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ORIGINAL RESEARCH ARTICLE

The EURO-FORTA (Fit fOR The Aged) List Version 2: Consensus Validation of a Clinical Tool for Improved Pharmacotherapy in Older Adults

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Abstract

Background The aging of our societies leads to a higher prevalence of multimorbidity and therefore polypharmacy, which often results in inappropriate drug treatment. To address this issue, numerous listing approaches, such as the Fit fOR The Aged (FORTA) list have been developed. FORTA's positive impact on the quality of medications and relevant clinical outcomes has been shown. Based on new emerging evidence and experiences with the existing FORTA lists, we aimed to update the FORTA lists in several European countries/regions.

Methods Two-step Delphi consensus procedures were conducted in Poland, UK/Ireland, Italy, Spain, the Nordic countries, The Netherlands and France. The existing European FORTA lists served as survey proposals.

Results Thirty-two experts agreed to take part in this study (return rate: 96.9%). The country/region-specific overall consensus for all items and participants after the first round was > 90%. FORTA lists from six participating countries, plus the FORTA list for the German-speaking countries, were collated into the new EURO-FORTA List, which now contains 267 items aligned to 27 indications. Three items were added to the EURO-FORTA List, and no drugs were deleted. Eight FORTA items were relabeled, and 96.9% of the labels remained unchanged.

Conclusion In this study, seven new country/region specific FORTA lists, as well as a new overarching EURO-FORTA List, were developed. An overall increase in the mean consensus coefficient and increases for all disease-specific mean consensus coefficients show a wider consensus among participants. The new lists have the potential to improve drug therapy in older people internationally.

1 Introduction

Aging populations represent a global phenomenon. In 2022, the worldwide number of people aged 65 years or over reached 771 million, and their share of the global population has been projected to grow by 60% between 2022 and 2050 [1]. This means that in 2050, 16% of the global population will be older adults [1]. Therefore, the prevalence of multimorbidity and related polypharmacy are expected to considerably increase and become an even more significant challenge for healthcare providers and societies [2–6]. Yet, older people are often excluded from clinical trials [7], resulting in evidence gaps regarding the efficacy and safety of many medications in this vulnerable population [2, 8]. To address this growing issue, methods/tools that may aid physicians to ameliorate drug treatment in older patients have been developed [9]. Due to the lack of evidence, these aids have mainly been based on the available evidence as well as experts' opinions [6].

Since 1997, numerous listing approaches have been created [6, 9–16]. The majority of these listing approaches, e.g. the Beers criteria® are drug-oriented listing approaches (DOLA; or DOLA+: with disease specification) [9], which mainly focus on drugs to be generally avoided (address overtreatment) in older people. In contrast, patient-in-focus listing approaches (PILA) such as the FORTA List provide

The members of the "FORTA Expert Panel Members" are listed in Acknowledgements section.

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Key Points

The aging of our societies leads to a higher prevalence of multimorbidity, and therefore polypharmacy, which often results in inappropriate drug treatment in older adults.

Fit fOR The Aged's (FORTA's) positive impact on the quality of medications and relevant clinical outcomes has been shown.

In this work, seven new country/region-specific FORTA lists, as well as a new overarching EURO-FORTA List, were developed.

disease-related negative as well as positive guidance (also address undertreatment) and require intricate knowledge about the patient [9]. Based on the few available clinical trials testing the impact of listing approaches on relevant clinical endpoints (such as falls or hospitalization) PILAs (e.g. the FORTA List) appear to be superior to DOLAs [9].

The FORTA classification was first introduced in 2008 [17]. Subsequently, the FORTA List was validated [16] and later updated in two-round Delphi processes [18, 19]. In a randomized controlled trial (VALFORTA trial) in older hospitalized patients [20], the use of this validated version of the FORTA List led to a significant amelioration of the quality of drug treatment (measured by the FORTA score [20]) in the FORTA intervention group compared with the control group ($p < 0.0001$) [20]. The FORTA score was simply the individual sum of over- and undertreatment errors [20]. In addition, relevant clinical endpoints such as activities of daily living (ADL) or the occurrence of adverse drug reactions were significantly improved through the FORTA intervention [20], representing the first evidence that a listing approach may have a positive clinical impact. Subsequently, secondary analyses of VALFORTA [20] showed that the FORTA intervention also significantly improved the medication quality at the disease-related, individual drug/drug class level [21, 22] and that higher FORTA scores are associated with impaired cognitive and physical function tests [22, 23].

