UNIKLINIK KÖLN | Institut für Medizinische Statistik, Informatik und Epidemiologie

PhytoVIS

Retrospective online survey

Survey on experiences with phytopharmaceuticals via an online based questionnaire

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Research question and objectives	As since 2004 in Germany the use of the majority of phytopharmaceuticals may not be covered by the statutory health insurance, GPs don't have the feasibility to prescribe herbal medicines nor to follow up the patients for treatment results concerning benefit and risk. Thus, the aim of this study was to collect and investigate the subjective experience of patients while using phytopharmaceuticals.
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1. Abstract

Title
Survey on experiences with phytopharmaceuticals via an online based questionnaire
Keywords
Observational study, phytopharmaceuticals, OTC medicine, user experience, efficacy, tolerability
Rationale and background
In 2004, upon introduction of the Health Care Reform Act (Gesundheitsmodernisierungs-

gesetz) in Germany, most phytopharmaceuticals were excluded from reimbursement by the statutory health insurance funds in Germany. In consequence, these products were mostly sold as self-medication drugs, thus nearly evading the monitoring through physicians. To further gain information on the usage of herbal medicines in the general public, PhytoVIS was established to investigate the personal experience of the population with the use of phytopharmaceuticals (positive effects like clinical efficacy as well as negative effects like unintended side-effects).

Study design

Singular interviewer-assisted retrospective online-survey

Setting

Four study centres in Germany with 20 000 patients; duration of the retrospective observational study from April 2014 to December 2016

Subjects and study size, including dropouts

A total of 20 870 patients participated in the survey. Since some patients reported intake of more than one phytomedicinal product, a total of 24 310 data sets was generated. Of those, 252 were empty, constituting dropouts. The remaining 24 058 data sets were included in the analyses.

Variables and data sources

Efficacy was analysed by:

- CGI-E (Clinical Global Impression Scale – Efficacy; primary outcome)
- Time to onset of action

Patients' data were collected by questioning the patients with direct or subsequent data entry in the database.

Results

For the PhytoVIS study, 20 870 patients were questioned, leading to 24 058 valid datasets. More than 2/3 of the participants were female (67.3%). Of those, 1.5% were pregnant and 1.0% were lactating. Regarding age distribution, the highest proportion (29.2%) of participants was between 31 and 50 years old, followed by 25.5% aged between 18 and 30 years. Of note, data from infants (0-23 months, 1.3%) and toddlers (2-5 years, 2.2%) were also collected by questioning their parents. Older people (>75 years) accounted for 5.7% of the participants.

Regarding the primary outcome (CGI-E), more than 40% (41.9%) of the datasets showed an excellent therapeutic effect without any side effects. No therapeutic effect was documented in 4.3% of all valid datasets. Of those, 9.3% (corresponds to 0.6% of all datasets) also documented side effects.

Secondary outcomes were recommendation of the product and place of purchase. The products were mainly recommended by pharmacists (35.0%), physicians (26.6%) and family members (22.4%). The products were predominantly purchased in pharmacies (83.9%). Other places of purchase played only a minor role. Of the 1 433 used products, the highest proportion (6.0%) attributed to a product used for gastrointestinal complaints, followed by 4.0%, 3.9% and 3.1% for single products used for upper airway infections, incl. common cold and cough.

The indication, for which the herbal medicinal products were used, were coded using MedDRA LLT or PT. Common colds attributed to more than 1/3 of all indications (common cold: 22.1%, cough: 7.7%, frontal sinusitis: 5.8%, sore throat: 3.5%). In 77.6% of all datasets, phytopharmaceuticals were used because of acute symptoms. This was paralleled by a duration of complaints (before start of treatment) ranging from one day to one week for 38.0% of all datasets. After using the phytopharmaceuticals, onset of action was mainly after more than one day (30.9% of all datasets). In 17.7% of the dataset, the onset of action was not evaluable.

Concomitant diseases and medications were reported in 38.8% and 46.1% of all datasets.

Hypertension was the most stated concomitant disease (17.6%), whereas L-Thyroxin was the most stated concomitant medication (2.3%).
Subgroup analyses for the primary and secondary endpoints showed no statistically significant or clinically relevant differences, but only tendencies.
In this study, adverse reactions were only documented, if the patients had to consult a physician because of the adverse reaction. This was the case for 172 of the 20 780 patients (0.7%). As expected, the CGI-E was lower for datasets with a documented adverse reaction (1.18 ± 0.90) than in datasets without adverse reactions (3.11 ± 0.93).

