New medicines in primary care

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DOI:
10.33612/diss.809910284

General introduction

Medicines are an essential part of modern healthcare and can have a profound effect on quality of life. Every year, new medicines become available for prescription. In 2021, 92 new medicines were recommended for marketing authorisation in Europe, of which 54 had a new chemical substance [1]. New medicines have been associated with decreased morbidity and increased longevity and health related quality of life and can therefore improve treatment outcomes and be beneficial for patients [2,3]. However, the long term safety of new medicines is often not known, and once used by a large and heterogenous population, new risks of these medicines can emerge, which may lead to harmful events [4-6]. In addition, new medicines are often expensive, thereby contributing to increasing healthcare costs [7,8]. Therefore, an urgent need exists for the rational use of new medicines, both in terms of quality of care and healthcare costs [9].

In the Netherlands, the general practitioner functions as gatekeeper of the healthcare system and plays an important role in the prescription of medicines [10]. The adoption of new medicines in primary care differs greatly between practices [11-13]. Variation between practices in itself is not remarkable, since patients characteristics and their preferences can differ. However, these factors comprise only part of the variation in medical treatment, indicating that other, non-medical, factors are also involved [14]. That part of variation indicates room for improvement in the rational use of new medicines in primary care. Insight in the prescription of new medicines by primary healthcare professionals, their considerations and factors that influence their decisions is therefore relevant.

HOW NEW MEDICINES BECOME AVAILABLE FOR PRESCRIPTION

Before a new medicine can be prescribed by a healthcare professional, it has to pass several assessments. Once the initial development phase is completed, a medicine has to be positively evaluated by registration authorities in order to become available on the market. For most new medicines in Europe, this assessment is performed by the European Medicines Agency (EMA). The EMA assessment focuses primarily on the quality and the benefit-risk balance of the new medicine, based on a comprehensive scientific evaluation of data. Only if the benefits of the new medicine outweigh its risks, it will be authorised [1].

Once a new medicine is being authorised, an evaluation of the eligibility for reimbursement is often the next step, which is in the European context usually advised upon by Health Technology Assessment (HTA) bodies. Benefit-risk analysis is again an important part of the evaluation, but the pharmacoeconomic evaluation of the new

medicine is an additional domain for evaluation [15,16]. The final decision whether a medicine is reimbursed, is based on its relative effectiveness and cost effectiveness, particularly compared to current standard of care. Also the total budget impact may be taken into account.

The registration and reimbursement of a new medicine are no guarantee that healthcare professionals will prescribe it. The actual prescription often depends on the guidance and information provided by professional organisations. In the Netherlands, the recommendations by professional organisations are known to have a profound impact on prescription behaviour [17,18]. In the assessment of new medicines by professional organisations, the relative value of the new medicine compared to other already available therapeutic options is taken into account, before it is recommended in professional clinical guidelines [19].

After all these formal evaluations, individual prescribers have to decide whether they are going to prescribe the new medicine, taking into account all former evaluations and adding the question whether the new medicine is the best option for an individual patient.

To summarize, the assessment of new medicines occurs at different moments, by different institutions and within different domains. The base of the evaluation of a new medicine is the assessment of its quality and the benefit-risk balance. Additional evaluation domains are used for the evaluation of reimbursement, clinical guideline recommendations and prescription. This thesis focuses on the final part in this process, the prescription, and considers three different aspects. At first, the assessment of new medicines by prescribers is studied in relation to the assessment of new medicines by official institutions. Second, the internal and external factors influencing the decision-making by prescribers are investigated. Third, the outcome of these processes, i.e. the prescription of new medicines, is quantified.

ASSESSMENT CRITERIA

As stated before, the benefit-risk balance is the base of every assessment of new medicines. In order to determine this balance, the assessment criteria have to be established. Agreement on (importance of) the studied outcomes and improvements on these outcomes that are warranted per disease area is the first step.

