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Switching, Adverse Effects and Use of Over-the-Counter Analgesics among Users of Oral Anticoagulants: A Pharmacy-based Survey

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Abstract: Oral anticoagulants are widely used but information on important aspects in that respect is not available from medical registers or clinical databases. Therefore, we conducted a survey including patients filling a prescription for oral anticoagulants at two large Danish community pharmacies. We collected information concerning the patients' knowledge of their anticoagulant treatment including prior drug switching. Further, patients were asked about use of over-the-counter analgesics, adverse effects and how the treatment affected their everyday life. Among 335 eligible patients, 301 (90%) agreed to participate. Atrial fibrillation was the most common indication (65%), and most patients filled a prescription for a non-vitamin K antagonist oral anticoagulant (NOAC) (58%). Among the 12% (n = 35) of participants who had switched oral anticoagulant treatment, 69% had switched from a vitamin K antagonist (VKA) to a NOAC. Switching was most frequently caused by inconvenience (34%) and adverse effects (23%). Although half of all patients had recently bought over-the-counter analgesics, purchase of ibuprofen and aspirin was rare (6%). More VKA users than NOAC users felt limited in their everyday life because of anticoagulant treatment (18% *versus* 9%). Among non-incident NOAC users, 21% had experienced adverse effects during their current treatment. Based on first-hand information from a large sample of anticoagulant users, we conclude that the main drug-related issues leading to anticoagulant switching and perceived limitations in everyday life were inconvenience and adverse effects. This varied between drug groups. Further, use of NSAIDs obtained over the counter was rare.

Non-vitamin K antagonist oral anticoagulants (NOACs) such as dabigatran etexilate, rivaroxaban, apixaban and edoxaban are widely used in the treatment and prophylaxis of thrombosis [1,2]. NOACs have been tested in large phase III trials [3]; however, knowledge of real-life utilization and effects of NOACs can only be obtained once the drugs have entered the market [4]. Further, it is important to study the use of vitamin K antagonists (VKAs) in the era of NOACs, as the two drug groups are being compared repeatedly [3,5].

Knowledge of drug use can be obtained from health care registers. The use of these registers holds several advantages including very large patient cohorts, lack of recall bias and often complete follow-up of an entire population [6,7]. However, these data sources only allow the study of events registered for administrative purposes, such as hospitalizations [8] and prescription fillings [9], while clinical data and information on minor events are typically not available. As an example, a recent descriptive study, based on health care registers, explored reasons for switching between oral anticoagulants (OACs) in atrial fibrillation patients [10]. While switching was common, a potential reason (i.e. registered clinical event) could only be identified in one of five patients, indicating that most switches are caused by minor events not captured by administrative registers. Similarly, these data sources may not capture non-serious adverse effects – a clinical issue of particular interest in the context of NOACs due to their recent market entry. Further, knowledge regarding concomitant use of OACs and other medications with antithrombotic properties is important [11]. Especially, use of OACs and non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a high risk of bleeding [12]. However, as NSAIDs can be purchased over the counter (OTC), use of NSAIDs in OAC users cannot be fully accounted for, when administrative registers are used as the only source of information [13]. Finally, information on patients' knowledge of and experience with OAC therapy is an important part of evaluating real-life OAC use and can only be obtained directly from patients [14,15].

Some of the limitations of the data obtained from healthcare registers may be overcome by the large multinational and prospective clinical registers that include both NOAC- and VKA-treated patients [1,16–18]. These registers, however, are most often restricted to patients with atrial fibrillation. Further, as they are based on information provided by the physician rather than by the patient, they are prone to both selection and information bias.

The objective of this study was to explore aspects of OAC therapy not readily available from registers. We did this

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through a face-to-face survey with OAC users filling a prescription for an oral anticoagulant at a community pharmacy.

Materials and Methods

The study was based on a survey. Survey participants comprised patients filling a prescription for an OAC and were consecutively recruited at two Danish community pharmacies.

Setting. This study was conducted at two large urban community pharmacies in two Danish regions: Copenhagen Sønderbro Pharmacy in Copenhagen and Marselisborg Pharmacy in Aarhus. Combined, the two pharmacies serve an average of 1250 patients per day and hand out 714 000 packages per year.

