New medicines in primary care

Dankers, Marloes

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Summary

New medicines can improve treatment outcomes and can be beneficial for patients. However, because of the often unknown long term safety of new medicines, their use can also be harmful. Therefore, both excessive enthusiasm and latency about new medicines can have impact on patients' health and life. Adding the often high costs of new treatments, it becomes clear that rational use of new medicines is particularly important, both in terms of quality of care and healthcare costs. Insight in the prescription of new medicines and the considerations of healthcare professionals to prescribe new medicines is therefore particularly relevant. The primary research objective of this thesis was thus to study the perspectives and practices of primary care healthcare professionals towards new medicines.

The introduction (**chapter 1**) describes the processes prior to the prescription of new medicines. New medicines have to undergo many evaluations in order to be authorised, reimbursed, recommended and prescribed. Before the actual assessment starts, assessment criteria have to be established. Consensus on importance of clinical outcomes and meaningful improvements on these outcomes, defined by Minimal Clinically Important Differences (MCIDs), are therefore the first step. Once available for prescription, healthcare professionals make the final decision to prescribe the new medicine or not. This process is known to be influenced by many factors. The early prescription of new medicines is often not equally distributed among physicians, meaning that both early adopters and laggards exist. This indicates room for improvement in the rational use of new medicines and offers directions for further research.

In **chapter 2**, the preferences for evaluation criteria of new medicines by individual healthcare professionals were studied and compared to those of registration authorities and professional organisations. Both studies in this chapter indicate that healthcare professionals largely agree with outcomes and MCIDs used in the evaluation of new medicines for chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus (T2DM) respectively, although they have stricter views on some criteria. This means that new medicines that are considered clinically relevant by registration authorities do not necessarily reflect healthcare professionals' perspectives on clinical relevance. This can lead to overestimation or underestimation of benefits and harms of new medicines. **Chapter 2.1** focuses on COPD. With an online survey among 227 healthcare professionals, the preferences for efficacy endpoints and cut-off values for improvement on these outcomes were studied. Exacerbations (51.0%), airway obstruction (46.9%) and health status (44.9%) were the most preferred efficacy endpoints. Preferred cut-off values for clinical relevance for the Transition Dyspnea Index (TDI) and St. George's Respiratory Questionnaire (SGRQ) were significantly higher than the MCIDs used by the European Medicines Agency (EMA), mean differences 1.5 (95% confidence interval

(CI) = 1.3 – 1.8, p < 0.001) and 7.0 (95%CI = 5.1 – 8.8, p < 0.001), respectively. The mean cut-off value for forced expiratory volume in 1 sec (FEV_1), was comparable to the MCID (mean difference 2.2, 95%CI = -19.9 – 24.3, p = 0.84). The results show that healthcare professionals largely agreed with efficacy endpoints used for the evaluation of new COPD medicines, but preferred higher cut-off values for clinical relevance for dyspnea and health-related quality of life than the registration authorities. **Chapter 2.2** addresses new medicines for T2DM and compares the preferences of healthcare professionals to those of the Dutch guideline committee. With a similar study design, the preferences of healthcare professionals towards endpoints and MCIDs for T2DM medicines were investigated. According to 211 healthcare professionals, severe hypoglycemia, mortality, quality of life, macrovascular morbidity, microvascular morbidity, hospital admissions and HbA1c are of critical importance in the assessment of new T2DM medicines. Other hypoglycemia and body weight were considered important. This was comparable to the views of the guideline committee. Only HbA1c and hospital admissions were valued differently by the committee (important but not critical). Healthcare professionals preferred a median MCID of 4 mmol/mol for HbA1c (guideline: 5 mmol/mol) and 3 kg for body weight (guideline: 5 kg weight gain and 2,5 kg weight loss). Preferred MCIDs for mortality and macrovascular morbidity were, mentioned as relative risk reductions (RRRs), 20% (guideline: 10% and 25%, respectively) and 50% for other hypoglycaemia (guideline: 25%). The MCID of 25% for microvascular morbidity, hospital admissions and severe hypoglycaemia corresponded to the guideline-MCID. An additional finding of this study was the difficulty healthcare professionals experienced with estimating and interpreting realistic benefits and risks of new medicines, indicated by the wide range of answers given (especially for RRRs) and the large proportion of respondents that did not answer the questions about MCIDs. From this study, it was concluded that healthcare professionals' preferences were comparable to the views of the guideline committee. However, healthcare professionals had a stricter view on the importance of HbA1c and hospital admissions and the MCIDs for mortality and other hypoglycemia.

In **chapter 3**, factors that influence the decision of individual healthcare professionals to prescribe new medicines were investigated, also focusing on the strategies pharmaceutical companies use to influence this decision-making. In this chapter, it is concluded that the attitudes of healthcare professionals are important in the decision to prescribe new medicines. Also, the pharmaceutical industry uses many strategies in order to influence this attitude and persuade healthcare professionals to prescribe new medicines. **Chapter 3.1** focuses on the argumentation of healthcare professionals to prescribe new and non-recommended insulins to T2DM patients. Four focus group discussions were organised with general practitioners (n = 11), practice nurses (n = 12), pharmacists (n = 6), diabetes nurses (n = 4) and nurse practitioners (n = 2). The argumentation for the