Outcomes used for the evaluations of new medicines can be subdivided into different categories. Categories are direct outcomes for clinical efficacy (e.g. mortality), surrogate outcomes for efficacy (e.g. HbA1c in the case of diabetes medicines), safety outcomes (e.g. adverse events) and patient reported outcomes (PROs), like quality of life [20-23]. The relative importance of the outcomes depends on the disease area that is studied, although direct outcomes and PROs are generally valued over surrogate endpoints [23-26]. To determine the relative importance of outcomes, relevant competent authorities often use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE uses a 9-point scale to define the importance of a specific endpoint [27].

After the definition of relevant endpoints, consensus has to be reached about the improvements a new medicine has to have on these endpoints in order to be considered sufficiently effective. Statistical significance is used to establish the chance of a result being caused by coincidence. Clinical relevance however merely focuses on the real benefit of a new medicine. The assessment of clinical relevance in addition to statistical significance has become increasingly important in the evaluation of new medicines [28,29]. To evaluate clinical relevance, Jaeschke et al. introduced the Minimal Clinically Important Difference (MCID) in 1989 [30]. An MCID is the smallest difference in the domain of interest which patients perceive as beneficial and which would mandate a change in patient treatment [30,31]. MCIDs can be used as cut-off values to decide whether a difference between two treatments is of clinical relevance [32] and therefore to quantify clinical relevance. The use of MCIDs in the evaluation of new medicines has gained more popularity in the last years, although their use differs among diseases and therapeutical areas [33]. For example in the field of chronic obstructive pulmonary disease (COPD), MCIDs are extensively studied and validated and a general consensus exists on which MCIDs should be used in order to evaluate COPD medicines [34]. Therefore, registration authorities, HTA bodies and professional organisations all use the same MCIDs to establish clinical relevance of new COPD medicines [35-37]. In other therapeutical areas, the use of MCIDs is less common. For example, for type 2 diabetes mellitus (T2DM) medicines, no validated MCIDs are available and the use of MCIDs is therefore less common in both registration, reimbursement and recommendation.

To summarize, important developments for a careful evaluation of the benefit-risk balance of new medicines are the definition of evaluation criteria, including the definition of outcomes, use of GRADE scaling to establish the importance of outcomes, calculation of statistical significance to rule out chance, and defining MCIDs to evaluate the clinical relevance of improvements on these outcomes. Although organisations may use additional evaluation domains, many attempts are made to harmonize the

criteria for the assessment of the benefit-risk balance, for example between regulatory authorities and HTA bodies [38,39] and HTA bodies and clinical guideline developers [40]. It is known from previous research that the views of individual healthcare professionals on added value of medicines do not necessarily correspond to the views of official institutions [24,41-43]. It is however not known how healthcare professionals value the evaluation criteria used by regulation authorities, HTAs and clinical guideline developers to establish clinical relevance.

FACTORS IMPACTING DECISION-MAKING

Once available for prescription, the healthcare professional has to decide to prescribe the new medicine or not. The decision to prescribe new medicines is impacted by the context and characteristics of prescribers and patients and by external influences (e.g. other healthcare professionals, organisation of care and pharmaceutical industry) [13]. In order to understand variation in the prescription of new medicines between practices, insight in the factors impacting the decision-making is essential.

The decision of healthcare professionals to prescribe new medicines is not solely based on pharmacological and medical criteria, but also depends on social, situational and psychological variables [44,45]. A systematic review from 2021 found a broad range of factors associated with the early prescription of new medicines, grouped into patient, prescriber, medicine, organisational, and external environment factors [45]. These factors, however, could not explain the extensive variation in the early prescription of new medicines [13]. Behavioural aspects and especially the attitude of healthcare professionals towards new medicines are thought to play an important role in the decision to prescribe new medicines [13,46]. These behavioural aspects remain underexplored and therefore call for further research [45].

One notable external factor that impacts the decision to prescribe new medicines is the pharmaceutical industry. Pharmaceutical companies try to stimulate the use of their specific new medicine by a broad range of marketing activities. The activities vary from direct attempts (e.g. medical representatives visiting the practice, marketing mailings and educations organised by a company) to indirect attempts (e.g. sponsored courses and ghost-writing) [47-49]. Marketing activities by pharmaceutical companies are known to influence the attitude of healthcare professionals towards new medicines [46,50] and impact the prescription of new medicines [47,49,51-53]. The latter effect is often underestimated by healthcare professionals [47,54-57]. Although the contents of marketing activities are widely studied [58-61], the way these activities try to impact

the decision-making by healthcare professionals is less understood. More insight in the factors leading to the decision to prescribe new medicines, and the strategies the pharmaceutical industry uses to impact this decision, is therefore warranted.

