical trials, as well as in company's marketing strategies (Schneeweiss *et al*., 2011). Understanding the processes involved in the diffusion of new medicines is important and may result in shorter lag-times for patients , i.e. less time between drug discovery and drug access (Morris *et al*., 2011).

The process of diffusion of new medicines is described by multiple theories with overlapping features from different scientific fields, e.g. diffusion science, dissemination science, implementation science and translation science (Green *et al*., 2009). A theory commonly used is the Diffusion of Innovation theory of Rogers (2010), which states that adopters of a new innovation, in this case drug prescribers, make choices on whether or not to embrace that innovation, by determining the benefits and risks of this innovation, with its inherent uncertainty (Rogers, 2010) (Makowsky *et al*., 2013).

All parties involved in the health care value chain, which aims to provide sufficient care to patients, can have an influence on the rate of diffusion (Mikkelsen, 2013). The role of physicians has been described relatively well in literature, illustrated by the recent review of Mikkelsen (2013) on factors and contexts that have influence on physicians prescribing patterns (Mikkelsen, 2013). However, this review did not focus on diffusion of innovation, in general or applied to the pharmaceutical market. In addition, Mikkelsen (2013) did not distinguish between physicians, e.g. primary or secondary care.

In contrast, this thesis focused on primary care physicians, i.e. general physicians and family physicians, specifically, as in multiple European countries the general physician (GP) is considered a gate-keeper between (new) drugs and patients (Linden *et al*., 2003). As a result, they prescribe a considerable amount of total prescriptions to a wide variety of patients, as opposed to medical specialists that normally treat an isolated population of patients (Trusheim *et al*., 2010). In addition, GPs are more likely to encounter new drugs from a wider variety of disease areas (Robertson *et al*., 2011). Moreover, specialists may have different inherent attitudes towards new medicines and their costs, as they may have less alternative treatment options (Pugh *et al*., 2003). Therefore, this thesis aimed to determine factors described in scientific literature that influence the diffusion of new drugs specifically amongst primary care physicians.

Healthcare systems differ between European countries and other countries, e.g. US and Australia. Therefore, only articles on adoption amongst European Union (EU) GPs were investigated. In addition, the aim was to provide an up-to-date review. Therefore, papers from 2005 up to 2013 were studied. This study aimed to answer the following research question:

- *Which factors that influence the diffusion of new drugs amongst EU primary care physicians are described between 2005 and 2013?*

Conceptual model

As a starting point for a conceptual the Diffusion of Innovation, as defined by Rogers (2010), was adopted, as it commonly used to investigate diffusion of interventions (Dingfelder and Mandell, 2011). In addition, those elements that had specific importance for the pharmaceutical market were determined. On the basis of this specification, a conceptual model was formed and sub-questions were created. In the following, the theory, conceptual model and sub-questions will be presented.

Diffusion of Innovation theory

The Diffusion of Innovation theory of Rogers defines four key areas of factors that determine the diffusion of a new innovation amongst adopters. Those areas are the innovation, communication channels, time, and social system (Rogers, 2010). Diffusion is defined as the process by which an innovation is communicated through channels over time among the members of a social system.

Innovation

An innovation is defined by Rogers as an idea, practice, or object that is perceived by the adopter as new. In this thesis a new drug was considered as the innovation. It was anticipated that definitions of new drug would differ between studies, as was identified by Morris *et al*. (2011). Therefore, a wide definition for new drugs was adopted. The definition of Segen (1992) was followed and a new drug was defined as any agent intended for therapeutic use in man, the composition of which is not generally recognised as safe and effective for use, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs (Segen, 1992).

Regarding the innovation, in total five factors are specified that can have an influence on diffusion (Rogers, 2010), which are presented below.

- Relative advantage defined as the degree to which an innovation is perceived as better than the idea it supersedes.
- Compatibility defined as the degree to which an innovation is perceived as being consistent with the existing values, past experiences and needs of potential adopters.
- Complexity defined as the degree to which an innovation is perceived as difficult to understand and use.
- Trialability defined as the degree to which an innovation may be experimented with on a limited basis.
- Observability defined as the degree to which the results of an innovation are visible to others.

Florentius (2006) studied the applicability of the Diffusion of Innovation theory for the pharmaceutical market. Regarding the five factors of Rogers he identified that for new drugs relative advantage is important, whilst the other factors are not. When comparing drugs, the other four factors are likely to be very similar and therefore less relevant. For instance, when assessing observability, the effects of a new drug will most likely be observed in the same fashion as a previous drug, e.g. a regular doctor's visit (Florentinus, 2006). This similarity between drugs can also be identified by the extensive amount of me-too drugs, i.e. drugs with highly similar chemical and pharmacological properties as existing drugs, that have entered the market in recent past (Eaglstein, 2013). As a result, in this study only relative advantage was included in the conceptual model.

Relative advantage in the eyes of the GP might be devised by different factors, as Florentius (2006) described that post market authorisation, a new drug will develop its own fingerprint. This unique fingerprint is a representation of key elements that are specific for that drug. Elements that form this fingerprint include reported side effects, accumulating research evidence, exposure to marketing, costs and reimbursement patterns (Florentinus, 2006).

Communication channels

A communication channel is defined by Rogers as the means by which messages get from one individual to another (Rogers, 2010). Within communication channels, change agents can be an important factor to influence diffusion (Ager *et al*., 2011). A change agent is defined by Rogers as an individual who influences adopter's innovation decision in a direction deemed desirable by the change agent (Rogers, 2010).

Ager *et al.* (2011) applied the model of Diffusion of Innovation theory to evidence-based practices (EBP), which includes new evidence-based drugs. They described that high quality change agents can influence adoption. In addition, they identified between two specific types of change agents, i.e. opinion leaders and organisational leaders (Ager *et al*., 2011).

First, opinion leaders within an communication channel, for instance peers, hospital doctors, policy makers or politicians, can have a considerable impact on the rate of adoption (Ager *et al*., 2011). As the article of Ager *et al*. lacked a specific definition for opinion leader the following working definition was adopted; an individual outside of the GPs practice that could have an influence on the GP's adoption of new pharmacotherapies.

Second, organisational leaders can have an impact on the organisation's ability to bring about and accept change, especially when these leaders are knowledgeable and skilled (Ager *et al*., 2011). Examples of organisational leaders include other GPs within the same practice, head administrators and supervisors. As the article of Ager *et al*. lacked a specific definition for organisational leadership the following definition for organisational leader was adopted; i.e. an individual inside a GP's practice or organisation that is capable of changing adoption behaviour of that GP.

Both opinion as organisational leaders were included in the conceptual model.

Time

Rogers states that in general time has a positively effect on diffusion of innovation (Rogers, 2010). It is likely, also for the pharmaceutical market, that time has an influence on adoption. As knowledge develops about a novel drug over time, uncertainty about its benefits decreases and knowledge about side-effects increases. As a result, physicians may be more inclined to prescribe a drug (Florentinus, 2006).

However, time is often measured as an outcome for diffusion of an innovation (Morris *et al*., 2011). In addition, this study focuses on new drugs, i.e. drugs that have been on the market for a limited amount of time. Therefore it may be difficult to study time specifically. Therefore, the factor time as such in was not included in the conceptual model.

Time is also described to be involved in the innovation-decision process, as decisions whether to adopt an innovation develop over time. Rogers described that characteristics of the adopter influence this decision making process, as some adopters are more 'innovative' than others.