prescription of non-recommended insulins was categorized into an existing behaviour model for guideline non-adherence, distinguishing argumentation in the domains knowledge, attitude and behaviour. The prescription of non-recommended insulins was largely driven by argumentation in the domain of attitudes. Lack of agreement with the guideline was the most prominent category of arguments within this domain. The belief that guideline-recommended insulins were less effective, positive experience with other insulins, marketing from pharmaceutical companies and the lack of uniformity in policy between healthcare professionals in the same practice were also identified as attitude-related barriers to prescribe guideline-recommended insulins. A small number of external barriers were identified, focusing on patient characteristics that prevented the use of recommended insulins, the existence of contradictory guidelines and other, mostly secondary care, healthcare providers initiating non-recommended insulins. **Chapter 3.2** studies persuasion strategies pharmaceutical companies use to influence the prescription of new medicines by healthcare professionals. A total of 68 marketing materials, collected by 20 general practices, were analysed according to the presence of seven common persuasion strategies, i.e. reciprocity, consistency/commitment, social proof, liking, authority, scarcity and unity. All seven strategies were found. Liking (64.7% of all materials) and authority (29.4%) were the most prominent strategies, followed by social proof (17.6%), unity (14.7%), scarcity (13.2%), reciprocity (11.8%) and consistency/commitment (2.9%). One new strategy, emotional pressure, was identified which was present in 30.9% of the materials. The wide range of used persuasion strategies indicates that pharmaceutical companies try to influence the decision-making process in many ways.

Chapter 4 describes the practice variation in the prescription of new medicines in primary care and the association of prescription of new medicines with specific patient characteristics, practice characteristics and prescription of other new medicines. In this chapter, it is concluded that large practice variation in the prescription of new medicines exists, especially in the first years after introduction, which cannot be explained by different patient or practice characteristics. In addition, no correlation exists between the early prescription of new medicines meant for different diseases. **Chapter 4.1** targets the prescription of new insulins to T2DM patients. A cohort of 7,757 patients with prescriptions for intermediate or long-acting insulins from 282 general practices was constructed using the Nivel Primary Care Database. A median percentage of 21.2% (interquartile range (IQR) = 12.5 – 36.4%) of all patients prescribed intermediate or long-acting insulins per practice received a prescription for newer insulins. The Intraclass Correlation Coefficient (ICC) was 0.20, meaning that twenty percent of the observed variability could be attributed to differences between practices. The ICC marginally decreased to 0.19 after multilevel modelling with patient and practice characteristics.

Female sex (odds ratio (OR) = 0.77, 95% confidence interval (CI) = 0.69 to 0.87), age ≥ 86 years compared with 40 – 55 years (OR = 0.22, 95% CI = 0.15 to 0.34), prescriptions for metformin (OR = 0.66, 95% CI = 0.53 to 0.82), sulfonylurea (OR = 0.58, 95% CI = 0.51 to 0.66), or other newer T2DM drugs (OR = 3.10, 95% CI = 2.63 to 3.66), and dispensing practices (OR = 1.78, 95% CI = 1.03 to 3.10) were associated with the prescription of newer insulins. It is concluded that the inter-practice variation in the prescription of newer insulins is large and can only be partially explained by patient- and practice-related differences. In **chapter 4.2**, another retrospective cohort study with prescription data from the Nivel Primary Care Database is described. This study investigated the uptake, practice variation and correlation in the prescription of direct-acting oral anticoagulants (DOACs) and incretin-based therapies. The study period ranged from introduction of these medicines, around 2007, until recommendation in guidelines, around 2019. Per year, 46 to 424 practices and 179,933 to 1,654,376 patients were included. The mean percentage of patients per practice using DOACs, compared to the use of DOACs and vitamin K antagonists (VKAs), or incretin-based therapies, compared to the use of all diabetes medication except insulin, increased to 54.9% and 9.7%, respectively in 2019. The ICC decreased from 0.75 to 0.024 for DOACs and from 0.33 to 0.074 for incretin-based medicines during the study period. No clear correlation was found between the prescription of DOACs and incretin-based therapies. In this study, it is concluded that different adoption profiles per new medicine group exist and that early adoption of new medicines is not likely to be a personal trait.

In the general discussion (**chapter 5)**, the results of the individual studies are placed in a broader perspective. Two main conclusions derived from the studies are discussed. At first, we conclude that the uptake of new medicines in primary care is unpredictable. This conclusion is based on three findings. First, we found great differences in the adoption of new insulins, DOACs and incretin-based medicines, indicating that the uptake is different for every new medicine. Second, we found large variation between primary care practices in the prescription of new medicines, which cannot be explained by variation in practice and patient characteristics. Third, the early uptake of one group of new medicines did not predict the early uptake of other new medicines. Together, these findings indicate that adoption profiles of new medicines differ per medicine group, and early adoption cannot be easily predicted by patient characteristics, practice characteristics or early prescription of other new medicines.

The second main conclusion of this thesis is that scientific evidence only plays a limited role in the deliberations leading to the prescription of new medicines. This conclusion is again based on three findings. First, a balanced evaluation of benefits and risks by healthcare professionals is hampered because of difficulties they experience

in interpreting and estimating realistic benefits and risks of new medicines. Second, individual attitudes of healthcare professionals, often related to argumentation that lacked scientific rationale, were most important in the decision to prescribe new medicines. Third, marketing materials from pharmaceutical companies aimed to influence prescription behaviour by use of multiple persuasion strategies. These findings illustrate that the decision to prescribe new medicines is not purely based on scientific rationale, but that many other factors influence this decision-making.

Both conclusions urge for initiatives to continuously stimulate the rational use of new medicines, like the programme MedicijnBalans of the Dutch Institute for the Rational Use of Medicine, to ensure that new medicines are prescribed to patients who need them and withheld from patients who do not.