Discussion

Analysis of the CGI-E revealed that most of the patients experienced a moderate or excellent efficacy without any side effects. As expected, the severity of side effects increased with decreasing efficacy.
When correlating the CGI-E with the reason for treatment, phytopharmaceuticals used for chronic ailments had the lowest CGI-E. Interestingly, phytopharmaceuticals used for prevention represented the most datasets with unchanged or worse conditions. While acute symptoms had the highest ratio of a marked efficacy, chronic ailments had the highest proportion of moderate and minimal efficacy. This could be due to nature of acute symptoms, which are relatively easy to cure, whereas chronic ailments are often difficult to treat. As expected, phytopharmaceuticals used for preventive interventions had the best outcome regarding side effects, whereas chronic ailments had the poorest outcome.
Side effects according to CGI-E also increased with increasing severity. This was related to the onset of action, where the CGI-E decreased with increasing time to onset of action. While efficacy decreased, side effects increased with increasing time to onset of action.
The CGI-E decreased with increasing number of concomitant diseases: Symptoms from concomitant diseases can outweigh the good efficacy of a phytopharmaceutical product and the patients experience the product as less effective.
Phytopharmaceuticals were mainly recommended by pharmacists and physicians, showing that many patients sought professional advice before usage. This correlates to the priority place of purchase: the large majority of phytopharmaceuticals was purchased in pharmacies. However, since the observational plan specified pharmacies as the primary location for conducting the interviews, this could be influenced by a location bias. Interestingly, when correlating dosage forms with the place of purchase, teas were mainly bought in the supermarket and organic grocery stores, but not in pharmacies or via online retailers.
Correlating the CGI-E with the way of recommendation revealed that there were no statistical or clinical differences in the CGI-E with regard to the way of recommendation. This was also the case for the CGI-E correlated to the place of purchase.
Generally speaking, the correlation between the way of recommendation and severity showed that the severity was highest for patients who consulted physicians or pharmacists. This could be because the level of suffering is high and therefore patients tend to seek professional advice for their illness.
The proportion of adverse reactions, for which patients had to consult a physician, was very low with 172 reported adverse reactions. The majority of adverse reactions occurred during daily use. By daily usage, it is more likely that adverse reactions occur, in contrast to usage when needed. As expected, the mean CGI-E of datasets reporting an adverse reaction was considerably but not significantly lower than for datasets without. Interestingly, more than half of the datasets stated a marked or moderate efficacy despite the adverse reactions.
As presumed, the proportion of adverse reactions increased with increasing age. Interestingly, no differences were detected regarding datasets with or without documented concomitant medications.

2. List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AMG	Arzneimittelgesetz (German Medicinal Products Act)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
DBL	Database lock
CGI-E	Clinical Global Impression Scale - Efficacy
CRO	Contract research organisation
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)
HLT	MedDRA High Level Term
IMSIE	Institut für Medizinische Statistik, Informatik und Epidemiologie (Institute of Medical Statistics, Informatics and Epidemiology)
IMSIE-MI	Institute of Medical Statistics, Informatics and Epidemiology – Medical Informatics
LLT	MedDRA Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities (Medizinisches Wörterbuch für Aktivitäten im Rahmen der Arzneimittelzulassung)
MPG	Medizinproduktegesetzt (Medical Device Act)
PT	MedDRA Preferred Term
SD	Standard deviation
TÜV	Technischer Überwachungsverein (Technical Inspection Agency)

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5. Milestones

Milestones	**Date**
Submission of documents to the ethics committee for counselling on professional regulations	24 March 2014
Date when funding contract was signed	10 April 2014
Start of the productive phase	08 July 2014
ENCePP Registry/Seal	21 July 2014
ENCePP Seal	27 August 2014
End of the productive phase	27 November 2017
Start of data cleansing	02 January 2017
End of data cleansing	21 June 2017
Start of statistical analysis	21 June 2017
End of statistical analysis	30 August 2017

6. Rationale and background

With the amendment of the medicines law (Health Care Reform Act, Gesundheits-modernisierungsgesetz) in Germany in 2004 [1], phytopharmaceuticals (together with all other non-prescription-bound medicines) were partly excluded from reimbursement by the German Statutory Health Insurance Funds. Beforehand, phytopharmaceuticals were to a large extent prescribed by the physician, guaranteeing supervision of the treatment. But following the Health Care Reform Act, these kinds of products were predominantly sold as self-medication drugs thus almost evading the monitoring through the physician. As a result, the documentation and evaluation of the effects of phytopharmaceuticals (positive effects like clinical efficacy as well as negative effects like unintended side-effects) as previously done by the doctor was losing relevance. In contrast, the role of the pharmacist as an advisor for the patient was getting more important.