In addition, an association between higher FORTA scores and ADL as well as instrumental ADL (IADL) were demonstrated in the prospective AgeCoDe–AgeQualiDe cohort of community-dwelling older people [24]. This study also indicated that higher FORTA scores are linked to a higher incidence of dementia and even mortality [24].

Since national habits and drug availabilities vary in different countries/regions we had developed several country/region-specific FORTA lists and a European FORTA list in recent years [6, 11, 12]. The aim of this work was to update the previous individual European and EURO-FORTA lists to account for newly emerged evidence and experiences with the previous FORTA lists [6].

2 Methods

All participating countries/regions from a previous EURO-FORTA study [6] were included and all expert panel members who previously participated in the first consensus validation of the EURO-FORTA List [6] were invited to take part in this study. To recruit additional experts, we utilized the same recruitment procedure (based on a self-developed algorithm) used in the previous EURO-FORTA project [18]. In brief, this algorithm enabled us to choose leading specialists in the field of geriatrics, geriatric psychiatry, neurology, clinical pharmacology, and pharmacy with high experience in geriatric pharmacotherapy from the chosen countries/regions, and therefore ensured an unbiased choice of European participants with specific expertise in this field [6]. Furthermore, we used the Web of Science citation indexing service [6, 25] to select additional specialists who met our scientific criteria, thereby allowing us to find experts with a high number of publications in the field of geriatrics and geriatric pharmacotherapy.

We then invited all selected specialists via email to participate in our study. After at least four experts per country/region had agreed to participate, we conducted a two-step Delphi process in each country/region (as previously described [16]). In this process, participants could evaluate the FORTA classifications for medications included in a proposed questionnaire. The proposed questionnaire was mainly based on the previous version of the country/region-specific FORTA lists (existing FORTA lists) with few modifications by the initiator (see below).

One of the four recruited experts from France did not participate in the first round (number of participants was fewer than four), therefore no second round was performed in France.

In all FORTA lists, the calculations of the consensus coefficient and the kappa index were performed as previously described [6, 16]. The EURO-FORTA labels were calculated by converting the country/region-specific FORTA labels into numerical values and the mean numerical value was reconverted to FORTA labels. The substances or indications proposed by the experts were added to the EURO-FORTA List if they were suggested by experts from four or more participating countries. Furthermore, the content validity of the final FORTA lists was assessed by MW and FP.

We used the Wilcoxon–Mann–Whitney test for the analyses of the changes in the mean consensus coefficient. Statistical significance was assumed at $p < 0.05$. Statistical

analyses were conducted in the Department of Medical Statistics, Biomathematics and Information Processing, Medical Faculty Mannheim, University of Heidelberg, using SAS version 9.4 software for Windows (SAS Institute Inc., Cary, NC, USA).

3 Results

Thirty-two geriatricians, geriatric psychiatrists, geriatric neurologists, pharmacists, and clinical pharmacologists representing Spain ($n = 4$), Italy ($n = 5$), England/Ireland/Scotland ($n = 4$), Poland ($n = 7$), the Nordic countries ($n = 4$ from Sweden, Finland and Iceland), The Netherlands ($n = 4$), and France ($n = 4$) agreed to participate in this study (electronic supplementary material [ESM] 1–7). In total, 11 European countries participated in this study, of which 6 countries were aligned to two groups. In addition, 20 experts from Germany/Austria/Switzerland [19] participated in the consensus validation of the FORTA list, which was an update of its previous version from 2018 [18]. This fourth version of the FORTA list for Germany/Austria/Switzerland ($n = 20$) has been published elsewhere [19, 26]. For the purpose of creating a EURO-FORTA List, this FORTA list was also used to calculate the new EURO-FORTA classifications.