The 314 Danish community pharmacies are privately operated but subjected to state regulation [9]. There is no upper limit for the amount of drug that can be dispensed at once, but patients in stable medical therapy usually receive 3 months of supply per dispensing [19]. About 1% of Danish residents, mostly elderly, receive their drugs as dose-dispensed medications, supplied in 14-day intervals [20].

Study population. The study population comprised patients filling an OAC for their own use within normal opening hours at one of the two pharmacies in the period of 10 March 2016 – 31 May 2016. An OAC was defined as either a VKA (warfarin or phenprocoumon) or a NOAC (dabigatran, rivaroxaban or apixaban). Patients were not included if the OAC was provided as dose-dispensed medicine or delivered to their home.

Survey. If the patients agreed to participate, they were surveyed by the dispensing pharmacist or pharmaconomist at the counter during dispensing of the prescription. Data were entered directly into an online questionnaire (see below). If a patient declined to participate or if the prescription was intended for another person than the one filling it, only the type of OAC as well as the sex and age of the patient (i.e. the person for which the prescription was intended) was registered.

Survey questionnaire. The survey questionnaire was designed specifically for this study by MH and ELG, both experts in OAC therapy, using REDCap (Research Electronic Data Capture) tools hosted at Odense University Hospital. REDCap is a secure, web-based application designed to support data capture for research studies [21]. The questions concerned: type of OAC, indication for OAC treatment, whether the patient had used other OACs within the last 2 years, and if so, why the OAC treatment had been switched and who, that is the patient or a physician, had been the initiator of the switch. Non-incident users, defined as all but those filling the first prescription of their current OAC treatment, were asked whether they considered their OAC treatment as a limitation in their everyday life and whether they had bought analgesics (acetaminophen, ibuprofen and combinations of aspirin and codeine or caffeine) OTC within the past 6 months. These latter two questions were added to the questionnaire 1 week after start of the data collection. Further, patients filling a prescription for a NOAC were asked whether they had experienced adverse effects of their current treatment. An English version of the questionnaire is available in the Supporting Information (Table S1) along with a flowchart describing the steps of the data collection (Figure S1).

Pilot test and validation. All personnel involved in the data collection were introduced to the survey questionnaire. As part of this training, the questionnaire was pilot-tested at both pharmacies during a 1-week period immediately before the study period. The pilot test included a total of 40 patients and led to rephrasing and changes in the order of questions as well as inclusion of two new questions. The pilot test further included an assessment of the validity of the collected data, as we considered reported data on prior switching between OACs to be the survey question most susceptible to recall bias [22]. To this end, we retrieved data on dispensed prescriptions for a sample of 20 patients from the pilot test stating that they had not switched between OACs within 2 years prior to the data collection. Dispensing data were obtained from the 'personal electronic medicine profile' [23], which is based on the Danish National Prescription Registry [24] and contains information on all dispensed prescriptions in the last 2 years. Through manual review of the 20 patients' prescription history, we identified one patient who had switched between OACs within the last 2 years and who did not report this during the interview.

Treatment indication. We reported indications in the following categories: (i) atrial fibrillation, (ii) venous thromboembolism, (iii) other thrombosis (subcategorized into ischaemic heart disease and unspecified), (iv) mechanical heart valves, (v) upcoming/recent knee- or hip replacement, (vi) other (unspecific and misperceived indication) and (vii) unknown to the patient. 'Venous thromboembolism' comprised patients reporting a prior thrombosis in the leg, lung or arm. Patients reporting prior thrombosis in the brain or head were assumed to comprise cases of cardioembolic ischaemic stroke and were therefore included in the 'atrial fibrillation' category. All other prior thromboses were categorized as such ('other thrombosis'). Misperceived indications were reported indications that from a clinical point of view could not be the real indications for OAC treatment (e.g. having a pacemaker or hypertension).

Analysis. Characteristics of OAC users are presented for three groups: (i) patients eligible for the survey who agreed to participate, (ii) patients eligible for the survey who declined and (iii) persons not eligible for the survey (persons filling a prescription not intended for themselves).

