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Factors influencing decision-making

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Non-adherence to guideline recommendations for insulins: a qualitative study amongst primary care practitioners

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ABSTRACT

Background

Guideline adherence is generally high in Dutch general practices. However, the prescription of insulins to type 2 diabetes mellitus patients is often not in line with the guideline, which recommends NPH insulin as first choice and discourages newer insulins. This qualitative study aimed to identify the reasons why primary care healthcare professionals prescribe insulins that are not recommended in guidelines.

Methods

Digital focus groups with primary care practitioners were organised. A topic list was developed, based on reasons for preferred insulins obtained from literature and a priori expert discussions. The discussions were video and audio-recorded, transcribed verbatim and coded with a combination of inductive and deductive codes. Codes were categorized into an existing knowledge, attitudes and behaviour model for guideline non-adherence.

Results

Four focus groups with eleven general practitioners, twelve practice nurses, six pharmacists, four diabetes nurses and two nurse practitioners were organised. 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. Most of those perspectives did not reflect disagreement with the guideline recommendations in general, but were about advantages of non-recommended insulins, which led, according to the healthcare professionals, to better applicability of those insulins to specific patients. The belief that guideline-recommended insulins were less effective, positive experience with other insulins and marketing from pharmaceutical companies were also identified as attitude-related barriers to prescribe guideline-recommended insulins. One additional category in the domain of attitudes was identified, namely the lack of uniformity in policy between healthcare professionals in the same practice. Only a small number of external barriers were identified, focusing on patient characteristics that prevented the use of recommended insulins, the availability of contradictory guidelines and other, mostly secondary care, healthcare providers initiating non-recommended insulins. No knowledge-related barriers were identified.

Conclusions

The prescription of non-recommended insulins in primary care is mostly driven by lack of agreement with the guideline recommendations and different interpretation of evidence. These insights can be used for the development of interventions to stimulate primary care practitioners to prescribe guideline-recommended insulins.

BACKGROUND

Substantial evidence exists that adherence to clinical practice guidelines positively affects the quality of primary care. Guideline adherence has been associated with more patient satisfaction with their treatment [1] and improved patient outcomes [2]. In addition, guideline adherence can improve the process and structure of care [3] and reduce costs [4].

A country with a long history of developing and implementing clinical guidelines in primary care is the Netherlands [2]. National guidelines covering the majority of conditions and diseases in general practice are developed by the Dutch College of General Practitioners (NHG) [5]. Virtually all (97%) Dutch general practitioners have a positive attitude towards those guidelines [6]. Moreover, 89% of Dutch general practitioners believe that guideline adherence contributes to better quality of care. Adherence to these guidelines among general practitioners is therefore generally high, around 75% [6,7], but varies among types of diseases and recommendations, with some areas of poor adherence [7,8].

One area with poor guideline adherence is the prescription of insulins for type 2 diabetes mellitus (T2DM) patients. In Dutch general practice, where the majority of insulins for T2DM are prescribed [9], less than 20% of T2DM patients needing insulin treatment starts with the guideline-recommended NPH insulin. Instead, insulin glargine 100 U/ml and insulin detemir – which are mentioned as less favourable, alternative options – are often initiated. In addition, approximately 25% of all insulin users uses one of the newer agents insulin glargine 300 U/ml or insulin degludec, which gained market access in 2013 and 2015, respectively [10]. Those two newer insulins are not recommended, because of the lack of evidence-based advantages in terms of efficacy or safety, and higher costs [11]. The Dutch guideline is in line with most international guidelines for the treatment of T2DM that also favour NPH insulin for insulin-naïve patients and do not recommend the use of insulin glargine 300 U/ml and insulin degludec [12,13]. In spite of this, the declining popularity of NPH insulin and rapid adoption of newer insulins is a worldwide trend [10,14-20], resulting in substantial increases in total insulin expenditures [20-24]. Although previous observational research showed that the prescription of newer insulins was related to several patient and practice characteristics, most reasons for this guideline non-adherence could not be elucidated [10]. According to Cabana et al., potential barriers to guideline adherence can be organised in a knowledge, attitudes, behaviour framework, which states that before a guideline can affect patient outcomes, it first affects healthcare professionals' knowledge, then attitudes and finally behaviour. In this model, the behaviour of the healthcare professional is determined by knowledge

(is the healthcare professional familiar with the guideline), attitude (is he or she willing to perform the recommendation) and external barriers (do factors which are beyond their control hamper the execution of the recommendation) [25]. It is yet unknown to what extent these barriers to physician adherence to guidelines also apply for the prescription of guideline-recommended insulins.

To ensure quality of primary care and prevent increasing expenditure on insulins for T2DM patients, insight in the reasons for guideline non-adherence concerning the prescription of insulins is of crucial importance. The aim of this qualitative study is therefore to identify the reasons why primary care healthcare professionals prefer non-recommended insulins, focusing on the prescription of other insulins than NPH insulin for insulin-naïve patients and the prescription of newer insulins to both insulin-naïve and prevalent insulin users.

METHODS

Focus group discussions were performed with primary care healthcare professionals to study their preferences and accompanying argumentation for insulin treatment in T2DM patients. Focus groups were preferred over individual interviews since they allow participants to interact with each other. Focus groups have therefore been associated with a wider range of views and ideas than can be collected by using individual interviews [26,27].

Setting

This study was carried out among Dutch general practitioners, practice nurses, diabetes nurses, nurse practitioners and pharmacists. In the Dutch healthcare system, most T2DM patients are treated in primary care [9]. The majority of general practices deploy nurses (i.e. practice nurses, diabetes nurses or nurse practitioners) to take care of T2DM patients [28,29]. While diabetes nurses and nurse practitioners have a formal prescriptive authority, practice nurses do not [30]. Practice nurses have, however, a prominent role in the management of T2DM patients, including advising general practitioners about the preferred treatment [31]. Pharmacists have no prescriptive authority, but do have an important advisory role in the pharmaceutical treatment in the Netherlands. They were also involved because of their insight in the actual prescription patterns, both from general practitioners and secondary care providers.

Two out of four focus group meetings were held during PharmacoTherapy Audit Meetings (PTAMs). Since this study was carried out during the second wave of COVID-19, recruiting general practitioners outside regular activities would have been extremely difficult. We

therefore planned to organise the focus group discussions during regular meetings with general practitioners, so no additional time-investment was necessary. PTAMs are regular meetings between general practitioners and pharmacists (and sometimes nurses) in the same region. PTAMS are organised to exchange information and views about pharmacotherapy with the aim of improving the prescribing and dispensing of medicines [32]. Almost all Dutch general practitioners and pharmacists participate in a PTAM in their region.

Since nurses are not always invited at PTAMs, two additional focus group meetings with practice and diabetes nurses were organised. Since the daily work of these professionals was less bothered by the COVID-19 pandemic, and to obtain a more heterogeneous representation than from PTAMs, these focus groups were specifically organised for the purpose of this research. To attract a broad range of nurses, individual participants were recruited through open enrolment.

Subjects

Both PTAMs and individual practice and diabetes nurses were recruited by an open call for participation through the newsletter and social media of the Dutch Institute for the Rational Use of Medicine (IRUM). A snowballing technique was used with the participants (PTAM or nurse) being asked to invite other PTAMs or nurses.

The two open enrolment groups with practice and diabetes nurses were organised with at least five participants and a maximum of eight. The number of participants in the PTAMs depended on local situations. All participants gave written informed consent before the start of the focus group discussions. According to Dutch legislation, approval by a medical ethics committee was not necessary, since no patients were involved in this study and the participants of the focus group discussions were not exposed to interventions [33].

Data collection

We prepared a topic list based on the model of Cabana et al. [25] and argumentation for preferred insulins obtained from literature and a priori expert discussions. The topic list was fine-tuned during several sessions within the research team. Covered topics were the preferred initial insulins, the prescription of newer insulins and corresponding argumentation in the domains of knowledge, attitudes and external barriers.