The return rate for all countries and both rounds was 96.9% ($n = 31$) for all countries/regions except Germany/Austria/Switzerland. Including Germany/Austria/Switzerland, the return rate was 98.1% ($n = 51$). Following the two-step Delphi consensus processes (one-step Delphi in France), country/region-specific FORTA lists for all eight countries/regions, with the number of items in each list ranging from 238 items in Nordic countries/regions to 300 items in Italy, were created (ESM 1–7 and [19, 26]). The country/region-specific overall consensus for all drugs/drug groups and participants after the first round ranged from 0.916 in France to 0.972 in Spain. Furthermore, the percentage of items for which a unanimous agreement existed regarding the suggested FORTA categories during the first round ranged from 50.9% ($n = 150$) in Germany/Austria/Switzerland to 82.3% ($n = 232$) in Spain (ESM 1–7 and [26]).

In total, seven new items were included (coronavirus disease 2019 [COVID-19] vaccination was included in all countries except Spain, France and the Nordic countries) and 27 items were removed in the regional FORTA lists (ESM 1 7 and [26]). Twenty-five of the removed items belonged to oncological diseases and were removed in the FORTA lists of the Nordic countries or France. Moreover, added items in all final lists included sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors for the treatment of heart failure and herpes zoster vaccination, which were proposed by the initiator before the initiation of the Delphi process and accepted during the two rounds in all countries/regions. Another initiator-based change of the proposed lists/survey questionnaires was the removal of iron for substitution in patients with no proof of iron deficiency.

FORTA lists from all participating countries except France were used to create the EURO-FORTA List Version 2 (total number of experts = 48). The total number of participating experts in France was fewer than four because one recruited panel member withdrew from the study before the first Delphi round. We therefore excluded the FORTA classifications from the France FORTA List from the EURO-FORTA List Version 2.

The EURO-FORTA List Version 2 now contains 267 items aligned to 27 indications (ESM 8–9). The final overall mean consensus for all medications and participants (= 0.956; range 0.931–0.972) was higher than in the previous version of the EURO-FORTA List (= 0.911; range 0.710–0.975) [6]. Compared with the previous version of the EURO-FORTA list [6], three new items, namely COVID-19 vaccination, herpes zoster vaccination, and SGLT2 inhibitors for the treatment of heart failure, were added to the EURO-FORTA List and no items were removed.

The FORTA classifications and additional data for the top two indications with the highest and lowest degree of consensus among all participating experts are shown in Table 1. Interestingly, similar to the previous EURO-FORTA List, the highest (= 0.981) and lowest (= 0.907) consensus coefficients were achieved in acute coronary syndrome and dementia-related depression. The results for oncological diseases (mean consensus coefficient for the indication of solid tumors was 0.997) are not included in Table 1 as many abstentions may have biased the results.

The differences of the disease-specific mean consensus coefficients between the old and new EURO-FORTA Lists were also compared. There was a disease-specific increase of the mean consensus coefficient in all indications, and the largest increases were observed in Behavioral and Psychological Symptoms of Dementia (BPSD): depression; BPSD: paranoia, hallucination; BPSD: sleep disorders; Parkinson's disease; and bipolar disorder. The increases were significant for two of these indications, namely BPSD: paranoia, hallucination; and Parkinson's disease (Table 2a).

Moreover, oncological diseases: solid tumors, oncological supportive therapy, oncological diseases: hematological neoplasias, acute coronary syndrome and epilepsy had the highest disease-specific mean consensus coefficient. In contrast, BPSD: depression, atrial fibrillation, type II diabetes mellitus, BPSD: sleep disorders and osteoporosis had the lowest disease-specific mean consensus coefficient in the EURO-FORTA List Version 2 (Table 2b).

For eight items belonging to six different indications, the consensual FORTA labels were different from the former FORTA labels (Table 3). Therefore, the original

Table 1 FORTA classes for items belonging to the indications with the highest and lowest overall mean consensus coefficient[a]