Switching between OACs was described according to type of switch: from VKA to NOAC, from NOAC to VKA, from one NOAC to another and from one VKA to another. Each type of switch was described according to proportion of switchers among the total number of users, initiator of the switch and specific reasons for switching.

Among non-incident OAC users, we estimated the prevalence of OTC use of analgesics, feeling limited by OAC treatment, as well as overall and specific adverse effects. The first two analyses were described according to type of OAC (VKA and NOAC), and the latter analyses only included NOAC users and were stratified by NOAC type.

Finally, we estimated the completeness of the data collection at Sønderbro Pharmacy by comparing the number of completed questionnaires with the number of prescription fills involving OACs during the period of 18 March – 31 May 2016.

Other. This study was approved by the Danish Data Protection Agency (record 2015-57-0008). According to Danish law, an approval from an ethics committee was not required for this study. All analyses were performed using either STATA Release 14.1 (StataCorp, College Station, TX, USA) or REDCap [21].

Results

The process of patient inclusion is shown in fig. 1. We assessed 415 patients for eligibility, which led to exclusion of 80 patients (19%) filling an OAC prescription intended for another person than themselves. The remaining 335 were asked to participate, and 301 (90%) of these agreed to participate. Table 1 presents characteristics of survey participants as well as non-participants.

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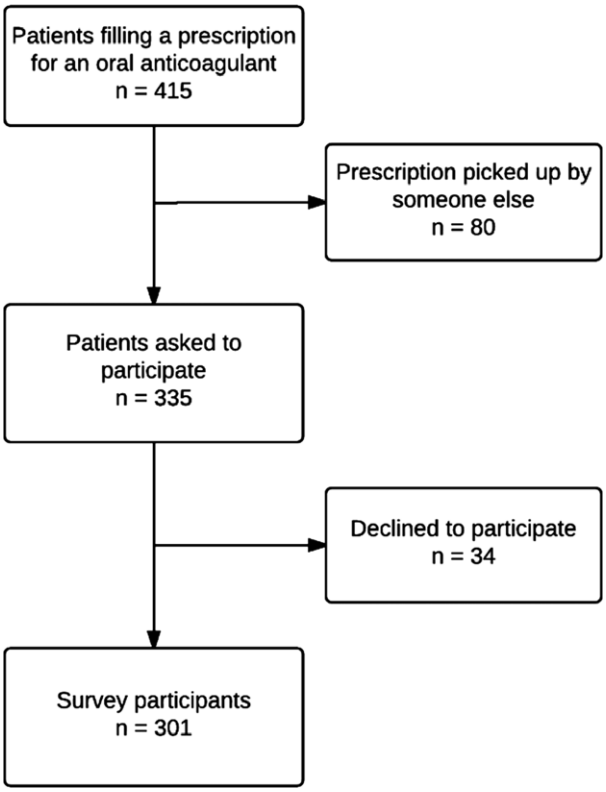

Fig. 1. Selection of survey participants. Flow chart describing the selection of patients for the survey.

The median age of participants was 72 years (interquartile range: 64–80), and the majority were male (61%). Overall, more participants filled a prescription for a NOAC than for a VKA (58% *versus* 42%). Except two prescriptions for phenprocoumon, all VKA prescriptions (n = 127) were for warfarin. Around half of NOAC prescriptions (n = 174) were for apixaban (45%), whereas dabigatran and rivaroxaban constituted 30% and 25% of NOAC prescriptions, respectively. Atrial fibrillation was the most common indication for OAC use (65%) followed by venous thromboembolism (18%). Compared to survey participants, OAC users who had their medication picked up by another person (n = 80) were older (78 years, IQR 68-85) and more often female (52%). In contrast, patients who declined to participate (n = 34) were younger (68 years, IQR 56-73) and more often male (79%) and users of VKA (53%), compared to participants.

Table 2 presents data on prior switching between OACs. A total of 35 (12%) of the survey participants had experienced a switch in oral anticoagulant treatment within the past 2 years. Switching from VKA to a NOAC (n = 24) constituted 69% of all switches and had occurred in 14% of the included NOAC users. Seven patients had switched from one NOAC to another, corresponding to 4% of NOAC users. Three had switched from NOAC to VKA and one patient from one VKA to another (phenprocoumon to warfarin), corresponding to 2% and 0.8% of VKA users, respectively. Most switches had been initiated by a physician (69%) and most often by a physician other than the patient's regular general practitioner (43% of all switches). The patient had been the initiator of the switch in

Table 1.