The focus group discussions were organised in October and November 2020. Due to the COVID-19 pandemic, we used a virtual focus group methodology using Zoom Video Communications. The discussions lasted 45 – 75 min and were facilitated by MD as moderator. MvdB and (in three of four groups) MvD were observers.

Data analysis

The discussions were video and audio-recorded and transcribed verbatim using automatic generated transcripts performed by AmberScript, which were manually verified and corrected. The transcripts were coded and analysed in Atlas.ti 9.1.5.0. Coding was performed with a combination of deductive and inductive codes. Deductive codes were derived from the argumentation for preferred insulins obtained from literature and a priori expert discussions and inductive codes from the focus groups itself. The coding focused on identifying reasons for prescribing of the preferred insulins. Those identified perspectives were subsequently classified into the categories of argumentation provided by the model of Cabana et al. (Fig. 1) [25]. This model distinguishes three domains of behaviour change: knowledge, attitudes and external barriers, which are further subdivided into categories. Barriers to guideline adherence related to knowledge can be classified into lack of familiarity with the guideline and lack of awareness. The domain of attitudes consists of lack of agreement (with specific guidelines or guidelines in general), lack of outcome expectancy, lack of self-efficacy and lack of motivation/inertia of previous practice. Both domains, together with external barriers related to patient, guideline and environmental factors define behaviour.

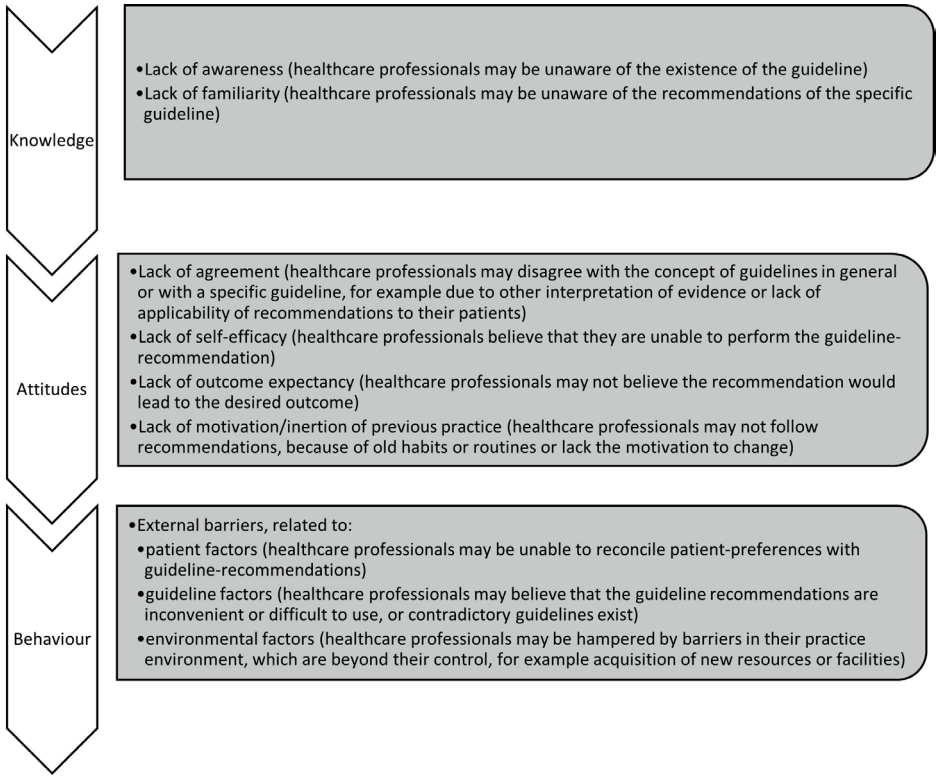

Figure 1: Domains and categories of guideline non-adherence, according to Cabana et al. [25].

Two out of four transcripts were independently coded by a second researcher (MvdB), using the codebook from the first coder (MD). Any disagreements were solved by discussion between both coders and a third researcher (LvD). The classification of codes into the model of Cabana et al. was discussed within the research team.

RESULTS

We conducted four focus group discussions. In the two PTAMs, eleven general practitioners, six pharmacists, two nurse practitioners and one practice nurse participated. The two open enrolment groups consisted of eleven practice nurses and four diabetes nurses. The exact number of different professionals per focus group meeting can be found in Table 1.

Table 1: Number of participating healthcare professionals in the different focus group discussions.

	PTAM 1	PTAM 2	Open enrolment 1	Open enrolment 2	Total
General practitioner	5	6			11
Pharmacist	3	3			6
Nurse practitioner		2			2
Practice nurse		1	6	5	12
Diabetes nurse			2	2	4
Total	8	12	8	7	35

PTAM = PharmacoTherapy Audit Meeting.

In most practices, the nurses had the most prominent role in initiating insulins, although the general practitioner held the final responsibility. In daily practice, most nurses operated largely independent of the general practitioner, initiating treatments by themselves, including the practice nurses without formal prescriptive authority. Since pharmacists do not initiate insulins themselves, the preferred choices of insulins below refer to general practitioners and nurses only. The perspectives of pharmacists are however included in the analysis of reasons for guideline adherence and non-adherence.

Choice of insulin

Healthcare professionals were familiar with the five different intermediate or long-acting insulins (NPH insulin, insulin detemir, insulin glargine 100 U/ml, insulin glargine 300 U/ml and insulin degludec) and appreciated their availability to customize the therapy for individual patients. However, almost all healthcare professionals had one preferred insulin they most often initiated and had most experience with.

> But it is often a-a-a prescribing preference, you start with something, gain experience with it and then run with it. *General practitioner, #1*

> But I am glad that there are opportunities to switch. And it is also a little customization that you're providing.
> *Practice nurse, #3*

A substantial number of participating healthcare professionals was guideline-adherent, i.e. preferred NPH insulin as first choice in most situations and did not regularly prescribe newer insulins. Positive experience and following the guideline were the most common reasons for the initiation of guideline-recommended insulins. Also, the lower costs and adequate efficacy were mentioned. In a minority of situations, guideline-adherence was prompted by the general practitioner who required the nurse to prescribe guideline-recommended insulins despite her[1] own preference for other insulins.

Reasons for guideline non-adherence

During the focus group discussions, two different situations of guideline non-adherence were discussed: the prescription of other insulins than NPH insulin (i.e. insulin glargine 100 U/ml, insulin glargine 300 U/ml, insulin detemir or insulin degludec) to insulin-naïve patients and the prescription of newer insulins (insulin glargine 300 U/ml and insulin degludec), regardless of the former use of other insulins. Some overlap in both situations exists, since the initiation of newer insulins to insulin-naïve patients automatically applies to both situations.

Almost half of the participants preferred the initiation of other insulins than NPH insulin to insulin-naïve patients. Insulin glargine 100 U/ml was the most popular alternative. Although most healthcare professionals did not regularly prescribe newer insulins, almost all had some experience with newer insulins. In most of the cases, newer insulins were prescribed to patients who were already using insulin, but had to switch to another insulin. In addition, a few healthcare professionals preferred the newer insulin degludec as first-choice for all their insulin-naïve patients. Others sometimes initiated newer insulins to insulin-naïve patients because of a specific situation requiring a deviation from their normally preferred insulin.

> I think to myself, wait a minute, I've done this before [the initiation of new insulins]. I prescribed someone their first Tresiba [insulin degludec], but what was the reason for this? Because the FlexTouch in particular is quite a pleasant device. And it involved someone with a hand disability […]. And then with that the FlexTouch turned out to be an ideal device. So basically I prescribed Tresiba out of practical considerations.
> *Diabetes nurse, #2*

In Table 2, all argumentation for the prescription of non-recommended insulins are classified according to the model of Cabana et al. and assigned to both situations of guideline-non-adherence, i.e. initiation of other insulins than NPH insulin to insulin-naïve patients and initiation of newer insulins, regardless of the former use of

1 Due to privacy reasons, all healthcare professionals are referred to as 'her', irrespective of sex.

other insulins. The majority of argumentation applied to both situations. Most of the mentioned reasons were in the domain of attitudes, and especially related to a lack of agreement with guideline recommendations. No barriers in the domains of knowledge were identified. We did discover one new perspective in the domain of attitudes, namely lack of uniformity in policy, which refers to healthcare professionals in the same practice with opposing preferences.