Florentius (2006) investigated if specific characteristics of GPs determined their likelihood to adopt a new drug, i.e. their innovativeness. He found that GPs that were early adopters of a first drug were not early adopters of a second. In addition, he argued that no specific patterns in early adoption are present and that adoption is highly drug-dependent. As a result, it seems that at least for drug adoption, there is no such thing as an innovative primary GP, but adoption varies between drugs (Florentinus, 2006).

In contrast, recently, Liu and Gupta described in their diffusion model for new drug adoption amongst physicians that a specific adopter characteristic, namely previous prescription volume in the disease category, had a direct influence on adoption (Liu and Gupta, 2012). This may be explained by a similar finding by Ager *et al*. (2011), who mention that prior knowledge about a drugs or its related underlining theories is positively related to the adoption of that therapy (Ager *et al*., 2011). Therefore, it was decided to include physicians' characteristics in the conceptual model, but to focus on previous prescription volume in the disease area.

Social system

Rogers defines a social system as a set of interrelated parties with a common goal that are involved in combined problem-solving. A number of items in the social system of primary care physicians can influence their adoption of new medicines.

A first item which is likely to influence adoption is interaction with patients (Florentinus, 2006). For example, patient's may put GPs under pressure by requesting a new medication (Florentinus, 2006). Reasons for acknowledging such patient's requests include maintaining a good doctor-patient relationship, time constraints and avoiding conflict (Florentinus, 2006). Similarly, Liu and Gupta (2012) described that patient's requests is a key determinant in their prediction model.

A second item that is described to influence diffusion of new drugs is marketing aimed at physicians, i.e. interaction with pharmaceutical industry (Florentinus, 2006). At the moment of market entry drug companies possess information about the new drug, since they have been studying it extensively (Florentinus, 2006). However, the potential adopter has limited information, which fuels uncertainty (Florentinus, 2006). As a result drug companies try to transfer information to physicians through marketing, often to high-light a new drug´s potential benefit (Florentinus, 2006). A specific tool that is often used by pharmaceutical industry is targeted detailing, in which pharmaceutical sales representatives (PSRs) visit GPs to discuss research evidence of new pharmacotherapies. Similarly, Liu and Gupta (2012) described that marketing efforts and specifically detailing influence adoption of new drugs by physicians.

The third item that may influence prescription decisions is the interaction with local community pharmacists (Florentius 2006). The role of the pharmacist within health care has been evolving from a passive supplier of drugs towards an active supervisor of drug prescriptions and even drug prescriber (Makowsky *et al*., 2013). Florentius *et al*. (2006) argues that improved involvement of community pharmacists has influenced GP prescribing. As a result, it is also likely this involvement it influences new drug adopting (Florentius, 2006). A specific tool that might be used to influence adoption is through high-quality pharmacotheurapeutic audit meetings (PTAM) (Florentinus *et al*., 2007). These are meetings between GPs and community pharmacists, where first-choice prescription patterns are discussed with the intent to improve the quality of prescribing (Eimers *et al*., 2008). In addition, information from industry can be discussed, sometimes with industry representatives

present (Florentinus, 2006). However, currently, presence of industry at such meetings is undesirable and is advised against (Eimers *et al*., 2008). Florentius describes these meetings to be a proper tool to influence early new drug description (Florentinus *et al*., 2007).

A last item that may influence prescription decisions is interaction with academia. Medical education from academia keeps GPs up-to-date about current medical developments. Mascarenhas *et al*. (2007) identified that continuous medical education is an important factor for physicians to adopt a new drug (Mascarenhas *et al*., 2007). A specific tool for academia to influence adoption of new drugs by GPs is through academic detailing, a process in which academia or sometimes non-profit educational research centres, such as the Dutch Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP), provide pharmacists and GPs with the most recent medical evidence (Fischer and Avorn, 2012). The intent of academic detailing is to improve prescribing behaviour by making it more evidence-based (Fischer and Avorn, 2012). This academic detailing may have a direct influence on prescribing patterns of primary care physicians (Chhina *et al*., 2013).

The four interaction items were included in our conceptual model, i.e. interaction with patients, pharmaceutical industry, community pharmacists and academia. In addition, three specific tools were included, i.e. targeted detailing, PTAMs and academic detailing.

The conceptual model is presented in Figure 1.

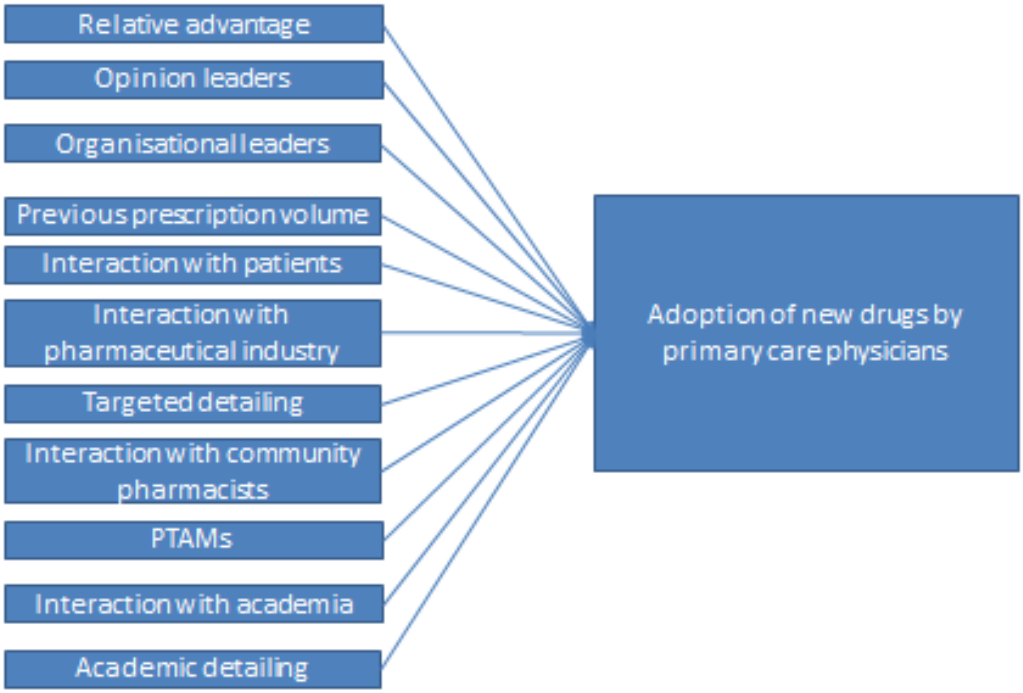

Figure 1: Conceptual model of factors that influence adoption of new drugs by primary care physicians

Sub-questions

On the basis of the conceptual model the following sub-questions were formed.

1. How does perceived relative advantage influence diffusion of a new drug amongst EU primary care physicians?
2. How do opinion leaders influence the diffusion of a new drug amongst EU primary care physicians?
3. How do organisational leaders influence the diffusion of a new drug amongst EU primary care physicians?
4. How does previous prescription volume in the disease area influence the diffusion of a new drug amongst EU primary care physicians?
5. How does interacting with patients influence the diffusion of a new drug amongst EU primary care physicians?
6. How does interaction with the pharmaceutical industry influence the diffusion of a new drug amongst EU primary care physicians?
7. How does targeted detailing influence the diffusion of a new drug amongst EU primary care physicians?
8. How does interaction with community pharmacists influence the diffusion of a new drug amongst EU primary care physicians,
9. How do PTAMs influence the diffusion of a new drug amongst EU primary care physicians?
10. How does interaction with academia influence the diffusion of a new drug amongst EU primary care physicians?
11. How does academic detailing influence the diffusion of a new drug amongst EU primary care physicians?