	EURO-FORTA class (2018)	FORTA class/consensus coefficient							Mean consensus coefficient	EURO-FORTA class 2022 (original FORTA class shown in parentheses if different from the consensus results)
		The Netherlands [$n = 4$]	Italy [$n = 5$]	Nordic countries [$n = 4$]	Spain [$n = 4$]	Poland [$n = 7$]	UK/Ireland [$n = 4$]	Germany/ Austria/ Switzerland [$n = 20$]		
Highest overall mean consensus coefficient (acute coronary syndrome = 0.981)										
Substance/group										
Renin-angiotensin-system blocker: ACE inhibitors	A	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	1.000	A
Acetylsalicylic acid	A	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	1.000	A
Unfractionated heparin and low molecular weight heparin	A	A 0.750	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	0.964	A
Frequency-lowering β-blockers, e.g. metoprolol or bisoprolol	A	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	1.000	A
Atorvastatin	A	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	A 1.000	1.000	A
Nitroglycerin spray, single use, acute as on-demand medication	A	A 1.000	A 1.000	A 1.000	A 1.000	A 0.929	A 1.000	A 0.947	0.982	A
Clopidogrel, prasugrel	B A for stent	B 0.875 A for stent 1.000	B 1.000 A for stent 1.000	B 1.000 A for stent 1.000	B 1.000 A for stent 1.000	B 1.000 A for stent 0.857	A 1.000 A for stent 1.000	A 1.000 A for stent 1.000	0.982 0.976	B A for stent
Thrombolytics, especially rTPA	B	C 1.000	B 0.833	B 1.000	B 1.000	B 1.000	B 1.000	B 1.000	0.976	B

Table 1 (continued)

	EURO-FORTA class (2018)	FORTA class/consensus coefficient							Mean consensus coefficient	EURO-FORTA class 2022 (original FORTA class shown in parentheses if different from the consensus results)
		The Netherlands [$n = 4$]	Italy [$n = 5$]	Nordic countries [$n = 4$]	Spain [$n = 4$]	Poland [$n = 7$]	UK/Ireland [$n = 4$]	Germany/ Austria/ Switzerland [$n = 20$]		
Nitrates, long-term	C	B 1.000	C 1.000	C 1.000	C 1.000	C 0.917	C 1.000	C 0.947	0.981	C
Gp IIb/IIIa antagonists	C	B 0.875	C 1.000	C 1.000	C 1.000	C 0.917	C 0.875	C 1.000	0.952	C
Ivabradine	C	B 0.750	C 1.000	C 1.000	C 1.000	C 1.000	C 1.000	C 1.000	0.964	C
Lowest overall mean consensus coefficient (BPSD: depression = 0.907)										
Substance/group										
SSRIs (citalopram/escitalopram, sertraline, fluoxetine in the usual dosages)	C	C 0.750	C 1.000	C 0.750	C 1.000	B 0.917	C 1.000	C 0.900	0.902	C
Mirtazapine (15–45 mg/day)	C	C 0.750	C 1.000	C 0.750	C 1.000	C 1.000	C 1.000	C 0.925	0.918	C
SNRIs (venlafaxine, duloxetine)	C	D 0.750	C 1.000	C 0.750	C 1.000	C 0.929	C 1.000	D 0.875	0.901	C

FORTA Fit fOR The Aged, *BPSD* Behavioral and Psychological Symptoms of Dementia, *ACE* angiotensin-converting enzyme, *rTPA* recombinant tissue-type plasminogen activator, *GP* glycoprotein, *SSRIs* selective serotonin reuptake inhibitors, *SNRIs* serotonin noradrenaline reuptake inhibitors

[a]Oncological diseases are not depicted as the high number of abstentions may have biased the results

Table 2 (a) Top five indications with the highest increase in the mean consensus coefficient. (b) Top five indications with the highest or lowest mean consensus coefficient

	Mean consensus coefficient (range)		*p* value (Wilcoxon–Mann–Whitney test)
	EURO-FORTA version 2	EURO-FORTA version 1	
BPSD: depression	0.907 (0.901–0.918)	0.710 (0.546–0.823)	–
BPSD: paranoia, hallucination	0.953 (0.922–0.988)	0.840 (0.641–0.928)	< 0.05
BPSD: sleep disorders	0.938 (0.929–0.948)	0.838 (0.658–0.961)	–
Parkinson's disease	0.978 (0.954–1.000)	0.886 (0.706–1.000)	< 0.05
Bipolar disorder	0.970 (0.925–1.000)	0.909 (0.723–0.983)	–