Table 2: Argumentation for non-recommended insulins, classified according to Cabana et al. [25].

	Specific argumentation	Initiation of other insulins than NPH insulin to insulin-naïve patients	Initiation of newer insulins
Knowledge			
Lack of familiarity			
Lack of awareness (of guideline)			
Attitudes			
Lack of agreement	Flexibility in time	X	X
	Hypoglycemia	X	X
	Release profile	X	X
	Future-proof	X	X
	Uniformity device	X	X
	Body weight	X	
	Flexibility injection site	X	
	Injection volume		X
Lack of outcome expectancy	Efficacy	X	X
Lack of self-efficacy			
Lack of motivation/ inertion of previous practice	Image/marketing	X	X
	Experience	X	X
Lack of uniformity in policy[a]	Opposing views in the same practice	X	X
External barriers			
Patient factors	Inability to resuspend	X	
	Ease of use		X
Guideline factors	Contradictory guidelines		X
Environmental factors	Continuation of prescriptions from other prescribers		X

[a] *Newly identified category, not described in the model of Cabana et al.*

Knowledge

According to Cabana et al., barriers in the domain of knowledge refer to the lack of familiarity with or awareness of the guideline [25]. No such barriers were identified during the focus group discussions.

Attitude

Perspectives concerning attitude were most frequent, with lack of agreement as the most prominent category.

Lack of agreement

Most perspectives concerning lack of agreement did not reflect disagreement with the guideline recommendations in general, but were about minor advantages which led to better applicability of non-recommended insulins to specific patients in the participants' view. Healthcare professionals preferred those insulins because of the flexibility, both in injection sites (only mentioned for insulins other than NPH insulin) and time. The flexibility in time was especially mentioned as an advantage for people who make long-distance flights, go on holiday, prefer to sleep in (for example during the weekend) or depend on caregivers for the administration of insulin. During the focus group discussions, this argumentation was put into perspective by some healthcare professionals, stating that the advantage of flexibility only applied to a minority of patients and should not justify the massive use of non-recommended insulins.

> Anyway, not everyone wants to sleep in on a Saturday or Sunday and not everyone likes travelling. So you know, I think that's also a reason to choose a cheaper variant, simply because many people in the Netherlands have and will develop diabetes and will require insulin at some point.
> *Practice nurse, #3*

Another perspective concerned the uniformity of devices. For patients combining an intermediate or long-acting insulin with a short-acting insulin, healthcare professionals preferred uniformity in injection devices to enhance the ease of use. In those situations, the type of injection device was more leading than the type of insulin. Healthcare professionals also sometimes chose for a non-recommended insulin taking the future into account. They argued it was better to start with an insulin that would be sufficient for the next years, especially for younger patients. Others opposed this reasoning and stated it was better to start with a cheaper insulin and switch only if necessary, taking into account the higher costs of non-recommended insulins.

> Yes, and that's why I think it's somewhat remarkable that practice nurse X just said "I prefer to start with this [insulin degludec], because then I might be able to continue it for a long time". Meanwhile I'm thinking, you don't know what will be sufficient for the patient. So if you are going to do that [prescribe newer insulins] in advance, you are already going to bet on a very expensive one, while a cheaper one may be sufficient.
> *Practice nurse, #2*

Other reasons for preferring non-recommended insulins were related to the release profile which gives a longer time-in-range for patients, making them feel better. Finally, the lower injection volume of insulin glargine 300 U/ml compared to insulin glargine 100 U/ml was mentioned as a reason for the prescription of this newer insulin.

Some healthcare professionals disagreed with the evidence the guideline referred to. According to the guideline, the differences between insulins in effects on hypoglycemia and body weight are marginal and therefore there is no reason to prescribe more expensive insulins [11]. Lower risk of hypoglycemia and less gain of body weight were however used as justification to prescribe other insulins. This argumentation was challenged by others, claiming that the fear of hypoglycemia, both by healthcare professionals and patients, was probably more relevant than the actual risk of hypoglycemia.

> But I doubt if it [choosing glargine 100 U/ml instead of NPH insulin because of the risk of hypoglycemia] is because of the fear rather than the actual risk of nocturnal hypoglycemia.
> *General practitioner, #1*

Lack of outcome expectancy

One perspective concerning the lack of outcome expectancy was identified. Some healthcare professionals preferred non-recommended insulins for poorly controlled T2DM patients, because they believed guideline-recommended insulins had a lower glucose-lowering potential than other insulins. For example, one general practitioner stated she usually prescribed NPH insulin, but chose another insulin if glucose levels were extremely high. She expected other insulins to have a more profound effect on glucose levels.

Lack of motivation/inertion of previous practice

Some healthcare professionals chose non-recommended insulins because they had positive experiences (apart from glucose control, which is categorized as 'outcome expectancy') after prescribing them. They also pointed out the positive image of 'innovative' insulins. Other healthcare professionals argued that image is mostly constructed by marketing of pharmaceutical industries and mentioned the difficulties of distinguishing real advantages of newer insulins from marketing activities.

> But I believe Insulatard [NPH insulin] has a somewhat pompous image. So sometimes you have a relatively young patient and you think, should I choose another one [insulin]? But I think that's more the result of marketing than the actual effect of the medicine.
> *Diabetes nurse, #2*

Lack of uniformity in policy

One additional category in the domain of attitudes was discussed, referring to a lack of uniformity in policy regarding the prescription of insulins. In some practices, the general practitioner and nurse did not have the same insulin preference, but were not aware of this difference. For example, one general practitioner thought she followed the guideline, prescribing NPH insulin to her patients. But when her actual prescription pattern was analysed, she discovered that most prescriptions were for other insulins. This was due to the preference of the practice nurse, whose prescriptions for non-recommended insulins were authorised by the general practitioner. On the other hand, some nurses stated they wanted to prescribe newer insulins to their patients, but were not allowed to do so, because the general practitioner stimulated them to adhere to the guideline.

> Ahh, I prefer NPH insulin. But I checked my actual prescriptions, and then I saw something else. Ahh… the practice nurse, she'd choose Lantus [insulin glargine 100 U/ml] every time.
> *General practitioner, #1*

External barriers

Patient factors

In some situations, patients' abilities restricted the use of guideline-recommended insulins. For example, patients using NPH insulin need to resuspend the insulin before administration. According to the healthcare professionals, not all patients are capable to do this, thus requiring another insulin. In the same domain, the ease of use of the device was mentioned as reason for the prescription of newer insulins. For example, dysfunctional hand function could require a switch to a non-recommended insulin with a better device applicability.

Guideline factors

One guideline-related factor was identified, concerning the prescription of insulin glargine 300 U/ml, namely the presence of contradictory guidelines. A guideline specifically aimed at diabetes nurses gave other recommendations about switching to insulin glargine 300 U/ml (at 40 or 80 units) than the guideline aimed at general practitioners, which led to confusion.

Environmental factors

As environmental factor, the continuation of prescriptions from former prescribers was pointed out. In most cases, this referred to secondary care providers initiating the use of newer insulins. Most healthcare professionals were familiar with internists and/or diabetes nurses from hospitals who initiated newer insulins to their patients, thereby stimulating primary care practitioners to iterate prescriptions for newer insulins. Also,

the continuation of insulin prescriptions from other general practitioners for newly registered patients was mentioned.

DISCUSSION

Although Dutch general practitioners are generally guideline-adherent, the prescription of insulins is often not in line with current treatment recommendations. The present study showed that this non-adherence is largely driven by the lack of agreement with the guideline recommendations, as well as other attitudes of prescribers. A few barriers related to environmental factors, namely patients' abilities, contradictory guidelines and continuation of prescriptions from other healthcare professionals, were discussed in relation to guideline non-adherence. No factors concerning the knowledge of guideline recommendations were identified.