Methods

In the following, the methods for the systematic review of the literature regarding factors that influence the prescription behaviour of EU primary care physicians are presented. First, the search strategy is described, followed by the selection procedure to select relevant articles and the data extraction and analysis strategy.

Search strategy

It was decided to include information from a wide variety of studies. First, because Morris *et al* (2011) identified that consistency in methodology of previous studies on drug diffusion was lacking, e.g. some studies took uptake into a clinical guideline as a cut-off point, whilst others focused on first documented use of the new drug. Second, because we wanted to determine underlying reasoning for prescribing new drugs. Therefore, both information on prescriptions numbers and patterns from quantitative studies, for instance drug utilisation studies, were investigated, as well as information from qualitative studies, for instance interview studies.

Database

The database that was selected as our primary source for information is PubMed. This database was chosen, because is often used for biomedical research (Bachmann *et al*., 2003). In addition, it provides an easy-to-use method to perform and record systemic reviews. With the PubMed search builder, subjects can be searched systematically, by including MeSH (Medical Subject Headings) and search terminology (Robinson and Dickersin, 2002). Moreover, searches and search results can be recorded and safely uploaded into reference-management software (Robinson and Dickersin, 2002).

Search string

Common MeSH terms in articles that address primary care adoption of medicines were identified and included in the search, i.e. Diffusion of Innovation, Physician's Practice Patterns, Drug Utilization, Family practice/physicians and Drug Prescriptions. In addition to the identified MeSH terms, the focus was on new medicines. Therefore, search terms that addressed this novelty aspect were included; i.e. new, novel, innovative, and recent. The terms and the MeSH term were combined with search terms specific to each sub-question. Those search terms can be found in Appendix I.

Additionally, this study's focus was on diffusion amongst EU primary care physicians. It was identified that no relevant studies were found by including the terms Europe or EU in the search. However, without including Europe or EU, articles that addressed member states were represented. As it was envisioned that it would be too labour intensive to search for all 28 member states individually, articles were screened geographical area in a second step in the selection procedure.

Article Selection

The search results were uploaded into the reference-management program Mendeley (version 1.10.3). Search results were screened by reading the title and the abstract. The following eligibility criteria were used to select relevant articles.

- Studies needed to address drug diffusion amongst primary care physicians.
- Studies could be both qualitative and quantitative studies, following the methods of Mikkelsen (2013).
- Information from other systematic reviews was eligible.
- Studies needed to address at least one of eleven factors defined in our conceptual model

- Studies needed to address new medicines, i.e. non-generic new pharmaceutical treatments.
- Studies were excluded when they were published before 2005 and after 2013.
- Studies needed to be written in English.
- Studies needed to be accessible to the investigator.

As mentioned, in a second step it was determined if selected studies addressed EU member states.

Quality assessment

The quality of the selected study was assessed. To be included, studies had to include a clear research goal, had to present their results in same article and had to provide limitations to their findings.

Data extraction

The selected articles were read entirely. The main characteristics of each study design were assessed. In addition, for each article it was assessed if it addressed one or more of the 11 sub-questions identified to be specific for the pharmaceutical industry. Data was collected in a data-extraction form, which can be found in Appendix II.

Data analysis

It was determined how each article related to each of the 11 sub-questions and it was determined how information from different articles related to each other. In addition, commonalties between studies were identified where possible.

Results

In this section the results from our literature search are presented. First, the search results are presented, followed by an overview of the main methodological characteristics of the included articles. Afterwards, specific findings for each of the sub-questions are presented in the order of the conceptual model.

Search results

The performed systematic search is summarized in the flow diagram in Figure II. This diagram is based on the methodology described Moher *et al*. (2009) part of the Preferred Reporting Items for Systematic reviews and Meta-Analyse (PRISMA) group (Moher *et al*., 2009).

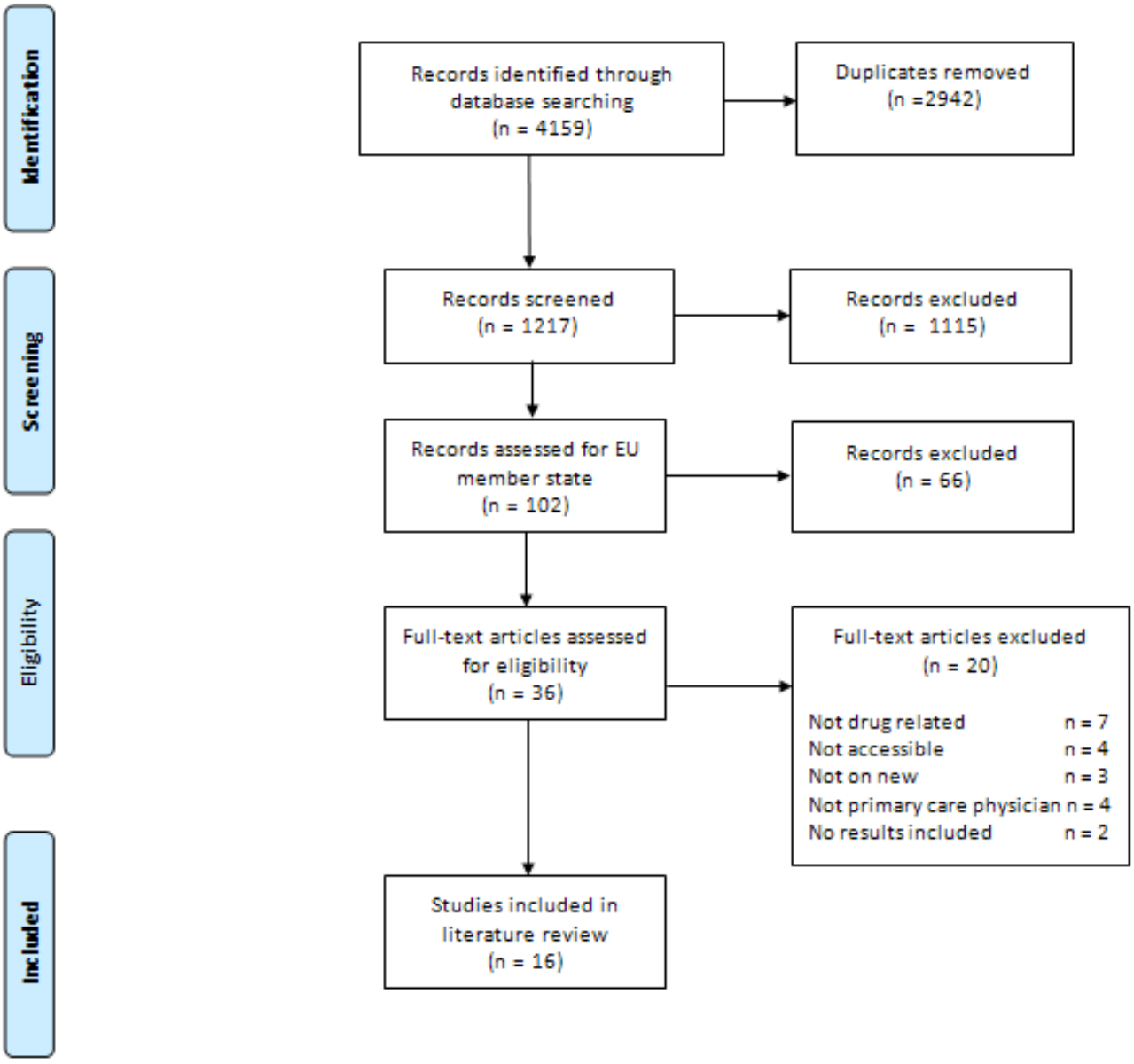

Figure II: Flowchart of search results (format adopted from Moher *et al*. (2009)

In total our search yielded 4159 records. After removing duplicates, the title and abstract of 1217 records were screened for eligibility using our predetermined eligibility criteria. Next, the remaining 102 records were screened on addressing EU member state. This yielded 36 articles of which the full-text was retrieved and read. From these articles, 20 were excluded for the following reasons.