Characteristics of survey participants and non-participants.

		Non-participants	
	Participants n = 301 (%)	Non-eligible (n = 80) (%)	Declined participation n = 34 (%)
Male sex	183 (61)	37 (46)	27 (79)
Age (IQR)	72 (64–80)	78 (68–85)	68 (56–73)
Oral anticoagulant			
Warfarin	125 (42)	29 (36)	18 (53)
Phenprocoumon	2 (0.7)	0 (0.0)	0 (0.0)
Dabigatran	52 (17)	16 (20)	6 (18)
Rivaroxaban	44 (15)	10 (13)	5 (15)
Apixaban	78 (26)	25 (31)	5 (15)
Indication[1]			
Atrial fibrillation	196 (65)	NA	NA
Venous thromboembolism	54 (18)	NA	NA
Prior thrombosis, other		NA	NA
Ischaemic heart disease	14 (5)	NA	NA
Unspecified thrombosis	17 (6)	NA	NA
Mechanical heart valves	25 (8)	NA	NA
Knee- or hip replacement	0 (0)	NA	NA
Other		NA	NA
Unspecific indication	5 (2)	NA	NA
Misperceived indication[2]	9 (3)	NA	NA
Unknown to the patient	15 (5)	NA	NA
Incident use of the redeemed oral anticoagulant	48 (16)	NA	3 (9)
Prior use of other oral anticoagulant (within 2 years)	35 (12)	NA	NA

IQR, interquartile range; NA, not applicable.

[1]The sum of indications exceeds 301 as 24 patients reported more than one reason for OAC use.

[2]Misperceived indication: reported indications that from a clinical point of view could not be the real indications for OAC treatment.

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Table 2.
Reported switches between oral anticoagulants including initiator of the switch and reasons for switching categorized by type of switch.

	VKA → NOAC (n = 24[1]) n (%)	NOAC→VKA (n = 3[1]) n (%)	NOAC→NOAC (n = 7[1]) n (%)
Initiator of the switch			
Patient	6 (25)	2 (67)	2 (29)
General practitioner	7 (29)	0 (0.0)	1 (14)
Other doctor	10 (42)	1 (33)	4 (57)
Other	1 (4)	0 (0.0)	0 (0.0)
Unknown	1 (4)	0 (0.0)	0 (0.0)
Reasons for switching[1]			
Thromboembolic event	2 (8)	1 (33)	0 (0.0)
Bleeding/anaemia	1 (4)	0 (0.0)	0 (0.0)
Adverse effects	2 (8)	2 (67)	4 (57)
High costs	0 (0.0)	0 (0.0)	1 (14)
Worsening in renal failure	0 (0.0)	0 (0.0)	2 (29)
Unstable INR values	7 (29)	0 (0.0)	0 (0.0)
Physician's preference	2	0 (0.0)	1 (14)
Prior treatment was inconvenient	12 (50)	0 (0.0)	0 (0.0)
Due to interactions with drug, food and alcohol	5 (21)	0 (0.0)	0 (0.0)
Due to the requirement of regular INR measurements	9 (38)	0 (0.0)	0 (0.0)
Other	2 (8)	0 (0.0)	0 (0.0)
Unknown to the patient	1 (4)	0 (0.0)	0 (0.0)

VKA, Vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; GP, general practitioner; INR, international normalized ratio.
One participant (n = 1) had experienced a switch from phenprocoumon to warfarin (0.8% of warfarin users). The initiator was the patient's regular GP, and the reason was unstable INR values.
[1]Proportion of switchers among the total number of included users of the drug that has been switched to: VKA → NOAC, 14%; NOAC→VKA, 4%;NOAC→ NOAC, 2%.
[2]As patients were allowed to provide > 1 reason for switching, the sum of reasons exceeds 100%.