Our study described two situations of guideline non-adherence: the prescription of other insulins than NPH insulin to insulin-naïve patients and the prescription of newer insulins to all patients. Due to the similarity in argumentation, both situations were analysed and described simultaneously. There are however some differences, especially in the moments when guideline non-adherence occurs. The Dutch guideline T2DM advises NPH insulin as the preferred insulin for all new patients, but provides some room to switch prevalent users of NPH insulin to insulin glargine 100 U/ml or insulin detemir. In contrast, newer insulins (insulin glargine 300 U/ml and insulin degludec) are discouraged for all patients, including prevalent users of insulin [11]. Participants in our study prescribed newer insulins most often to prevalent users, who – according to the healthcare professionals – needed to switch their insulin. Although less frequent, newer insulins were also prescribed to insulin-naïve patients.

The prescription of non-recommended insulins was mostly related to perspectives in the domain of attitudes, which is in accordance with previous studies towards guideline non-adherence in different therapeutical areas in the Netherlands [6,34]. Most argumentation identified in our study indicated different perspectives on the efficacy (glucose-lowering potential), safety (hypoglycemia, body weight) and applicability (flexibility in injection time and site, applicability of device) of the insulins to patients. This indicates that guideline-non adherence to insulin recommendations is mostly intentional and a deliberate decision of healthcare professionals, which is in line with the results of other studies towards guideline non-adherence [6,34,35]. However, the validity of argumentation in the domains of attitudes can be argued – which also occurred during the focus group discussions –, albeit on different levels. First, some perspectives identified

in this study can be challenged with the current evidence. For example, the guideline committee that developed the Dutch primary care guideline on T2DM concluded after thorough review of the literature that no clinically relevant differences in hypoglycemia risk exists between intermediate- and long-acting insulins [11]. Nevertheless, the lower risk of hypoglycemia was frequently used as justification by participants in our study to prescribe non-recommended insulins. Reasons like these led often to discussions between the participants in the focus groups, indicating that contrasting interpretation of evidence is indeed an important factor that explains the differences between prescribers in the prescription of insulins. Second, some argumentation (for example flexibility in injection site) do not refer to discussions about evidence, but to the question whether these 'customization' perspectives justify the use of more expensive insulins by large groups of patients. In general, guidelines are developed based on population advantages, taking into account the long term outcomes on population level. In daily practice, decisions might be more influenced by other considerations, like short term outcomes on patient level, and less on cost-efficacy on population level [36-38]. Both views can be contradictory if a non-recommended treatment would account for minor advantages for patients at higher costs. Finally, marketing and image of newer insulins were mentioned as important factors in the attitudes towards insulins. Most healthcare professionals were aware of this mechanism, realising that the positive and innovative image of newer insulins was probably mostly constructed by marketing and therefore no valid reason for the prescription of newer insulins. Still, the innovative image did account for the prescription of non-recommended insulins.

We did identify one new category of attitude-related barriers, namely the lack of uniformity in policy. This barrier reflected opposing views in the same practice, with healthcare professionals not being aware of each other preferences. This barrier could lead both to guideline-adherence, in the case one healthcare professional was stimulating the other to prescribe guideline-recommended insulins, and (unintentional) non-adherence, in the case healthcare professionals were not aware of each other's preference for non-recommended insulins. This newly identified barrier in addition to the model of Cabana et al. most probably reflects the increasing complexity and number of different healthcare professionals in primary care since the development of the model of Cabana in 1999 [28,31] and points out the importance of good communication and coordination of policy between healthcare professionals.

The lack of knowledge-related barriers for guideline adherence found in our study was not surprising, because of the long history of using clinical guidelines and the prominent role of current guidelines in the post-graduate education of healthcare professionals in primary care in the Netherlands [34]. In addition, T2DM is a frequent condition in

primary care [39] and healthcare professionals are well educated about this disease. It can however not be excluded that knowledge-related barriers were overlooked, because healthcare professionals being more familiar with the guideline and treatment of T2DM were more likely to sign up for the focus group discussions. Some external barriers to follow the guideline were identified. The first external barrier reflected barriers at patient level, referring to physical limitations that prevented the use of specific insulins or devices. Second, one guideline-factor was identified, namely the availability of different recommendations about the number of units that require switching from insulin glargine 100 U/ml to insulin glargine 300 U/ml. Third, as environmental barrier, the continuation of prescriptions from other prescribers were mentioned. Although these perspectives were mentioned less often than the barriers in the domain of attitude, these external barriers and explicitly the role of the secondary care should not be marginalized. New medicines initiated by secondary care providers are often subsequently iterated in general practice. Due to this mechanism, primary care providers will become familiar with new medicines, which can lead to adoption of these medicines by the primary care provider herself [40].

The main strength of our study is the use of focus groups with different professionals. Since we included all healthcare professionals, irrespective of their preferred insulins, this resulted in a balanced overview on the preferences and perspectives of the prescription of insulins. In addition, the use of the existing framework to classify barriers to guideline adherence allowed for a thorough evaluation of argumentation. There are also some limitations. The qualitative study design is by definition a possible source of bias, as the interpretation of argumentation and the classification into domains and categories can be subjective. By using two coders and the verification of the coding and classification by a third researcher, we minimised this risk. In addition, since four focus group discussions were budgeted, we did not formally went on with organising until data saturation was reached. However, because few new perspectives were identified during the last focus group and the views of a large number of 35 healthcare professionals were included, we presume data saturation and a complete overview on the topic. Furthermore, selection bias might have occurred in this study, since healthcare professionals interested in the dynamics between guideline-recommendations and actual prescription behaviour were probably more likely to sign up for the focus group discussions. In addition, the use of PTAMs as focus groups might also have limited the range of perspectives found in our study. PTAMs are organised to coordinate and align prescription behaviour. Likely, beliefs and perspectives of healthcare professionals participating in the same PTAM are more uniform than from a random population of healthcare professionals. To obtain a broader view, we additionally organised two focus group discussions for nurses with open enrolment.

The results of our study can be used to develop interventions directed at healthcare professionals in primary care to stimulate rational prescribing of insulins. The prominence of barriers in the domain of attitudes suggests that interventions to stimulate better prescription behaviour should be directed to the views and perspectives of healthcare professionals on insulins, rather than on external barriers and knowledge of the guideline. Most perspectives did not reflect disagreement with the guideline recommendations in general, but were about minor advantages which led to better applicability of other insulins to specific patients in the participants' view. The finding that healthcare professionals in the focus group discussions regularly challenged each other's argumentation for non-recommended insulins indicates that there is indeed opportunity for improvement and points out the importance of good and regular communication. Therefore, thorough explanation of treatment recommendations in guidelines, including the description of clinically relevant differences and cost-efficacy is warranted and could stimulate qualitative and cost-effective prescription of insulins.

CONCLUSIONS

This study shed light on the reasons why Dutch primary care practitioners often prefer non-recommended insulins. Lack of agreement with the guideline recommendations and different interpretation of evidence are the most prominent reasons for the prescription of non-recommended insulins. These insights can be used when developing interventions directed at healthcare professionals to stimulate the qualitative and cost-efficient prescription of insulins in primary care.

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3.2

Marketing of medicines in primary care: an analysis of direct marketing mailings and advertisements

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ABSTRACT

Introduction

Marketing materials from pharmaceutical companies attempt to create a positive image of marketed, often new, medicines. To gain more insight in strategies pharmaceutical companies use to influence primary care practitioners' attitudes towards marketed medicines, we investigated the use of persuasion strategies in direct marketing mailings and advertisements from pharmaceutical companies sent to general practitioners.

Methods

General practitioners in the Netherlands were recruited to collect all direct marketing mailings, meaning all leaflets, letters and other information sent by pharmaceutical industries to the practice during one month (June 2022). Direct marketing mailings and advertisements in collected medical journals concerning medicines or diseases (together called marketing materials) were analysed according to presence of one of the seven common persuasion strategies, i.e. reciprocity, consistency/commitment, social proof, liking, authority, scarcity and unity, as well as marketed medicine and year of introduction.