- Not addressing drugs (7)
- Not accessible for the investigator (4)
- Not addressing new, i.e. a novelty aspect (3)
- Not on primary care physicians (4)
- No results included in the study (2)

As a result, in total 16 articles were included in this literature review.

Main characteristics

The main methodological characteristics of the 16 studies are presented in a table in Appendix III. Studies investigated nine different EU member states. Studies focused on The Netherlands (6), Denmark (2), Spain (2), Germany (1), Ireland (1), Slovenia (1), Swiss (1), Sweden (1) and the United Kingdom (UK) (1).

All but one of the included studies applied quantitative studies, a literature review being the exception. Twelve studies assessed relationships in their data studies retrospectively and seven studies included self-reported questionnaire data. Other data sources were prescription, dispensing, pharmacy and reimbursement databases. Sample sizes differed between studies, ranging from 68 GPs up to 2500 GPs.

Common studied drugs were selective COX-2 inhibitors (6 studies), esomeprazole (4 studies), angiotensin II receptor blockers (3 studies), rosuvastatin (3 studies) and tiotropium (3 studies).

Twelve studies investigated impact adoption of GPs directly, whilst other studies assessed influences at the practice level (1), on prescribing to patient's (1), on prescribing in general (1), or did not specify (systematic review).

None of the studies applied the same primary outcome measurement. All studies addressed a novelty aspect. However, descriptions differed amongst studies and five did not define "new.

All included articles addressed at least one of our predetermined sub-questions.

Information on sub-questions

The systematic search yielded a total number of 16 articles. As a result, it was decided to present our results in a similar fashion as Klemm *et al*. (2003) did in their literature review. Similar to our literature review they investigated a variety of concepts (n=6), whilst retrieving a small amount of research articles (n=9). They described the information per concept and used transition words to highlight possible connections or absence of connections between articles (Klemm *et al*., 2003).

Relative advantage

As identified earlier, a wide definition for the perceived relative advantage was adopted, as it could be formed by research evidence, marketing, costs and reimbursement patterns. In total three of sixteen included addressed the impact of perceived relative advantage on new drug adoption.

The systematic literature review of Mason (2008) studied the influences of price, cost and financial incentives on UK GP's prescribing. They identified on the basis of 28 included articles (mostly self-reported data) that costs may inform decisions on new drug prescribing. However, concerns about the safety and efficacy of the new drug are most important in deciding which drug to prescribe (Mason, 2008).

Similarly, Greving *et al*. (2006) identified that a number of factors determined adoption, including higher benefits of angiotensin II receptor blockers (ARBs). They studied the factors that determined the adoption of ARBs in 70 Dutch GPs by combining prescription data and the results from a questionnaire. The perceived improvement in benefits of ARBs was found to be associated with higher adoption levels (Greving *et al*., 2006).

Also, Garjón *et al*. (2012) found that the most innovative drug included in their study was adopted most widely and rapidly. They studied differences between Spanish specialists (189) and GPs (253) in adoption of eight new drugs. For each study drug the level of innovativeness was determined. One drug was rated as a drug with modest therapeutic benefits, i.e. tiotropium, whilst the others were rated to have no therapeutic innovation. It was determined by the investigators that tiotropium was adopted most rapid and widely by GPs. However, they also stated that this cannot be confirmed as the main reason for adoption, as extent of therapeutic innovation was not the only factor studied. For instance, differences between adoption amongst GPs and specialists were also studied (Garjón *et al*., 2012).

Opinion leaders

An opinion leader was considered a person outside of the GPs practice that could have an influence on the GP's adoption of new pharmacotherapies. Interaction with patients, pharmaceutical industry, pharmacists and academia were not included in the analysis of opinion leaders, as these interactions will be discussed further on. In total four out of sixteen studies addressed opinion leaders. One study specifically mentioned opinion leaders, whilst three focused on the influence of specialists on GPs drug adoption.

Pombo-Romero *et al*. (2013) studied diffusion of new drugs in social interaction systems in 1355 Spanish primary care physicians. They identified that within their medical community there were 20 GPs that were early adopters of ezetimide. In addition, they described that these GPs were at the centre of their medical community and therefore could be seen as charismatic opinion leaders.

Furthermore, they described that these leaders increased adoption through social interaction with other GPs within their medical communities (Pombo-Romero *et al*., 2013).

Florentius *et al*. (2009) studied if specialists influence new drug prescribing in 103 Dutch GPs, by analysing dispensing data of five drugs; i.e. combination of salmeterol/fluticasone, rofecoxib, esomeprazole, tiotropium and rosuvastatin. They identified that an influence of specialists is noticeable for all drugs. However, it seemed that this influence was not the only factor involved in the adoption process of new drugs by GPs, as differences were present between drugs. They found that first prescriptions by specialists ranged from 27% up to 60%, indicating that a large part of the GPs initiated prescriptions without influences from specialists (Florentinus *et al*., 2009).

Similarly, Greving *et al*. (2006) identified in their study, which combined Dutch prescriptions data with questionnaire data that patients that were referred by specialists were more likely to be assigned to ARBs by GPs. They described that most GPs indicated that they normally continued prescriptions by hospital physicians (Greving *et al*., 2006).

Likewise, the literature review of Mason *et al*. (2008) described that specialists initiate a substantial part of new drug prescriptions. However, they also identified that communication between specialists and GPs is of poor quality, limiting the impact of this so-called "power of specialists" (Mason, 2008).

Organisational leaders

An organisational leader was considered an individual inside a GP's practice or organisation that is capable of changing adoption behaviour of that GP. In total four out of sixteen studies addressed the topic of organisational leaders.

Bourke and Roper (2012) studied the factors that determined the prescribing of new drugs by approximately 2500 Irish GPs, using prescribing data and data on GP's characteristics. They identified that practices, which employed a nurse, took significantly lower time to adopt two study drugs, i.e. esctialopram (at the 1% level) and combination of drospirenone and oestrogen (at the 5% level). Similarly, it was identified that practices, which employed a secretary, took significantly lower time to adopt two study drugs, i.e. desloratadine (at the 5% level) and combination of drospirenone and oestrogen (at the 1% level). It should be noted that the relevance may be small as total time to adoption was shortened by two weeks in both cases (Bourke and Roper, 2012).