	EURO-FORTA version 2 Mean consensus coefficient (range)
Highest mean consensus coefficient	
Oncological diseases: solid tumors	0.997 (0.975–1.000)
Oncological supportive therapy	0.992 (0.995–1.000)
Oncological diseases: hematological neoplasias	0.983 (0.975–1.000)
Acute coronary syndrome	0.981 (0.952–1.000)
Epilepsy	0.979 (0.924–1.000)
Lowest mean consensus coefficient	
BPSD: depression	0.907 (0.901–0.918)
Atrial fibrillation	0.907 (0.732–1.000)
Type II diabetes mellitus	0.919 (0.843–1.000)
BPSD: sleep disorders	0.938 (0.929–0.948)
Osteoporosis	0.941 (0.889–1.000)

FORTA Fit fOR The Aged, *BPSD* behavioral and psychological symptoms of dementia

EURO-FORTA labels [6] for most of the items ($n = 256$; 96.9%) were confirmed in this study.

4 Discussion

In this work, the European FORTA lists were updated in Delphi consensus procedures. While there is an abundance of listing approaches and criteria for the amelioration of drug therapy in older people, the number of listing approaches that take patient characteristics and demands into account, and have been validated in randomized controlled trials with relevant clinical endpoints, is very limited [9, 22]. Thus far, the FORTA lists appear to be the only drug lists that label drugs both negatively and positively, with labels to be used on the basis of patients' diagnoses, conditions, and personal preferences. Thus their application requires intricate knowledge of the patients' demands. In the VALFORTA trial, we were able to show that the use of FORTA significantly improves quality of drug treatment as well as relevant clinical endpoints such as the occurrence of adverse drug reactions (the number needed to treat was 5) [20] and ADL in older hospitalized patients.

A recent study by Krüger et al. [27] examined the frequency of potentially inappropriate medication (PIM) use and the association between PIM use and cognitive function in community-dwelling older adults; the FORTA List was the best list to predict cognitive decline if compared with other PIM lists [27]. An association between higher FORTA scores and ADL, as well as IADL, in a cohort of community-dwelling older people has also been shown [24]. Furthermore, higher FORTA scores were linked to a higher incidence of dementia and even mortality in the same cohort of community-dwelling older adults [24]. Therefore, the new lists produced in this work in reflection of regional specialties relating to the pharmacopoeias, drug use habits, and drug preferences should become internationally relevant for the amelioration of drug treatment in older adults.

In the EURO-FORTA List, the number of items has just increased from 264 to 267 compared with the previous version of the EURO-FORTA List, thus it should not represent a greater challenge to the prescribers than the former versions.

An overall increase in the mean consensus coefficient of the new EURO-FORTA List compared with the previous version was observed; for all existing indications, the disease-specific mean consensus coefficients also increased,

Table 3 Items with an original FORTA class that was different from the new consensus results

Diagnosis/substance	Suggested FORTA class (EURO-FORTA 2018)	FORTA class							EURO-FORTA Class 2022 (original FORTA class shown in parentheses if different from the consensus results)
		The Netherlands [$n = 4$]	Italy [$n = 5$]	Nordic countries [$n = 4$]	Spain [$n = 4$]	Poland [$n = 7$]	UK/Ireland [$n = 4$])	Germany/Austria/Switzerland [$n = 20$]	
Cardiac insufficiency/diuretics	B	A	A	A	A	A	B	B	(B) A
Osteoporosis/denosumab	A	B	B	B	B	B	A	A	(A) B
Type II diabetes mellitus/metformin	B	A	A	B	A	A	B	B	(B) A
Type II diabetes mellitus/acarbose	B	C	B	B	C	B	C	C	(B) C
Type II diabetes mellitus/gliflozins (SGLT-2 inhibitors)	D	B	B	D	C	B	C	C	(D) C
BPSD: paranoia, hallucination/aripiprazole (2–15 mg/day)	D	C	C	C	D	D	C	D	(D) C
Bipolar disorder/lithium	C	B	C	C	B	C	B	B	(C) B
Parkinson's disease/pramipexole	B	B	C	B	B	C	C	C	(B) C

FORTA Fit fOR The Aged, *SGLT2* sodium-dependent glucose co-transporter 2 inhibitors, *BPSD* behavioral and psychological symptoms of dementia

suggesting a wider consensus among participating experts and a higher clinical validity. The lowest disease-specific mean consensus was still over 90%. As a general observation, the FORTA consensus procedures involving experts for several updates tend to demonstrate greater homogeneity in the assessments over time, possibly reflecting a better understanding of the FORTA principles and criteria.