Results

Twenty general practices collected 68 unique marketing materials concerning 37 different medicines. Direct factor Xa inhibitors (n = 12), glucagon-like peptide-1 analogues (n = 5) and sodium-glucose co-transporter 2 inhibitors (n = 4) were the most frequently marketed medicines. The median year of introduction of all marketed medicines was 2012. All seven persuasion strategies were identified, with liking (64.7% of all materials) and authority (29.4%) as most prominent strategies, followed by social proof (17.6%), unity (14.7%), scarcity (13.2%), reciprocity (11.8%) and consistency/commitment (2.9%). In addition to those strategies, we identified emotional pressure (30.9%) as one commonly used new strategy.

Conclusion

Marketing materials sent to general practices use a wide range of persuasion strategies in an attempt to influence prescription behaviour. Primary care practitioners should be aware of these mechanisms through which pharmaceutical companies try to influence their attitudes towards new medicines.

INTRODUCTION

New medicines have been associated with increased longevity and can have benefits in terms of morbidity and health related quality of life [1,2]. However, not all new medicines have an added therapeutic value [2]. In addition, the benefit-risk ratio of new medicines has not been fully elucidated yet and new medicines are often more expensive than alternative treatments [3,4]. There is therefore an urgent need for the rational use of new medicines, both in terms of quality of care and healthcare costs, especially in the light of aging populations and rising healthcare costs [5].

In the Netherlands, primary care functions as gatekeeper of the healthcare system and plays an important role in the prescription of medicines [6]. The uptake of new medicines in primary care is often not equally distributed among physicians [7], and previous attempts to construct a universal profile of early adopters of new medicines failed [8,9]. The attitude of primary care practitioners towards new medicines is likely to play a major role in the decision to prescribe new medicines and might explain the large differences between healthcare professionals in the adoption of new medicines [10]. This attitude can be affected by a variety of factors, including marketing activities from pharmaceutical companies [11-13]. Marketing activities have been known for decades to stimulate the prescription of new medicines [14-19].

Marketing of new medicines in primary care reflects a broad set of activities, including both direct contact (e.g. medical representatives visiting the practice and educations organised by a company) and indirect contact (e.g. sponsored courses and ghost-writing) [14,19,20]. In the Netherlands, the marketing of medicines is strictly regulated and excessive inducement and financial relations between pharmaceutical companies and healthcare professionals are prohibited [21]. Marketing of medicines therefore often happens in more subtle ways and includes the use of direct marketing mailings. Direct marketing mail is described as any marketing material that is delivered physically to a prospect's mailbox, and thus covers all kinds of paper-based marketing materials, including newsletters, flyers and brochures [22]. Another paper-based marketing activity is the use of advertisements in (medical) journals [23]. The contents of these direct marketing mailings and advertisements, further referred to as 'marketing materials', are bound to a code of conduct. This code is supervised by the Dutch Foundation for the Code for Pharmaceutical Advertising. It outlines the requirements that marketing materials must adhere to, such as providing mandatory information (e.g., about indications and adverse events) and specifies the manner in which this information is presented [21].

Although the contents of marketing materials are regulated by the Dutch code, the manner in which materials aim to influence someone's attitude towards medicines are more difficult to regulate. Influencing someone's attitude can be achieved in different ways. To explore the influence strategies used in marketing materials, we used the generally accepted framework by Cialdini [24]. This framework describes seven strategies for persuasion, that could be used to convince the recipient of the advantages of a product [24,25]. Although different taxonomies to classify persuasion strategies exist, the framework of Cialdini is widely accepted and numerous studies have shown the effectiveness of those persuasion strategies in influencing attitudes and behaviour in different areas, including pharmaceutical marketing [26-28]. This framework therefore provides a useful basis to investigate persuasion strategies in marketing materials. Table 1 provides an overview and short description of these strategies. Whether all strategies occur in direct marketing mailings and advertisements from pharmaceutical companies and whether this occurs to a similar extent is unknown.

Table 1: Description of persuasion strategies by Cialdini and examples of how they can occur in pharmaceutical marketing [24,26].

Principle	Description	Example
Reciprocity	Feeling indebted to those who have helped you.	A gift from a pharmaceutical company makes healthcare professionals feeling indebted, which may lead them to change their practice in favour of the gift-giving company.
Consistency/ commitment	The urge to behave consistently and to commit to earlier decisions or opinions.	Agreeing to a small request (for example, a medical representative who asks a healthcare professional whether they agree that there should be more attention to disease X, or to try a new medicine on a small number of patients) increases the likelihood that the healthcare professional will start prescribing the medicine again in larger quantities.
Social proof	The practice of deciding what to do by looking at what others are doing.	The use of opinions of colleagues in marketing activities to sway healthcare professionals to adopt a particular therapy (e.g., 80% of your colleagues prescribe X).
Liking	The principle of being more likely to comply with requests made by people that are liked.	Industry representatives acting friendly towards healthcare professionals and appear to ask nothing in return, or the use of endearing pictures of patients to raise sympathy.
Authority	The use of individuals or institutions who are authoritative, credible and knowledgeable.	The use of key opinion leaders to convince healthcare professionals of the benefits of new medicines.
Scarcity	The concept that opportunities are more valuable when they are limited.	The marketing of a new medicine as 'one of a kind', or available to only a select number of practices.
Unity	The concept of shared identity which opens up to persuasion attempts.	A focus on cooperation and shared goals between industry and professionals will make professionals more willing to do something for the company they feel connected to.

To gain more insight in the strategies pharmaceutical companies use to influence primary care practitioners' views towards new medicines, the aim of this study was to investigate the presence and use of different persuasion strategies in marketing materials from pharmaceutical companies sent to general practitioners.

MATERIALS AND METHODS

Participant recruitment

General practitioners were recruited to collect all direct marketing mailings sent to the practice during one month. Based on a previous – non-published – pilot study, a number of 20 general practices was presumed to be enough to obtain a representative overview of direct marketing mailings. General practitioners were recruited in March and April 2022 by a call in the newsletter and social media channels of the Dutch Institute for the Rational Use of Medicine (IRUM) and members of the research team. In addition, a call was published in the Dutch Journal of Medicine ('Nederlands Tijdschrift voor Geneeskunde') [29]. Finally, symposia and conferences aimed at healthcare professionals where IRUM was represented were used to invite general practitioners.

General practitioners willing to participate were further informed about the purpose of the study and the data - including practice characteristics - that were to be collected. Practices willing to participate gave consent to participate by e-mail or telephone up to May 1, 2022. A digital confirmation of participation (by e-mail) was obtained for all practices. To investigate the representativeness of practices, publicly available information on the practice characteristics location, number of general practitioners per practice, practice type (solo, duo or group), dispensing status and urbanisation of the location of the practice were identified by internet search.

According to Dutch legislation, approval by a medical ethics committee was not necessary, since no patients were involved in this study and the participating healthcare professionals were not exposed to interventions [30].

Data collection

General practitioners were asked to collect all physical marketing mailings from pharmaceutical companies sent by mail from June 1 to 30, 2022. Detailed instructions were sent in the first week of May 2022. The instructions were repeated on May 31, including a final reminder to start the collection. Instructions included the collection of all direct marketing mailings, including leaflets, letters and other information sent by mail to the practice by pharmaceutical industries. Medical journals including advertisements

were not to be collected, although practices were invited to collect sponsored inserts. In case of doubt, the practice was invited to collect the mailing, enabling the researches to make a selection afterwards, if necessary. A reminder to end the collection was sent by e-mail on June 30, 2022. The materials were subsequently either picked up by a member of the research team or sent to the IRUM. Practices that did not start the collection or lost their collected materials were excluded from further analysis.

Data analysis

An overview was made of all materials received per practice by the principal investigator (MD). Multiple brochures for the same medicine in one envelop were considered as one material. Medical journals and sponsored inserts or adjusted covers were counted as separate materials. Thereafter, the selection of relevant direct marketing mailings and advertisements was made. The selection was based on two criteria regarding the sender of the mail (pharmaceutical company) and the subject (medicine or disease, to include disease awareness). All other materials were excluded.