Findings of Olhsson *et al*. (2009) suggested that therapeutic traditions within a practice can have a considerable impact on the prescribing patterns of individual GPs. They studied the influence of factors related to health care practice (HCP) on adoption by physician in 159 Swedish HCPs of the new drug rosuvastatin. They identified that adoption was greatly grouped within practices throughout the study period, as prescriptions co-occurred within more often than would be expected randomly (Ohlsson *et al*., 2009).

Similarly, Pombo-Romero *et al*. (2013) identified in their retrospective quantitative modelling study that Spanish, GPs which work in the same unit and are in direct contact with each other, showed significant ($p < 0.001$) similarities in their prescription patterns. Therefore, they argued that endogenous social effects were present, i.e. effects originating from a tendency of individuals to match their behaviour to their group (Pombo-Romero *et al*., 2013).

In contrast, absence of organisational leaders may also impact adoption. Greving *et al*. (2006) identified in their retrospective quantitative study, using Dutch prescribing data and physician survey data that in solo practices adoption of ARBs was higher than in larger practices (adjusted odds-ratio of 1.35 with 95% confidence intervals (CIs) 1.10–1.65) (Greving *et al*., 2006).

Previous prescription volume

In this thesis the physician's characteristic previous prescription was volume studied. In total four studies addressed this topic.

Layton *et al*. (2008) studied the adoption patterns of first-line NSAIDs, second-line NSAIDs, preferential COX-2 inhibitors and selective COX-2 inhibitors in 2894 Dutch prescribers (GP and specialists). They examined three prescriber characteristic, i.e. prescriber type (GP, medical specialist or other), NSAID prescribing preference (prescribing preference ratio <3 were classified as coxib prescribers; 3–8 as no-preference prescribers; and >8 as NSAID prescribers) and percentile prescribing proportion (50^{th}, or 80^{th} percentile, or total (100%) prescribing proportion). Prescribing preference ratio was determined by the number of first prescriptions issued for existing drugs versus the number of first prescriptions issued for newly approved. They identified that no characteristic of a prescriber could predict their adoption of a new drug (Layton *et al*., 2008).

Similarly, Dydbahl *et al*. (2005) concluded that there no consistent relationship between previous drug prescribing volume and new drug adoption. They studied the relationship between previous drug prescribing and the adoption by 113 Danish GPs of new drugs within the same drug class. In total, four drug classes were studied, i.e. esomeprazole, selective COX-2 inhibitors (celecoxib and rofecoxib), triptans other than sumatriptan and ARBs. They identified that 'high prescribers', i.e. GPs in the upper quarter of overall prescribing, for esomeprazole and new triptans showed a higher preference for new drugs. All other relationships were not significant, indicating no consistency in the relationship between new drug adoption and previous prescription volume (Dybdahl *et al*., 2005).

Likewise, Dydbahl *et al* (2011) found no statistically significant relationship for any of the examined variables, including self-rated clinical interest in specific disease areas. They studied the preference of 68 Danish GPs for two new drug groups selective COX-2 inhibitors and ARBs compared with older alternatives (Dybdahl *et al*., 2011).

In contrast, Bourke and Roper (2012) found in their retrospective quantitative study, using Irish prescribing data and GP characteristics data, for all six study drugs a significant relationship (at the 1% level) between the size of GPs prescribing portfolio and time to adopt a new drug; i.e. a larger portfolio was resulted in a shorter adoption time. However, overall it should be noted that effect size is relatively small as it ranged from one to two weeks (Bourke and Roper, 2012). In addition, it is debateable to which extent differences in portfolio size can be considered a proxy for previous prescriptions volume in a specific disease area.

Interaction with patients

In total, two studies were identified that included statements on the influence of interaction of patients on adoption of new drugs by primary care physicians. One studied the impact interacting with patients of in general, whilst the other studied specific characteristics of patients that might influence adoption of new medicines.

The literature review of Mason (2008) that studied the influences of price, cost and financial incentives on UK GP's prescribing identified that the patient-doctor relationship played a central part in prescribing of new drugs. In addition, they described that for GPs patient-centred care was perceived as more important than cost-containment (Mason, 2008).

Olhsson *et al*. (2009) studied how socioeconomic characteristics of patients shaped prescriptions of new drugs by Swedish physicians. They identified that the new drug rosuvastatin was prescribe more often to patients with a high socio-economic standard or to young patients. As a result, they argued that patient characteristics other than their medical needs might have an influence on prescriptions behaviour of new drugs (Ohlsson *et al*., 2009).

Interaction with pharmaceutical industry

In total, two studies addressed the impact of interaction pharmaceutical industry in general on prescribing of new medicines by GPs.

The literature review of Mason (2008) that studied the impact of price, cost and financial incentives on UK GP's prescribing identified a perception amongst their included studies that the pharmaceutical industry is a key determinant in the adoption of new drugs (Mason, 2008).

Moreover, Greving *et al*. (2006) identified in their retrospective quantitative study using Dutch prescribing and survey data that GPs commonly using commercial information had a significantly higher prescribing rate for the new ARBs compared with older pharmacotherapy, i.e. odds ratio was 2.0 with 95% CI 1.5–2.6. However, the investigators described that this does not confirm a causal relationship, as this was only one of multiple variables investigated (Greving *et al*., 2006).

Targeted detailing

The topic of targeted detailing was addressed in three studies. However, it should be noted that these studies addressed the impact of PSRs visits on general prescribing behaviour. One study focused on prescribing behaviour, whilst two studies investigated the attitude of primary care physicians towards the impact of PSR visits on their prescribing behaviour.

Muijers *et al*. (2005) studied the relationship between the regularity of visits from PSRs and the quality of prescribing in 1019 Dutch GPs, including 322 solo GPs, using survey data and data from pharmacy databases. Quality of prescribing was determined by assessing a GP's compliance with general practice guidelines. They found a significant negative association (beta coefficient of multiple linear regression of –0.23, with CIs –0.32 and –0.15) in solo practices between PSR visit frequency and compliance with guidelines (Muijrers *et al*., 2005).

Lieb and Brandtönies (2010) studied the impact that PSRs' visits have on the quality of prescribing in 208 German physicians, including 76 primary care physicians, using electronic questionnaire data. They determined how physicians perceived the impact of PSRs on their prescribing behaviour, as well as their colleagues prescribing behaviour. The investigators identified that physicians perceived their

colleagues to be three to four times more likely to be influenced than themselves (Lieb and Brandtönies, 2010).

Similarly, Klemenc-Ketis (2013) identified that no specific PSR characteristic showed an association with prescribing behaviour. They studied if specific characteristics of PSRs had an influence on prescription behaviour of 247 Slovenian family physicians. Physicians rated the importance of 12 characteristics in a survey, which was compared with their prescribing behaviour (Klemenc-Ketis, 2013).

Interaction with community pharmacists

Our search yielded one study on the impact of interacting with community pharmacists.

Besides studying targeted detailing, Muijers *et al* (2005) also studied the impact of the Dutch GPs attitude towards community pharmacists and their prescribing quality (compliance with guidelines). They identified that no significant relationship between the quality of prescribing and the GP's opinion about the role of the community pharmacist. In addition, they identified that quality of prescribing was not correlated with daily interaction between GP's and community pharmacists. As a result, they argued that there is a discordance between the potential impact of community pharmacists and their actual impact (Muijrers *et al*., 2005).