The wide range of perspectives from several European countries, the generally high European mean consensus coefficients, and the fact that over 96% of the proposed FORTA classes in the EURO-FORTA List were accepted, reveal that the FORTA labels have a high validity across all participating countries/regions; novel evidence did not necessitate to change the majority of labels. In previous studies, this high degree of agreement was also observed in JAPAN (over 96%) [12] and the US (over 95%) [11]. For both countries, the first EURO-FORTA List [6] was mainly used as the proposal. Thus, these results indicate a high degree of homogeneity of drug use within Europe, Japan and the US, although significant differences between these lists from different continents do exist.

The changes of few labels/additions of items reflect the highly needed progress of evidence for older people. The introduction of SGLT2 inhibitors into the treatment of heart failure [28–31] or the availability of novel vaccinations (COVID or herpes zoster) [32–35] as translated into positive FORTA labels clearly reflect that medical progress in drug/vaccine development may also benefit older people. For instance, the evidence for the evaluation of SGLT2 inhibitors for the treatment of heart failure originates from large RCTs including many older adults, in which the overall benefit of using dapagliflozin [31] or empagliflozin [29] in older

patients with heart failure was shown, and the strength of these trials can be considered as Level B [30] (or level B-R [36]). Nevertheless, due to the exclusion of older people (especially the frail elderly and residents of long-term care facilities [37]) from clinical trials, the strength of the evidence for other medications included in the FORTA lists is still widely based on consensus of the participating experts and/or small studies, retrospective studies, or registries. Future RCTs and meta-analyses are still urgently needed to improve the level (quality) of evidence and the related assessments for a large number of substances. All in all, updates of drug assessment projects are indispensable to enable older people to participate in these beneficial processes. We aim to regularly update all FORTA lists at 3-year intervals, which may still be too long to reflect all innovations without delay.

4.1 Limitations

Delphi processes may not cover all available evidence and the expert opinions could be biased by personal experiences. The survey proposal may have a directive impact on the assessments, although here, the former versions of the FORTA lists were used with few modifications. Live consensus panel meetings have not been performed as most of the participants were familiar with the Delphi process from previous consensus procedures. Moreover, systematic reviews for all items may have had an impact on the results but could not be performed for up to 300 assessments due to limited resources. In some countries/regions, the number of participating raters was low and may therefore not be representative for the respective countries and not for all groups of patients. The transferability of the results may also be limited due to variations in national prescribing patterns and drug availability in other European countries not participating in this study. However, based on previous harmonization efforts in the European drug market, we expect such differences to be small.

Moreover, even though an algorithm [6] was used to find the experts, important specialists in the field may have been overlooked. The unwillingness of the invitees to participate may have led to the selection of less qualified experts. Yet, the homogeneity of responses does seem to indicate that the experts independently came to similar conclusions.

5 Conclusion

Based on the experiences with the previous versions and new evidence in the field of geriatric drug treatment, eight country-specific FORTA lists and an overarching EURO-FORTA List were validated. These updated drug lists may help to improve drug treatment and relevant clinical endpoints in older adults.

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Declarations

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Conflict of interest Martin Wehling was employed by AstraZeneca R&D, Mölndal, as Director of Discovery Medicine (translational medicine) from 2003 to 2006, while on sabbatical leave from his professorship at the University of Heidelberg. Since returning to this position in January 2007, he has received lecturing and consulting fees from Bristol Myers, Bayer, Boehringer-Ingelheim, LEO, Mundipharma, Novartis, Pfizer, Polyphor, Helsinn, Allergan, Allecra, Novo-Nordisk, Heel, AstraZeneca, Roche, Santhera, Sanofi-Aventis, Shire, Berlin-Chemie, and Daichii-Sankyo. Christel Weiss and Farhad Pazan have no conflicts of interest to declare.

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Consent for publication Not applicable.

Availability of data and material The data are available from the corresponding author on request.

Author contributions FP and MW participated in the research design, and facilitated recruitment and data collection. FP conducted the survey. FP, MW and CW participated in data analysis. All authors participated in manuscript writing/editing, and reviewed and approved the final version of the manuscript.

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