To further gain information on the usage of these medicines in the general public, observational studies can be conducted. In contrast to randomized controlled trials (RCT) where the safety and efficacy of an intervention are analysed in a tightly controlled patient collective, the features of observational studies are that the interventions are tested in real-world patients [2-7]. Particularly also patients with concomitant medications and diseases, which would be excluded from RCTs [8, 9], are analysed in observational studies – including the assets and drawbacks from such a real-life setting.

This major change in the modalities of use of phytopharmaceuticals in real life was not yet systematically evaluated scientifically, e.g. in observational studies. The available information in Germany is mainly limited to sales figures on the one hand and data from the obligatory pharmacovigilance reporting system on the other. At this point, the PhytoVIS project steps in: It is a study using a database specifically set up for the collection of data regarding the use of phytopharmaceuticals which is called the PhytoVIS database.

6.1 The PhytoVIS database

The purpose of the PhytoVIS project was the investigation of the patient's experience with the use of phytopharmaceuticals. The intention was not to confirm the efficacy of these compounds – this is up to approval studies. Rather the patients' subjective experience of effects and ADRs (adverse drug reactions) perceived while using phytopharmaceuticals was documented and analysed.

PhytoVIS was initiated in 2011 with the intention of gaining further knowledge in the area of healthcare research of phytopharmaceuticals. Its aim was to develop an online instrument with which physicians and pharmacists could document, in retrospect, the experience gained by their patients/customers with herbal medicinal products. In the evaluation phase, which was conducted in Germany and Switzerland, 200 data sets were collected. During this phase, it

became clear that physicians and pharmacists were incapable of collecting the data due to their day-to-day-business. Therefore, for the upcoming pilot phase, advanced students of human medicine or pharmacy were chosen to conduct the interviews. This was implemented in the subsequent pilot phase, where 1 000 datasets were collected. In this phase, PhytoVIS was established and validated, in particular, the method of data collection through students and the handling of the eCRF.

7. Research question and objectives

The aim of this study was to enable a view on the experiences of patients in Germany using phytopharmaceuticals in a self-medication setting and to give a broad basis for generating hypotheses for future healthcare research, including questions about the safe use of phytopharmaceuticals.

The focus was not placed on particular groups, but instead on all (natural) persons who have used a phytopharmaceutical product during eight weeks prior to the survey. The purpose was to gain information why patients use phytopharmaceuticals (indication, severity and duration of disease), modes of use (dosage form, frequency), efficacy (onset of action, CGI-E) and safety (CGI-E, adverse reactions for which a physician was consulted).

8. Amendments and updates

Not applicable.

9. Research methods

9.1 Study design

The study was designed as a singular retrospective online survey to gain data on the modes of use of phytopharmaceuticals in the broad public. The survey was conducted in pharmacies and medical practices. The interviews were performed by students of pharmacy or medicine in the course of a four-week internship.

9.2 Setting

The study was conducted from April 2014 to December 2016 with four centres in Germany (Cologne, Kiel, Mainz and Frankfurt). It was planned to acquire data of a minimum of 20 000 patients who had used phytopharmaceuticals within eight weeks before the survey. The interviews were conducted in medical practices or pharmacies using an online questionnaire. Advanced students of human medicine or pharmacy conducted the interviews in the course of a four-week internship in which the students had to perform at least 100 interviews. The students were trained on doing the interviews in a standardised way beforehand. Either by qualified staff of the IMSIE-MI (Department of Medical Informatics of the Institute of Medical Statistics, Informatics and Epidemiology, Cologne) or by a training video (Mainz, Frankfurt, Kiel): the students got general information on the PhytoVIS project, the conduct of the four-week internship as well as an introduction in the use of the questionnaire and the online-tool.

9.3 Subjects

The study population was not restricted in any way: any natural person had to be interviewed. The only inclusion criterion was that patients had to have taken an herbal medicinal product during the last eight weeks before the survey: This was queried with the introductory question “Haben Sie in den letzten acht Wochen ein pflanzliches Arzneimittel eingenommen?” (Did you take an herbal medicinal product in the last eight weeks?). Notably, persons who had used herbal substances of homeopathic or food-supplement status were not eligible.