Although medical journals were not meant to be collected and included in this analysis, we decided post hoc to include medicine advertisements in collected journals as well. This was done because of the large number of collected medical journals, despite the instruction not to do so. Moreover, advertisements in medical journals fulfilled both inclusion criteria (sender and subject) and were therefore suitable for analysis.

After inclusion and before further analysis, the marketing materials were anonymized. All unique direct marketing mailings and advertisements were classified according to the name of the marketed medicine, the medicine class (based on the Anatomical Therapeutic Chemical Classification system (ATC) 5th level) and the year of marketing approval. The year of marketing approval was based on the marketed indication. If multiple indications were marketed, the year of approval for the first indication was mentioned. The median year of approval of the medicines in all marketing materials (meaning that medicines that were marketed multiple times were also included multiple times) was calculated to gain insight in the novelty of marketed medicines. Subsequently, for every marketing material the persuasion strategies according to Cialdini's classification were captured. Prior to this analysis, a research guideline with a description of each persuasion strategy including examples from former collected marketing materials was developed and finetuned during several discussion sessions with the research team. This guideline was developed with deductive and inductive research, meaning that we analysed the pilot materials on the presence of both the strategies according to Cialdini's classification (deductive analysis) and other strategies (inductive analysis). During this development, one additional persuasion strategy,

namely emotional pressure, was identified. This additional strategy made use of the sense of responsibility or even sense of guilt of healthcare professionals, resulting in emotional pressure to do the right thing (i.e., prescribing the company's medicine). This was achieved by emphasizing the responsibility of the healthcare professional to take care of patients, often by mentioning the action the healthcare professional had to perform ("you can help her", "your patients need you to"). The strategy had some overlap with commitment, liking and unity. However, the sole focus on sense of responsibility and sense of guilt was considered as a distinct strategy to persuade the healthcare professional to prescribe the marketed medicine. After careful considerations and thorough discussions with the research team, this strategy was therefore added to the research guideline. The analysis of the collected materials was performed independently by two researchers who were primarily involved in the development of the guiding document, one with a background in pharmacy (MD) and one in marketing (PV). In addition, two other independent research assistants, one with a background in pharmacy (KW) and one in marketing (RJ), performed the analysis after being trained in using the guiding document. Cohen's kappa was calculated to measure inter-rater reliability between the two primary investigators and the investigators with the same background. Consensus was to be reached by the two primary investigators, with the opinion of a third independent researcher if needed in case of disagreement.

All results were analysed with IBM SPSS Statistics 28.0.1.1 (15).

RESULTS

Baseline characteristics

Twenty-two practices signed up for the collection. Twenty out of 22 practices started and finished the collection and were thus included in the analysis and reported upon below. The characteristics of all included practices can be found in Table 2. Practices were well distributed across the Netherlands, 9 out of all 12 provinces were represented. The mean number of general practitioners per practice was 3.9 (range 1 - 11). Three participating practices were dispensing practices.

A total of 361 materials were collected (range 0 – 92 per practice) by the 20 included practices. One of the twenty practices only recently opened and did not receive any materials. Two other practices spontaneously reported incomplete collection, due to changing staff or inadequate communication between professionals. After removal of all duplicates, 149 unique materials (range 0 – 43 per practice) remained. Seventeen items were medical journals, which contained 38 unique medicine advertisements. 132 were

Table 2: Characteristics of participating practices.

	Number of practices (%)
Practice type	
Solo	1 (5.0)
Duo	6 (30.0)
Group	13 (65.0)
Number of general practitioners per practice	
1	1 (5.0)
2 to 4	12 (60.0)
≥ 5	7 (35.0)
Dispensing status	
Yes	3 (15.0)
No	17 (85.0)
Urbanisation level of location of practice[a]	
Very strong	4 (20.0)
Strong	5 (25.0)
Moderate	0 (0)
Little	9 (45.0)
Not	2 (10.0)

[a] *Level of urbanisation is defined as very strong (≥ 2500 addresses/km^2), strong (1500 - 2500 addresses/km^2), moderate (1000 – 1500 addresses/km^2), little (500 - 1000 addresses/km^2) or not (< 500 addresses/km^2) [31].*

other marketing materials, of which 30 fulfilled the inclusion criteria (range 0 – 14 per practice). A total number of 68 marketing materials were included for analysis (Figure 1).

Characteristics of marketing materials

Six different types of marketing materials were identified. Advertisements in medical journals (n = 38) were most prominent, followed by marketing brochures (n = 13), sponsored inserts or covers of medical journals (n = 6) and invitations for education organised by pharmaceutical companies (n = 5). In addition, five information letters from companies about registration or reimbursement of medicines and one invitation to a company's stand with information on a specific disease on an upcoming medical symposium were identified. The identified materials concerned a total of 37 different marketed medicines (S1 Table). Eleven marketing materials did not mention a specific medicine. Direct factor Xa inhibitors (n = 12) were the most frequently marketed

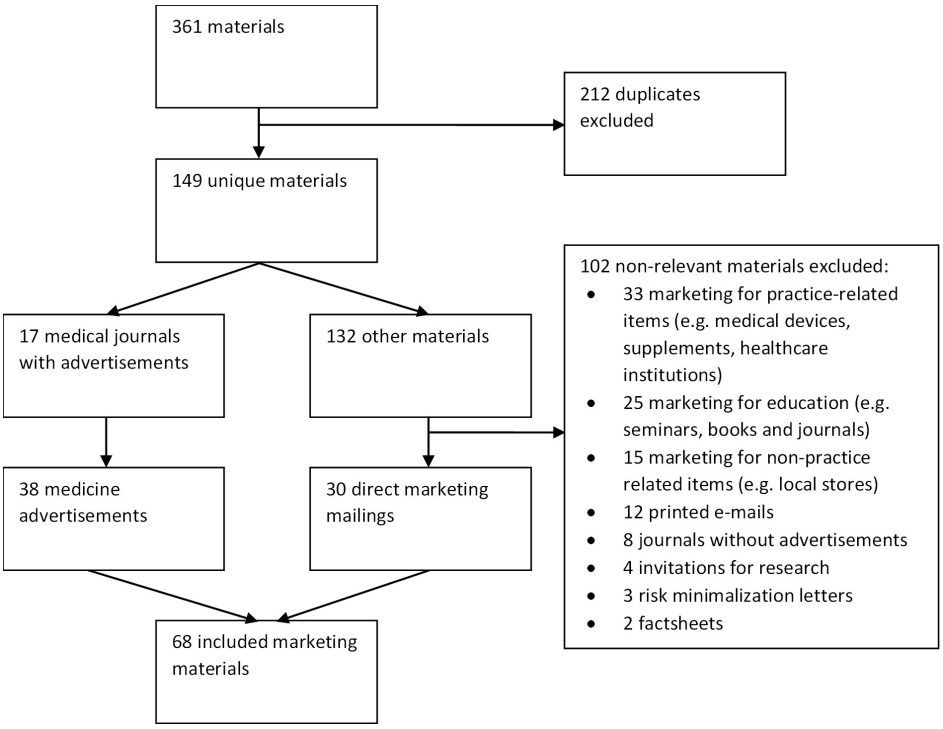

Figure 1: Selection of marketing materials.

medicines, followed by glucagon-like peptide-1 (GLP-1) receptor agonists (n = 5) and sodium-glucose co-transporter 2 (SGLT2) inhibitors (n = 4). The median year of introduction of all medicines was 2012 (range 1966 – 2022).

Persuasion strategies

For the allocation of persuasion strategies, the Cohen's kappa coefficient between the two primary investigators was 0.65, indicating, according to Cohen, substantial agreement [32]. The agreement between two researchers with the same background was slightly higher (0.71 for both pharmaceutical experts and 0.80 for both marketing experts). Ultimately, agreement between the two primary researchers was reached in all cases without the need for a call from a third researcher. The frequency of identified persuasion strategies, based on consensus between the two primary investigators, can be seen in Table 3. A total of 126 persuasion strategies were found in 68 materials. No large differences existed between direct marketing mailings and advertisements. All different seven categories defined by Cialdini were identified, with liking (64.7% of all marketing materials) and authority (29.4%) as the most represented persuasion strategies. We identified emotional pressure as an additional category, which was present in 30.9% of all materials.