PTAMs

In total three studies addressed the influence pharmaceutical meetings to improve prescribing quality, described as either pharmacotheurapeutic audit meetings (PTAMs) or physicians-pharmacists quality circles (PPQCs).

Florentius (2007) studied the influence of the quality of PTAMs on prescribing on new drugs in 103 Dutch GPs, using questionnaire and dispensing data. Quality of PTAMs ranged from level 1 to level 4, meaning no structured meetings and frequent meetings with actual decisions and evaluation of those decisions, respectively. They identified that GPs participating in level 4 PTAMs were two times less likely to prescribe a new drug than GPs attending level 1 or 2 (odds ratio of 2.24 with 95% CIs 1.04 to 4.81 vs. odds ratio of 2.31; 95% with CIs 1.30 to 4.09, respectively) (Florentinus *et al*., 2007).

In addition to interaction with PSRs and community pharmacists, Muijers (2005) studied the influence of the quality of PTAMs on quality of prescribing of Dutch GPs, using pharmacy and survey data. Quality of PTAMs was determined by nine survey questions on basic quality requirements. They found no statically significant relationship between the quality of PTAMs and quality of prescribing (Muijrers *et al*., 2005).

In contrast, Niquille (2010) results suggested an improvement in prescribing quality. They studied over a nine-year period the impact of PPQCs on cost control among six Swiss PPQCs, which were described as a stable group of three to ten GPs and at least one skilled pharmacist that discusses interdisciplinary continuing education, costs, drug choice and prescription volume. They conducted a pilot study among six PPQCs and compared prescribing behaviour of participating GPs with the prescribing behaviour of other GPs, i.e. matched controls. They identified after participating in a PPQCs GPs´ prescriptions of ARBs remained stable, which was in concordance with clinical practice guidelines, whilst prescriptions of the controls steadily increased (Niquille *et al*., 2010).

Interaction with academia

Two studies were selected that described the influence of academia and scientific evidence on the adoption of new drugs by GPs.

Greving *et al*. (2006) suggested in their retrospective quantitative study, using Dutch prescribing and physician survey data that scientific evidence had no influence on adoption of new drugs. They determined that GP usage of scientific medical journals was not significantly related with adoption of the new ARBs (Greving *et al*., 2006).

Similarly, the literature review of Mason (2008) indicated that scientific evidence was not always most important in prescribing new medicines by primary care physicians. It described that there are differences between GPs in their usage of scientific evidence in prescribing decisions. In addition, it indicated that on occasion the evidence-based approach was ignored, when faced with specific patient preferences or on the basis of their own beliefs (Mason, 2008).

Academic detailing

In total, two studies addressed the topic of academic detailing. Continuing education and continuing medical education (CME) were interpreted as descriptions of academic detailing.

Dybdahl *et al*. (2011) studied the influence of the perceived need for CME and current CME activities of 68 Danish GPs on their adopting of new drugs. They found that adoption of one of two drug classes studied (ARBs) was statistically significant with current CME activities. As the other relationships were not significant, a consistent relationship was not determined (Dybdahl *et al*., 2011).

Similarly, Greving *et al*. (2006) identified in their retrospective quantitative study, using Dutch prescribing and GP survey data that there is no significant relationship between continuing education and the adoption of the new ARBs. This indicated that academic detailing was not a determining factor for these GPs in their adoption of new drugs (Greving *et al*., 2006).

Discussion

Uptake of drugs in physicians prescription patterns can be seen as a final hurdle for new drugs to reach patients (Landsman *et al*., 2014). Recent prior research has investigated factors that influence prescribing patterns of physicians (Morris *et al*., 2011). However, they did not distinguish between types of physicians. In addition, they did not investigate, which factors influence diffusion of new drugs amongst physicians. In this study, the aim was to indentify factors described in scientific literature that have an impact on the diffusion of new medicines amongst primary care physicians, focusing on European member states. A systematic literature review was performed on eleven pre-specified concepts.

In total, 16 articles were retrieved, all but one using quantitative measure to determine relationships. Most studies were performed retrospectively and a considerable amount incorporated self-administered questionnaire data. Both study design elements have considerable limits (Brener *et al*., 2003) (Schwarz, 2007). In addition, sample sizes differed largely between studies. Moreover, this limited amount of data did not consistently measure outcomes and did not incorporate similar definitions of a new drug, whilst some studies did not specify 'new' at all. Also, only nine out of 28 member states were addressed, whilst five out of 16 studies focused on the Netherlands. As a result, any commonalties identified between studies should be seen in the light of their limitations and generalisability of these results may be limited.

With the previous in mind, this study identified that six out of the eleven studied concepts could have an impact on the adoption of new drugs by primary care physicians; i.e. perceived relative advantage, opinion and organisational leaders, interaction with patients and with the pharmaceutical industry, and PTAMs. Other concepts were not consistent between studies.

First, articles on perceived relative advantage of a new drug compared to existing drug seemed to be in line, as they indicated that more (perceived) relative advantage can improve new drug diffusion amongst EU GPs. These results are line with Prosser *et al*. (2003), who determined the factors that influence the uptake of new medicines by UK GPs. They, identified through interviewing GPs that most did not hesitate to prescribe a new medicine, when they perceived it to have significant benefits over current treatments, even though the new drug was more costly (Prosser *et al*., 2003).

Second, one Spanish study indicated that opinion leaders, other GPs, could influence adoption of new drugs. In addition, three studies indicated that specialist may be opinion leaders in drug diffusion. These results are in line with Iyengar *et al*. (2010) that studied opinion leadership in three American cities. They found that in study of self-reported opinion leadership amongst physicians that opinion leadership was correlated with an increase in adoption of new drugs (Iyengar *et al*., 2011). Nair *et al*. (2010) also identified that physician prescription behaviour is influenced by specialists (Nair *et al*., 2010). Similarly, Prosser *et al*. (2003) describes that hospital doctors influenced GPs decisions for initiating prescriptions (Prosser *et al*., 2003).

Third, included studies showed that nurses and secretaries might be considered opinion leaders. In addition, therapeutic traditions inside a practice may also influence adoption. In contrast, absence of organisational leaders also seemed to influence adoption, as solo-GPs also adopted new drugs more rapidly. Although, adoption among nurses has been studied previously (Robert *et al*., 2011)(Sandström *et al*., 2011)(Zanaboni and Wootton, 2012), the influence of nurses on adoption of new drug among primary care physicians has not been identified. The same applies to secretaries, a

topic that has had limited attention in general. Therapeutic tradition has been studied further by Ohlsson and Merlo (2009) and once more they identified that therapeutic traditions in HCPs seem to influence physicians prescription patterns across drug classes (Ohlsson and Merlo, 2009). Lastly, Watkins *et al*. (2003) also identified that English single-handed GPs were more likely to prescribe newer medications (Watkins *et al*., 2003).

Fourth, studies described that patients' needs other than their medical needs influenced the prescribing and adoption patterns of primary care physicians. These results are also in line with Prosser *et al*. (2003), who similarly described that request from patients can result in less evidence-based decision-making and a tendency towards new drugs. Similarly, our study found that scientific evidence might be ignored by GPs, when faced with patients' requests. In addition, they argued that for prescribing of drugs for chronic diseases this may be the least favourable, as initial exposure to the drug may results in additional requests later on and less resistance from the GP to those requests (Prosser *et al*., 2003)

Fifth, included studies indicated that interaction with industry seemed to influence (speed up) adoption of new drugs by GPs. These results are again in line with Prosser *et al*. (2003), who indentified that pharmaceutical industry was the primary source of information for GPs, which influenced their prescribing. In addition, they described that information collected from PSRs influenced prescribing initiation (Prosser *et al*., 2003). In contrast, our study did find a consistent pattern for the influence of PSRs on new drug adoption.