PRESCRIPTION OF NEW MEDICINES

Considering the many factors influencing the prescription of new medicines, it is no surprise that the uptake of new medicines in primary care is not equally distributed among physicians [11]. The uptake of new medicines often follows the universal diffusion of innovations, described by Rogers et al. [62]. They distinguish five categories of adopters, ranging from innovators and early adopters to laggards. This diffusion of innovation has also been described for new medicines [12]. A small proportion of general practitioners seems to be accountable for a disproportionate share of all early prescriptions for new medicines [13,63]. Among general practitioners, a distinction can be made between practitioners with a 'wait and see' policy to practitioners who are more willing to experiment [46]. The differences in adoption of new medicines lead to extensive practice variation in the prescription of new medicines, especially in the first years after their introduction [13,64].

Practice variation in itself is not problematic. Differences between patients and practices can call for different approaches and treatments [14]. However, the variation previously found in the prescription of new medicines could often not be explained by different patient or practice characteristics [13,46]. This non-explainable part of practice variation indicates room for improvement in the rational use of new medicine. After all, rational use of medicine would imply that the same patients are treated with the same medicines, irrespective of the healthcare professional they encounter [14]. The last part of this thesis therefore focuses on practice variation in the prescription of new medicines, in order to gain more insight in the rationality of prescription behaviour.

OBJECTIVES OF THIS THESIS

This thesis aimed to gain insight into the perspectives and practices of healthcare professionals in primary care towards new medicines. To achieve this aim, the following objectives were posed:

- To compare the preferences for evaluation criteria of new medicines by individual healthcare professionals with those of registration authorities and professional organisations.

- To establish the factors that are associated with the decision of individual healthcare professionals to prescribe new medicines, also focusing on the strategies pharmaceutical companies use to influence this decision-making.
- To assess the practice variation in the prescription of new medicines in primary care and investigate the association of prescription of new medicines with specific patient characteristics, practice characteristics and prescription of other new medicines.

OUTLINE OF THE THESIS

This thesis consists of three parts divided into individual chapters. The first part of this thesis focuses on healthcare professionals' preferences for outcomes and MCIDs used in the evaluation of new medicines in relation to the standards used by registration authorities and professional organisations (**Chapter 2**). The study in **chapter 2.1** compares the preferred endpoints and MCIDs of healthcare professionals for the evaluation of new COPD medicines and compares those outcomes to the endpoints and MCIDs used by registration authorities. **Chapter 2.2** describes a comparable study in the field of T2DM. The views and perspectives of healthcare professionals towards endpoints and MCIDs are compared to those used by professional organisations for the development of a new T2DM guideline in primary care.

Chapter 3 of this thesis describes the considerations of primary healthcare professionals leading to the decision to prescribe new medicines, also focusing on the role of the pharmaceutical industry in this decision-making. **Chapter 3.1** assesses the reasons why primary care healthcare professionals decide positively or negatively about new medicines that are not recommended in guidelines, focusing on non-recommended insulins. **Chapter 3.2** describes an analysis of persuasion strategies used in marketing materials for new medicines from pharmaceutical companies.

The next part of this thesis (**chapter 4**) outlines the prescription patterns of new medicines in primary care. In **chapter 4.1**, a retrospective cohort study aims to identify practice variation and analyses the patient and practice characteristics associated with the prescription of new insulins. **Chapter 4.2** describes the prescription patterns of direct oral anticoagulants (DOACs) and incretin-based therapies in primary care over a 13-year period and studies the association between the prescription of both new medicine classes.

The general discussion, **chapter 5**, provides an overview of all findings in this thesis and discusses implications for the improvement of rational use of new medicines and recommendations for further research.

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