Table 3: Frequency of persuasion strategies found in collected marketing materials.

Persuasion strategy	Overall (n = 68) n (%[a])	Direct marketing mailings (n = 30) n (%[a])	Advertisements (n = 38) n (%[a])
Reciprocity	8 (11.8%)	7 (23.3%)	1 (2.6%)
Consistency/commitment	2 (2.9%)	2 (6.7%)	0 (0%)
Social proof	12 (17.6%)	7 (23.2%)	5 (13.2%)
Liking	44 (64.7%)	19 (63.3%)	25 (65.8%)
Authority	20 (29.4%)	9 (30.0%)	11 (28.9%)
Scarcity	9 (13.2%)	3 (10.0%)	6 (15.8%)
Unity	10 (14.7%)	6 (20.0%)	4 (10.5%)
Emotional pressure[b]	21 (30.9%)	9 (30.0%)	12 (31.6%)

[a] *Percentages do not add up to 100% because multiple strategies can be used in one marketing material.*
[b] *Newly identified category, not described by Cialdini.*

Reciprocity

Reciprocity refers to the obligation to help those who have helped you and is often expressed by providing someone with something that could be considered as a gift. In the marketing materials, examples of reciprocity were found eight times. For example, some invitations for sponsored educations advertised free meals and accreditation points. Other examples were offering free samples, books and placebo-inhalers. Most identified gifts were relatively small. The gifts were both aimed at the practice as a whole (for example training inhalers) or at individual general practitioners (for example accreditation points).

> Invitation for a sponsored education with free meals and accreditation points.
> *#Marketing material 37, invitation for education.*

Consistency/commitment

Consistency refers to behaving consistently and to commit to earlier decisions or opinions. In marketing materials, this can be achieved by the use of (semi-)rhetorical questions. A positive answer on these often obligate questions automatically implies that the marketed medicine is the best option. This mechanism was identified two times in the collected materials.

> "Do you and your patients prefer ease of use and ease of prescription?"
> *#Marketing material 24, brochure.*

Social proof

Social proof is the use of opinions of colleagues to promote a product. In marketing materials, this can be achieved by using opinions or actions of other healthcare

professionals. A referral to a healthcare professional who is positioned as an expert in the field, was considered as authority and not social proof.

In the collected materials, we found several marketing materials stating 'the most prescribed medicine for disease X'. Remarkably, in a specific therapeutic class, the statement of being the most prescribed medicine was found for two different medicines, referring to different investigations. Social proof was also used more subtly by the use of specific pictures referring to other physicians' actions, for example by using white coats or stethoscopes.

"Most prescribed [medicine class X] in the Netherlands."
#Marketing material 4, brochure.

Liking

Liking is the creation of a positive feeling about a company or product. Liking was the most identified persuasion strategy and used in almost two-thirds of all marketing materials. Liking was most often achieved by the use of sympathetic pictures, for example of friendly-looking patients, beautiful landscapes and animals. Liking was achieved by portraying patients as sad people who could be helped on one hand and as self-confident people who had already been helped by the product on the other hand.

A portrait of a happy-looking boy playing the guitar accompanied with the phrase "Be who you want to be"
#Marketing material 59, advertisement.

Authority

Authority refers to the use of individuals or institutions who are authoritative, credible and knowledgeable. In addition, authority can also be created by focusing on the authority of the product itself, by emphasizing the status of the medicine. Authority was identified twenty times and attained by mentioning the authority of the pharmaceutical company as well as the use of authority of others to emphasize the medicines' benefit. Authority of the company was for example emphasized by mentioning the years of experience in a specific field. Materials also referred to the authority of others, for example by referring to guidelines, official institutions like registration authorities and professional organisations, and individual medical experts. Authority was also achieved by focusing on the seniority of the product.

"[Medicine X] has been a reliable [medicine group X] for almost 50 years and has been used by 3 million Dutch women."
#Marketing material 8, sponsored cover.

Scarcity

Scarcity refers to limited options that are considered more valuable. In marketing materials, this can be achieved by focusing on the unique status of a product. The collected marketing materials made use of this scarcity by referring to a medicine as 'the only one'. Often, the phrase 'the first and only' was used. Emphasized characteristics referred among others to indications, dosage forms and mechanisms of action.

"[Medicine X] is the first and so far only selective [medicine group X] registered for the aforementioned indication."
#Marketing material 19, information letter.

Unity

Unity is the principle of shared identity, which can be explained as shared identity between the producer and healthcare professionals. In marketing materials, this was expressed by positioning the company next to the professional, to emphasize that they were on the same side and had the same goals. This was often done by using the word 'together', but also by phrases like 'we can help you' and statements implying that the company was helping the healthcare professional by providing them with therapeutic options for their patients.

"Together we tackle overweight."
#Marketing material 38, invitation for education.

Emotional pressure

In addition to the persuasion strategies defined by Cialdini, one more strategy was identified in the materials, which was the second most common, after liking. This strategy made use of the sense of responsibility or even sense of guilt of healthcare professionals. This strategy was often achieved by addressing healthcare professionals to do what was best for their patients (i.e. prescribing the company's medicine).

"Provide your patients with [disease X] and ['old' medicine X] with better chances with ['new' medicine Y]."
#Marketing material 79, advertisement in magazine.
An image of a granddaughter hugging her grandfather, accompanied with the phrase: "838 additional hugs from grandfather, due to the protection you provide your [disease X] patients with."
#Marketing material 15, sponsored cover.
"For which T2DM patient do you want to do more?"
#Marketing material 13, brochure.

DISCUSSION

Marketing materials sent by pharmaceutical companies to general practitioners used a wide range of persuasion strategies, of which liking and authority were the most common.

All other persuasion strategies defined by Cialdini [24], i.e. reciprocity, consistency/ commitment, social proof, scarcity and unity, were also used, often in combinations. In addition to these strategies, one additional category, coined 'emotional pressure', was identified. The presence of eight different persuasion strategies in 68 marketing materials indicates that pharmaceutical companies use a wide range of strategies to influence the attitudes of healthcare professionals towards prescribing their (new) medicines.

The identified persuasion strategies were achieved by use of text and images and often a combination of these. Persuasion strategies in marketing materials were identified on different levels. Although most materials were aimed at creating a positive image of a specific medicine, marketing materials also focused on disease awareness or positively portraying the company itself. The identified persuasion strategies have been associated with different motives of persuaders. Reciprocity, liking and unity have been primarily associated with cultivation of a relationship. Social proof and authority are often used to reduce uncertainty, and consistency and scarcity are regularly involved if call to action is the primary goal [24]. The presence of all these different persuasion strategies in the marketing materials implies that all goals are being pursued. However, with liking and authority as the most prominent Cialdini strategies [24], it can be argued that building a relationship and reducing uncertainty are the most prominent goals of the investigated materials.

In addition to the persuasion strategies described by Cialdini [24], we identified one additional strategy, which was described as emotional pressure. This strategy makes use of the sense of responsibility of healthcare professionals, implying that the prescription of the marketed medicine is the best care they can provide for their patients. The importance of emotion in persuasion has been recognized before [33,34]. In consumer research, a similar tactic of using emotions to elicit feelings of accountability and responsibility has been studied in the promotion of socially responsible products and behaviours [35]. This newly identified strategy in addition to the model of Cialdini most probably reflects the unique situation of medicine marketing, where the choice for a specific product is made by a professional, rather than by a consumer. Since the Cialdini principles are not exclusively developed for medicine marketing, this might explain why this principle based on professional attitude was identified in the collected marketing materials, but not described in Cialdini's framework.