Last, high-quality PTAMs seemed to lower new drug adoption. However, their influence on overall prescribing was not consistent. This was particularly interesting as general interaction with pharmacists was not an influencing factor. These results indicate that influencing adoption of new drugs amongst primary care physicians was only possible in structured meetings of high quality, in which concrete decisions were made and evaluated. These findings are similar to Gallagher and Gallagher (2012), who studied working relationships between GPs and pharmacists. They argued that good quality communication between pharmacists and GPs is paramount in providing patient with adequate quality care. In addition, they highlighted that GPs should also make an effort and be proactive when interacting with pharmacists (Gallagher and Gallagher, 2012).

There are considerable limits to our findings. As mentioned, our search generated a limited amount of studies, which focused on a limited amount of EU member states (potentially overrepresented the Netherlands) and applied different methods to assess new drug adoption by GPs. In addition, our methods may be questioned. First, the chosen definition of a new drug could be considered wide. This is reflected in our results, as a large variation between what was considered new was identified. However, this may also be the result of inconsistency in the designs of studies addressing adoption amongst primary care physicians. Second, a single database was selected to collect data, i.e. PubMed. As a result, articles may have been missed from journals not represented in this database. Nonetheless, PubMed is a widely accepted database for biomedical research (Bachmann *et al*., 2003). Third, some studies did not focus specifically on GPs, either by choice or because investigators were not able to assess GP data. For example, in the study of Ohlsson *et al*. (2009) only Information on prescribers of drugs was available in their database and in the study of Dybdahl *et al*. (2005) all doctors in a practice shared the same prescriber code, not allowing to differentiate between GPs. This also highlights our last limitation; i.e. differences between EU states. Although, the health care

systems of all included member states ranked in top 40 globally in the last WHO investigation and all European health care systems aim for universal availability of physicians at minimal or no costs, differences between them may be present (WHO, 2014) (Bago d'Uva and Jones, 2009). For instance, Bago d'Uva and Jones (2009) studied differences in health care utilisation amongst EU countries. They identified that specialists on the whole treat more wealthy patients. Therefore, differences in gross national product between member states may result in different patient populations being treated by GPs. In addition, certain country specific characteristics may influence these treatment patterns, for instance in Ireland private doctors are paid a fee-for-service. A large part of the Irish high-income population purchases private insurance to cover these fees. As a result, they tend to be treated more often by specialists than the less-wealthy Irish population. Countries without these fees for specialist treatment may have different treatment patterns (Bago d'Uva and Jones, 2009).

A strong point of this study is the fact that multiple studies assessed the adoption of the same drug or drug class. For example, the results adoption of selective COX-2 inhibitors was investigated in seven studies in four different countries, i.e. Denmark, Ireland, Spain and The Netherlands. Secondly, Layton *et al*. identified that GP characteristics other than previous prescription volume were not worthwhile to investigate. Similarly, the literature review of Mason (2008) identified no relationship between new drug adoption and the GP characteristics gender, years employed and part-time vs. full-time. This strengthens our choice to focus on previous prescriptions volume only. Lastly, all identified studies addressed at least one of our predefined sub-questions, whilst some addressed multiple questions.

Interestingly, this study found that nurses and secretaries may have a positive influence on the adoption of new drugs amongst primary care physicians. To the best of our knowledge this had not been highlighted previously and may be a topic of future research.

It was also identified that prescribing behaviour of GPs might not always be consistent with scientific research. Wallace *et al*. (2012) identified in a literature review a number of facilitators that might improve the adoption of evidence from systematic reviews and meta-analyses. Among the most commonly cited were peer-group support, e.g. peer charismatic opinion leaders, and the notion that the content of the evidence should include information on benefits, harms and costs and is recent, transparent and well-timed (Wallace *et al*., 2012). A similar suggestion was also highlighted by Garjón *et al*. (2012), who stated that timing of providing scientific information should be more coordinated with the moment a drug reaches the market. This in line with Malmström *et al*. (2013), who identified that in Europe models to facilitate adoption of a new science-based and cost-effective drug are essential to optimise their utilisation (Malmström *et al*., 2013). Therefore, it is recommended that future academic detailing tries to incorporate such strategies, as it might alter its impact on new drug prescribing amongst GPs.

Conclusion

This study aimed to investigate the factors that influence the adoption of new drugs amongst EU primary care physicians, by performing a systematic literature review. Our literature search yielded a limited amount of data, i.e. 16 articles that mostly assessed adoption retrospectively in nine EU member states. In addition, the methodology between studies differed substantially, e.g. primary outcome measure and definition of new drug, although the studied drugs were similar. As a result, the generalisability of our findings is considerable hampered.

Nevertheless, six out of eleven predetermined concepts seemed to influence the adoption of new drugs by EU GPs. First, a higher perceived relative advantage seemed to speed up adoption. Second, charismatic GPs were found to influence adoption, as opinion leaders may influence drug adoption. In addition, the power of specialists may be important. Third, nurses and secretaries were identified as organisational leaders that can have a positive influence on adoption rate. Fourth, interacting with patients and more specifically patients' requests seem to influence adoption, whilst resulting in less less-evidence based drug prescribing. Fifth, interaction with the pharmaceutical industry had a positive influence on the uptake of new medicines by GPs. Last, this study found that high-quality PTAMs slow down adoption, whilst making prescribing more evidence based. Future efforts of academia to influence evidence-based drug adoption amongst primary care physicians and prescribing in general could benefit from these findings.

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Appendices

Appendix I

Included search terms per sub-question

1. **Relative advantage,** advantage, comparative advantage, competitive advantage, benefit, advantage, improvement, relative effectiveness, relative efficacy, effectiveness, additional value.
2. **Opinion leadership,** colleague, supervisor, lead, leader, trendsetter, catalyst, modernize, progress consumer elite, opinion elite, charismatic leadership, informal, leadership, frontrunner, influential, prominent, advice, opinion, guidance,
3. **Organisational leadership,** colleague, supervisor, manager, boss, general practice, practice office, organisation, internal, in-house, guidance, leader, leadership, support, funding, backing reformer, organizer, facilitator,.
4. **Previous prescription volume,** doctor, GP, MD, medical practitioner, distinct, innate, prescribing, volume, amount, pattern, quantity, disease, area, field, class.
5. **Interaction with patients,** patient, involvement, communication, requests, desire, wish, hope, medical needs, needs, pressure, doctor-patient relationship, avoiding conflict, time constraints, workload, patients organisation, satisfaction, meetings,
6. **Interaction with pharmaceutical industry,** industry, marketing strategy, sale, salesman, sales representative, promotion, launch, campaign, advertising, market development, pharmaceutical industry, industry involvement, education, information transfer, off-label, conflict of interest, journal, paper, Pharmaceutical marketing services
7. **Targeted detailing,** marketing, pharmaceutical industry, physician, doctor, GP, directed, focussed, visits, meetings, adds, advertising, drug detailing, pharmaceutical sales representatives
8. **Interaction with community pharmacists,** pharmacists, active, dynamic, involvement, participation, prescribing, supply, inform, monitor, recommend, suggest,
9. **PTAMs,** meeting, evaluation, assessment, appraisal, prescribing, membership, physician, pharmacists, membership, industry representative, quality circles, quality and outcomes framework.
10. **Interaction with academia,** university, science, scientific, education, teaching, instruction.
11. **Academic detailing,** physician, university, academia, non-profit, research, studies, results, outcome, update, training.