29% of cases. The dominant cause of switching from VKA to NOAC was inconvenience due to interactions with other drugs, food and alcohol and the requirement of regular INR tests (50% of switches from VKA to NOAC). On the other hand, adverse effects were the most common cause of switching away from a NOAC (60% of switches from NOAC to VKA or NOAC to NOAC).

Table 3 presents purchase of OTC analgesics within the past 6 months. Half (48%) of the non-incident OAC users (n = 223) had bought analgesics OTC, and acetaminophen constituted 87% of all analgesics. Drugs containing NSAIDs (i.e. aspirin and ibuprofen) had been bought by 3% and 8% of VKA and NOAC users, respectively. The nine participants who had purchased ibuprofen were all NOAC users.

Table S2 in Supporting Information specifies the adverse effects experienced by the non-incident NOAC users (n = 141). Of these, 29 (21%) had experienced adverse effects during treatment, most often gastrointestinal symptoms (38% of all reported adverse effects). The frequency of adverse effects for dabigatran, rivaroxaban and apixaban was 33%, 13% and 15%, respectively. Most adverse effects (86%) were still present on the day of the survey. None of the patients who had previously switched from one NOAC to another due to adverse effects reported adverse effects to their current NOAC treatment.

Table S3 in Supporting Information shows the reported reasons for feeling limited by OAC therapy. Everyday life limitations caused by anticoagulant treatment were reported by 18% of non-incident VKA users (n = 99) compared to 9% of non-incident NOAC users (n = 128). While VKA users primarily felt limited by the restrictions related to diet and alcohol consumption, most NOAC users felt limited due to adverse effects (bruising and tiredness).

Table 3.
Purchase of over-the-counter analgesics within the last six months among non-incident users of oral anticoagulants.

	Overall (n = 223) n (%)	VKA users (n = 97) n (%)	NOAC users (n = 126) n (%)
Any	106 (48)	44 (45)	62 (49)
Acetaminophen	92 (41)	41 (42)	51 (41)
Ibuprofen	9 (4)	0 (0)	9 (7)
Aspirin/codeine and aspirin/caffeine	5 (2)	3 (3)	2 (2)
None	107 (48)	51 (53)	56 (44)
Unknown	10 (5)	2 (2)	8 (6)

VKA, Vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant.

A total of 213 patients had been assessed for eligibility for the survey at Sønderbro Pharmacy during the period of 18 March – 31 May 2016. In the same period, there had been 414 transactions involving OACs, yielding a completeness of the data collection at Sønderbro Pharmacy of 51%.

Discussion

By collecting information directly from OAC users, we found that most patients knew why they received OAC therapy as well as the reason behind prior drug switching. Inconvenience (dietary restrictions and regular INR measurements) was the

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dominating reason among VKA users for switching away from VKA therapy. Nearly one in five NOAC users reported ongoing adverse effects, and adverse effects were also the most common reason for switching from a NOAC to another OAC. Finally, although recent purchase of OTC analgesics was common, only few patients had bought NSAID analgesics.

Similar to results from the European Heart Rhythm Association survey [14], we found that the majority of patients knew why they received anticoagulant therapy. Further, most patients could report the specific reason(s) for a prior switch between OACs. Similarly, the low proportion of patients who had purchased OTC NSAIDs indicates awareness of the precautions that should be taken when using OACs among patients as well as the pharmacy staff [25,26]. In this context, it is remarkable that only NOAC users reported purchasing ibuprofen. This might reflect more awareness of the risks associated with NSAIDs in VKA users [12] compared to NOAC users [27]. Further, as NOAC use is less complex than VKA use, one may speculate that physicians may find it less important to introduce initiators of NOACs to the safety aspects of anticoagulant use compared to initiators of VKAs. Importantly, the risk associated with use of NSAIDs in NOAC users is expected to be similar to the risk in VKA users, and use of NSAIDs should generally be avoided in OAC users [12,28].