The presence of persuasion strategies in marketing activities of pharmaceutical companies has been described before [26]. However, to the best of our knowledge, this is the first study to investigate the use of the persuasion described by Cialdini in marketing

materials from pharmaceutical companies. In previous research, direct marketing brochures and advertisements have been shown to have little or no educational value [36-38]. In addition, studies have also shown that marketing materials contain inaccurate or even misleading statements [23,36-39]. Although marketing activities have been shown to directly influence prescription behaviour [14-18,20,40,41], healthcare professionals still underestimate their vulnerability to marketing, thinking they themselves are not affected by marketing activities [14,18,24]. In the advertising literature, this is known as the third person effect, the illusion that advertising influences other people but not me [42]. The strategies used however have been proven to influence behaviour, even if the recipient is not aware of this. The crux of these persuasion strategies is that they produce a distinct kind of automatic, mindless compliance [24]. The ultimate effect of the identified persuasion strategies, also in relation to other marketing activities such as visits by medical representatives and sponsored educations, was not investigated in this study and calls for further research. However, because of the proven efficacy of these persuasion strategies [24,25], and the proven impact of other marketing activities by pharmaceutical companies on prescription behaviour [14-18,20,40,43], there is no reason to believe that the marketing materials would not influence healthcare professionals. The lack of educational value and the wide presence of persuasion strategies makes it even more clear that direct marketing mails and advertisements should be viewed as promotional information and emphasizes the urge to create awareness of the mechanisms marketing materials use to influence decision-making.

Our study focused solely on marketing materials sent to general practices. The decision to include advertisements in addition to direct marketing mailings was made post hoc. Since the identified persuasion strategies in direct marketing mailings and advertisements did not really differ, the decision to include both seems justified. Marketing brochures and advertisements from other sources – for example symposia, sales representatives or medical journals not collected by the general practices – were not included. In addition, other marketing activities such as digital marketing and indirect marketing were not assessed in this study. Different marketing activities from pharmaceutical companies are known to reinforce each other and have a synergistic effect on prescription behaviour [14,41]. It is therefore important to realise that the persuasion strategies identified in this study are only a small part of all attempts to influence prescription behaviour. Although marketing materials are only a small part of all marketing activities, it has been present for decades. Already in 1939, the amount and effect of direct marketing mailings towards healthcare professionals were investigated. At that time, the average number of advertising mail per healthcare professional was approximately four pieces per day [18]. In our study, the number of unique marketing materials per general practice in four weeks' time ranged from 0 to

43. It is not known whether the wide range of received materials reflects a real difference in the extent of that pharmaceutical companies target general practices, or a difference between practices in the adherence to collection instructions. A number of practices spontaneously reported incomplete or inadequate collection, indicating that no firm conclusions about the number of marketing materials could be made. The number of collected marketing materials in our study indicate that marketing materials should still be seen as a relevant element of all marketing activities.

A wide range of introduction years of the marketed medicines was identified in this study. The novelty of the marketed medicines was less than anticipated, with 2012 as median introduction year and 1966 as first introduction year. The wide range of introduction years is probably related to the relatively slow uptake of new medicines in Dutch general practices [44,45], explaining why pharmaceutical companies continue marketing activities years after the launch of their product. It also points out the importance of alertness to marketing activities, even if medicines are not considered to be new anymore.

The main strength of this study is the large number of included marketing materials – obtained from brochures and medical journals collected by general practices – and the focus on persuasion strategies in text and image, resulting in a clear overview of how medicines are marketed in direct marketing mails and advertisements by pharmaceutical companies. There are however also some limitations. First, it is not known whether the included marketing materials were representative for all marketing materials, since we included only marketing materials sent to a limited number of practices during one month and it is not known whether all practices followed the exact instructions. In addition, the decision to include advertisements as well was made post hoc, indicating that the included advertisements did not reflect the total number of advertisements in this month. However, although the marketed medicines are likely to be time-dependent, the identification of all different persuasion strategies makes it unlikely that the conclusions about the use of persuasion strategies would significantly alter when including other marketing materials. Second, the allocation of persuasion strategies to marketing materials can be subjective. However, the interrater analysis showed a substantial agreement between the different assessors and the use of two researchers with marketing expertise and pharmaceutical expertise minimised this risk.

This study provides a clear overview of marketing materials sent to general practices in June 2022 and sheds light on the used persuasion strategies. Primary care practitioners should be aware of these mechanisms used by companies, to ensure that they are as little as possible influenced by this kind of marketing. Furthermore, practitioners should

be educated in recognizing and countering these kind of persuasion strategies in order to prevent unwanted influence [46]. Training in resistance strategies [47] may provide a valid starting point.

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SUPPLEMENT

S1 Table: Characteristics of marketed medicines.

Medicine	Medicine group	Number of materials	Year of marketing approval[a]
Allergen extracts[b]	Allergen extracts	1	2003
Allergen extracts[b]	Allergen extracts	1	2006
Apixaban	Direct factor Xa inhibitors	2	2011
Bempedoic acid	Other lipid modifying agents	1	2020
Benralizumab	Other systemic drugs for obstructive airway diseases	1	2018
Bimekizumab	Interleukin inhibitors	1	2021
C1-inhibitor, plasma derived	Drugs used in hereditary angioedema	1	2011
Clobetasol	Corticosteroids, very potent (group IV)	1	2004
Dapagliflozin	SGLT2 inhibitors	2	2012
Denosumab	Other drugs affecting bone structure and mineralization	1	2010
Dexamethasone (ocular)	Corticosteroids, plain	1	2010
Dexamfetamine	Centrally acting sympathomimetics	1	2021
Dulaglutide	GLP-1 receptor agonists	1	2014
Edoxaban	Direct factor Xa inhibitors	1	2015
Empagliflozin	SGLT2 inhibitors	2	2014
Emtricitabine, tenofovir alafenamide and bictegravir	Antivirals for treatment of HIV infections, combinations	1	2018
Filgotinib	Selective immunosuppressants	1	2020
Finerenone	Aldosterone antagonists	3	2022
Formoterol and beclometasone	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	1	2007
Formoterol, glycopyrronium bromide and beclometasone	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	1	2017
Formoterol, glycopyrronium bromide and budesonide	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	1	2020
Hydrocortisone	Glucocorticoids	1	2011
Liraglutide	GLP-1 receptor agonists	3	2015
Lisdexamfetamine	Centrally acting sympathomimetics	1	2019

S1 Table: Characteristics of marketed medicines. (continued)

Medicine	Medicine group	Number of materials	Year of marketing approval[a]
Medroxyprogesterone	Progestogens	2	2011
Methenamine	Other antibacterials	1	1966
Naloxegol	Peripheral opioid receptor antagonists	1	2014
Norelgestromin and ethinylestradiol	Progestogens and estrogens, fixed combinations	1	2002
Norethisterone	Estren derivatives	1	1990
Ofatumumab	Selective immunosuppressants	1	2021
Plastic IUD with progestogen[c]	Intrauterine contraceptives	1	2021
Plastic IUD with progestogen[c]	Intrauterine contraceptives	1	1996
Rivaroxaban	Direct factor Xa inhibitors	9	2008
Semaglutide	GLP-1 receptor agonists	1	2020
Testosterone[d]	3-oxoandrosten (4) derivatives	1	2016
Testosterone[d]	3-oxoandrosten (4) derivatives	1	2005
Testosterone[d]	3-oxoandrosten (4) derivatives	1	2002
Tildrakizumab	Interleukin inhibitors	1	2018
Tiotropium bromide	Anticholinergics	1	2001
Upadacitinib	Selective immunosuppressants	1	2019
Vilanterol, umeclidinium bromide and fluticasone furoate	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	1	2017

GLP-1 = glucagon-like peptide-1, IUD = intrauterine device, SGLT2 = sodium-glucose co-transporter 2.

[a] *The year of registration refers to the year of registration for the marketed indication. If multiple indications were marketed, the first year was mentioned.*

[b] *The marketing materials for allergen extracts were for different patented products and have therefore different years of introduction.*

[c] *The marketing materials for levonorgestrel were for different dosage forms and have therefore different years of introduction.*

[d] *The marketing materials for testosterone were for different dosages and dosage forms and have therefore different years of introduction.*