Appendix II

Data extraction form

Name	**Year**	**Country**	**Type of study: Qualitative/Quantitative/Review Retrospective/prospective**	**Innovative drug(s)**	**Disease area**	
Number of physicians	**Description of physician**	**How is adoption measured?**	**How is new defined?**	**Found with which search terms?**		
Relative advantage	**Opinion leader**	**Organisational leader**	**Previous prescription volume**	**Interaction with patients**	**Interaction with pharmaceutical industry**	**Targeted detailing**
Interaction with community pharmacists	**PTAM**	**Interaction with academia**	**Academic detailing**	**Limitation study**	**Strengths study**	**Other notables**

Appendix III

Table of main methodological characteristics of included studies

Study	EU member state	Type of study	Participants	Study drugs	Primary outcome	Definition of new
(Bourke and Roper, 2012)	Ireland	Retrospective quantitative study of the GMS Prescribing Database and the GP Characteristics Database	It is estimated that there are approximately 2,500 GPs in Ireland. Data covers around a quarter of all Irish GPs	1) esctialopram 2) esomeprazole 3) rofecoxib 4) desloratadine 5) nicotine 6) combination of drospirenone and oestrogen	The first prescription of a new drug by a GP	New drugs that were introduced to the Irish market during the period October 1999–March 2004
(Dybdahl *et al.*, 2005)	Denmark	Retrospective quantitative study with data from the Odense University Pharmaco-epidemiologic Database	Included for analysis of esomeprazole 108/55 (solo/group) practices, of COX-2 inhibitors 113/61 practices, of new triptans 106/54 practices, and of angiotensin II receptor blockers 78/44 practices	1) esomeprazole, 2) selective COX-2 inhibitors (celecoxib, rofecoxib) 3) triptans other than sumatriptan 4) angiotensin II receptor blockers	The preference proportion; i.e. the number of patients receiving a new drug for the first time divided by the number of patients receiving a new or an old drug for the first time	Introduced into the Danish market from 1994 through 2000
(Dybdahl *et al.*, 2011)	Denmark	Retrospective quantitative study using population-based prescription data and data collected by postal questionnaire	68 single-handed GPs	1) selective COX-2 inhibitors 2) angiotensin II receptor blockers	Preference for two new drug groups was defined as the percentage of patients receiving a new drug among first-time users of either the new drug or an older alternative	On the market in 2004

(Florentinus *et al.*, 2007)	The Netherlands	Retrospective quantitative study using dispensing data and a postal questionnaire	103 GPs working in 59 practices	1) combination of salmeterol and inhaled fluticasone 2) selective COX-2 inhibitor rofecoxib, 3) esomeprazole, 4) tiotropium 5) rosuvastatin	The decisions to start therapy with a new drug or with an existing drug within the first 6 months after market introduction	Within 6 months after market introduction
(Florentinus *et al.*, 2009)	The Netherlands	Retrospective quantitative study of dispensing data and questionnaire data	103 GPs	1) combination of salmeterol/fluticasone 2) selective COX rofecoxib 3) esomeprazole, 4) tiotropium 5) rosuvastatin	Compared time to prescribing between GPs that initiate therapy before one of their patients received the drug from a medical specialist and GPs that waited for specialist to prescribe first before prescribing themselves	Data during the first six months after market introduction
(Garjón *et al.*, 2012)	Spain	Retrospective quantitative study using data from the prescription database of the Navarre Health Service	441 physicians (189 specialists and 253 family physicians)	1) efditoren, 2) duloxetine 3) selective COX-2 inhibitor etoricoxib 4) ezetimibe 5) levocetirizine 6) olmesartan 7) pregabalin 8) tiotropium	The diffusion of each drug was studied among the group of adopter physicians. The adoption time of a drug was defined as the month in which the physician made a first prescription	Drugs were the latest licensed of their therapeutic group for their indications
(Greving *et al.*, 2006)	The Netherlands	Retrospective quantitative study using prescribing data and physician questionnaire data	70 GPs	Angiotensin II receptor blockers	Prescribing of angiotensin II receptor blockers to patients with hypertension in the year 2000	Angiotensin II receptor blockers were introduced in the market in 1995. However, until 2002 no evidence on hard endpoints was available

(Klemenc-Ketis, 2013)	Slovenia	Quantitative observational study using postal questionnaire data	247 Family physicians	All prescriptions	Prescribing index; i.e. last year's prescribing compared to current year's prescribing	All prescriptions
(Layton *et al*., 2008)	The Netherlands	Retrospective quantitative study using data from a pharmaceutical claims database	2894 prescribers	1) oral NSAIDs 2) selective COX-2 inhibitors (rofecoxib, celecoxib and valdecoxib) 3) preferential COX-2 inhibitors (meloxicam and nabumetone) 4) non-selective NSAIDs (diclofenac, naproxen ibuprofen, piroxicam and ketoprofen)	The characteristics of prescribers issuing >10 prescriptions were examined	Not specified
(Lieb and Brandtönies, 2010)	Germany	Quantitative study using electronic questionnaire data	208 physicians of which 83 neurologists/ psychiatrists, 76 primary care physicians and 49 cardiologists	All prescriptions	How doctors perceived the extent to which their prescribing behaviour, or that of their colleagues, was influenced by pharmaceutical industry representatives	Not specified
(Mason, 2008)	United Kingdom	Systematic literature review	Not specified (review included 28 studies)	All prescriptions	Determinants of uptake, the causes of geographical variations, and the influence of price, cost and financial incentives on prescribing behaviour	"New" terms were included in the search
(Muijrers *et al*., 2005)	The Netherlands	Retrospective quantitative study using questionnaire	1019 GPs of which 322 were solo GPs	All prescriptions	Factors that are correlated with the differences in prescribing between GPs	Not specified

		data and existing pharmacy data				
(Niquille *et al*., 2010)	Switzerland	Quantitative controlled pilot study	General physicians and pharmacists	18 drug classes	The cost-containment impact of the physicians-pharmacists quality circles over a 9-year period (1999–2007)	Not specified
(Ohlsson *et al*., 2009)	Sweden	Retrospective quantitative study using prescriptions data	159 health care practices	Rosuvastatin	The outcome variable was prescription (yes vs. no) of rosuvastatin	Rosuvastatin was introduced in the Swedish reimbursement system in July 2003. Prescriptions followed for a year after July 2003
(Pechlivanoglou *et al*., 2010)	The Netherlands	Retrospective quantitative study using pharmacy dispensing records	192 patients	Risperidone long-acting injectable therapy	The differences in treatment complexity among patients	Period of two years after the introduction of risperidone long-acting injectable therapy to the Dutch market in May 2003
(Pombo-Romero *et al*., 2013)	Spain	Retrospective quantitative modelling study using drug reimbursement data	1355 primary care physicians	Ezetimide	The proportion of potential adopters who have effectively taken on a particular technology at any given time	Not specified