Inconvenience such as dietary restrictions, drug–drug interactions and repeated INR testing was the by far most common reason for switching away from a VKA as well as for feeling limited by VKA therapy. This is accordance with a recent study by Belen *et al.* [29] reporting inconvenience with warfarin therapy as the main cause of NOAC initiation in 60% of 174 patients. How this information was reported (from patients or physician) is, however, not described in the study. In contrast to our findings, Beyer-Westendorf *et al.* [18] found 'unstable INR' as the dominating cause (58%) of switching from VKA to a NOAC among 716 patients included in the Dresden NOAC Registry, whereas inconvenience was not stated as a potential reason for switching. Unstable INR was the reason for switching in 29% of patients in the present study. This discordance is likely caused by differences in data collection. In our study, information was obtained directly from patients, whereas information on reasons for switching was reported by physicians in the Dresden NOAC Registry [18]. Physicians may tend to provide reasons justifying a switch from a medical point of view (e.g. an assumption of more effective stroke prophylaxis). Another explanation may be that the reason is perceived differently by patients and physicians, as unstable INR values lead to frequent INR testing and thereby inconvenience to the patient.

Among NOAC users, the most common drug-related issue seemed to be adverse effects. One in five NOAC users reported ongoing adverse effects and adverse effects were the dominant cause of switching away from a NOAC as well as for feeling limited by NOAC therapy. Adverse effect is a well-known cause of decreased adherence to medications [30]. Importantly, even minor non-adherence to NOACs can decrease effectiveness significantly due to their short half-lives [31]. As revealed by the present and other studies [32,33], switching to another NOAC seems to be a common approach in patients experiencing adverse effects of a NOAC. Of note, although switching between NOACs is generally considered safe [28], no studies have examined the risks associated with this type of switching.

Major drug-related issues of oral anticoagulant therapy were strongly dependent on the class of oral anticoagulant. This highlights the need for individualized oral anticoagulant therapy, especially when choosing stroke-prophylactic agents for patients with atrial fibrillation [34]. When discussing the choice of oral anticoagulant agent with patients, these differences in drug-related issues should be considered.

The principal strength of the study is that by obtaining first-hand information on issues related to use of OACs, we were able to study patients' knowledge, experience and subjective view of OAC treatment in detail. Other strengths included the use of trained pharmacy staff and the high response rate (90%).

The study also has several limitations. The fact that we only included patients who appeared at the pharmacy resulted in exclusion of a group of OAC users who were older and more often female than the interviewed sample. However, the median age of OAC users of 72 years in the present study corresponds well with recent studies including large samples of OAC users [35]. Furthermore, the sex distribution in our sample is similar to that of sex-stratified data on all drug sales of OACs in Denmark in 2015 (made available from Danish online drug statistics [36]). In our study, no patients stated to fill NOAC due to 'upcoming/recent knee- or hip replacement', although register-based studies have found this to be the indication of around 10% of all newly initiated NOAC treatments [37]. This may be explained by these patients only being prescribed a NOAC once and therefore being less likely to be captured in this setting. Furthermore, patients with recent surgery may be less likely to go to the pharmacy themselves. This, along with the estimated inclusion rate of 51% of OAC users, does leave room for some degree of selection bias. However, the incomplete inclusion is most likely caused by the pharmacy staff being busy or forgetful and is therefore less likely to infer selective exclusion or inclusion of a specific group of patients. Therefore, we believe that the OAC users included in this study are representative of Danish OAC users.

The data that we considered most susceptible to recall bias were the information of prior drug switching going up to 2 years back. Yet, the finding that only 1 in 20 patients failed to report a previous switch does not indicate a strong degree of recall bias.

Conclusion

In this survey, patients seemed well informed of their treatment with regard to indication and reasons for treatment changes. The main drug-related issues of oral anticoagulant therapy among VKA users and NOAC users were inconvenience and adverse effects, respectively. Finally, purchase of OTC analgesics containing NSAID was uncommon.

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Conflict of Interest

LM and AWH declare no competing interests. MH has received speaker honorarium from Bristol-Myers Squibb and Pfeizer. ELG has received speaker honoraria from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, MSD and Pfizer and has previously participated in advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim and Bristol-Myers Squibb. AP has participated in projects funded by Boehringer Ingelheim, with funds paid to his institution. LMRH is a former employee at MSD Pharma.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Survey questionnaire.

Table S2. Adverse effects.

Table S3. Limitations in everyday life.

Fig. S1. Flowchart describing the steps of the data collection.

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