9.4 Variables

9.4.1 Efficacy variables

Efficacy was documented using the Clinical Global Impression Scale – Efficacy (CGI-E) as well as the onset of action.

The time to onset of action was clustered in: “after a few minutes”; “after a few hours”, “more than one day” (>1 day); “more than 1 week” (>1 week) and “not assessable”. The patients had to choose one of these options.

Efficacy was also determined using the CGI-E [10, 11]. The CGI-E depicts a 16-field matrix, asking for the relation of side effects to therapeutic effects. Each field correlates with a score

between a minimum of 0.25 and a maximum of 4.00. CGI-E scores higher than 1.00 indicate that the therapeutic effect outweighs side effects. At a score of 1.00, the effects counterbalance each other, whereas with a score <1.00, the side effects outweigh the therapeutic effects.

Table 1: Clinical Global Impression Scale - Efficacy (CGI-E). Each field depicts a combination of therapeutic and side effects, resulting in a CGI-E score.

Therapeutic effects	Absence of side effects	No significant impairment through side effects	Significant Impairment through side effects	Side effects outweigh the therapeutic effect
Excellent – well-marked	Score 4.00	Score 2.00	Score 1.33	Score 1.00
Moderate – marked improvement	Score 3.00	Score 1.50	Score 1.00	Score 0.75
Minimal – slight improvement	Score 2.00	Score 1.0	Score 0.67	Score 0.50
Unchanged – worse	Score 1.00	Score 0.50	Score 0.33	Score 0.25

9.4.2 Safety variables

In addition to the CGI-E index, safety was documented by asking for adverse reactions for which the patients had to consult a physician. In detail, the patients were asked to describe the symptoms, onset, duration and the assessment of the consulted physician.

9.5 Data sources and management

Patients' data were collected by questioning the patients with direct or subsequent data entry in the database.

9.6 Bias

The site Cologne contributed to almost half of the study data, but this did not result in location bias. This effect was balanced by the participation of other sites throughout Germany (universities of Frankfurt, Kiel and Mainz). Since students of medicine and pharmacy acted as interviewers, the different focus in their education was expected to lead to bias. In a preceding pilot stage, which was conducted from July 2012 to October 2013 and gained nearly 2 000 data sets, this interference was not seen.

Bias could also be generated through the selection of patients. To avoid this, the manual handed out to the students defined the procedure for surveying the patients: The students were instructed not to be selective and to approach the next available patient for the interview.

Bias can also arise from pooling the data across indications and products due to the purpose of use and indication (prophylactic or therapeutic use, spontaneous course of the disease etc.). This was also addressed in the analysis.

9.7 Study size

It was planned to interview 20 000 patients.

9.8 Data transformation

Data entry in the eCRF was done by the interviewer. A secure server system, which was hosted by IMSIE-MI was used. The questionnaire was implemented on the web-based data capture tool secuTrial® (version 4.1.0.8, interActive Systems, Berlin, Germany).

After database lock (DBL) incomplete data sets were removed from the database (Dropouts). Medical indications were coded by MedDRA High Level Term (HLT) and Lowest Level Term (LLT) or Preferred Term (PT), respectively. Data handling procedures were documented in a data handling report.

9.9 Statistical methods

9.9.1 Main summary measures

Demographic and other baseline characteristics (sex, age, concomitant disease, dispensing site and recommendation) as well as all efficacy and safety variables were analysed using descriptive statistics. Categorical data are expressed as absolute or percentage of frequency.

9.9.2 Main statistical methods

The study was planned as a singular retrospective survey. Statistical analysis was done descriptively, with frequency and percentages. Data is expressed as absolute frequencies, percentages or mean + SD, if applicable.

9.9.3 Missing values

Missing values were not carried forward but regarded as missing values.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality Control

The Department of Medical Informatics of the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE-MI) was certified by the TÜV Rheinland (ISO9001:2008) for planning,

implementation, informatics, statistical analysis and publication of clinical studies within the scope of the AMG (Arzneimittelgesetz, German Pharmaceutical Act) and MPG (Medizinproduktegesetz, Medical Devices Act), as well as outside the scope of the MPG and non-interventional studies.

The observational plan of this study was prepared according to the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) guidelines [12] and the corresponding checklist for study protocols [13]. The study was registered in the EU PAS register and received the ENCePP seal for adequate study quality. The project got also a positive vote from the Independent Ethics Committee of the University Hospital of Cologne (see approvals section).

Interviewers received training beforehand (see above) and a test system was provided for training. The students received the documents “Declaration of Consent”, “Participation Information” and “User Manual”. The students were provided with a username and password only after signing the “Declaration of Consent”, and the “Participation Information”. This information was only used for the purpose of communication and technical administration of the questionnaire environment and for data entry into the system. Unauthorized data entry was prevented by using individual authentication codes.

The questionnaire was based on the web-based data capture tool secuTrial® (version 4.1.0.8, interActive Systems, Berlin, Germany). Mainly drop-down menus were available. Only a few free text fields were provided to ensure consistent data entry. Several fields required data entry to avoid missing values. The standardized training of the interviewers further increased the quality of the survey by generating consistent data beginning with the first entry.

The interviews were conducted in pharmacies or medical facilities. Thus uncertainties (by the patient or the student) could be clarified directly by checking with the health-care professional on site. Because the survey was anonymous, the obtained patient data cannot be traced back to the interviewee. Personal data was clustered, further enhancing the anonymity of the patients. After completion of the survey, data was stored according to local legal requirements. At the end of the study, the validity of the data was checked by two data reviewers for medical and logical plausibility.

10. Results

10.1 Participants

Age or gender was not restricted in this study. Of the 20 870 participants, 32.7% were male and 67.3% were female. Of those, 1.5% (205) were pregnant and 1.0% (139) were lactating. Age was clustered to ensure anonymity of the patients (Table 2).

Table 2: Demography of the participants.

Age (Cluster)	Frequency	Percentage [%]
0-27 days	26	0.1
28 days - 23 months	252	1.2
2-5 years	468	2.2
6-11 years	527	2.5
12-17 years	739	3.5
18-30 years	5 322	25.5
31-50 years	6 085	29.2
51-65 years	4 386	21.0
66-75 years	1 865	8.9
>75 years	1 200	5.7
Total	20 870	100.0

Most datasets were collected in the range of 31-50 years, followed by 18-30 and 51-65 years. Of note, infants, toddlers (or rather their parents) and adolescents were also interviewed and provided data on the use of phytomedicinal products (Table 2).

10.2 Descriptive data at baseline

Not applicable. Since this was a singular retrospective survey, there is no baseline data available.

10.3 Outcome data

10.3.1 Primary outcome – CGI-E

The primary outcome was determined by the therapeutic effect in relation to the experienced side effects, as displayed by the CGI-E (Table 3).

Table 3: Clinical Global Impression Scale - Efficacy (CGI-E) for all valid datasets. Data is expressed as frequency and percentage.

Therapeutic effects	Absence of side effects	No significant impairment through side effects	Significant Impairment through side effects	Side effects outweigh the therapeutic effect
Excellent – well-marked	10 087 (41.9%)	588 (2.4%)	95 (0.4%)	14 (0.1%)
Moderate – marked improvement	8 435 (35.1%)	851 (3.5%)	142 (0.6%)	18 (0.1%)
Minimal – slight improvement	2 521 (10.5%)	210 (0.9%)	42 (0.2%)	17 (0.1%)
Unchanged – worse	902 (3.7%)	48 (0.2%)	38 (0.2%)	50 (0.2%)

Analysis of the CGI-E showed that in 44.8% of all datasets the therapeutic effect was indicated as excellent/well marked. Only a small fraction (0.5%) documented excellent efficacy paired with significant side effects. In almost 40% of the datasets, the therapeutic effect was rated as moderate. Side effects were reported in 0.7% of the datasets with moderate/marked improvement. In 11.7% of the datasets, the therapeutic effect was marked as minimal/slight improvement. A slight improvement but also side effects were documented for 0.3% of all datasets. No therapeutic effect after the usage of phytopharmaceuticals was documented in 4.3% of all datasets. In 0.6% of the datasets, side effects went in line with an unchanged or worsened condition.

Of the datasets with excellent/marked efficacy, 1.1% was impaired by significant or even stronger side effects. Of the datasets that documented moderate/marked improvement, 1.8% was also affected by side effects. Minimal/slight improvement along with side effects was documented in 2.5% of the datasets with minimal/slight improvement. The proportion of significant side effects further increased to 9.3% for the datasets with unchanged or worsened symptoms.

10.3.2 Secondary outcome

As secondary outcomes, recommendation of the herbal medicinal product and place of purchase were documented. For both questions, it was possible to give multiple answers.

Recommendations were mainly made by pharmacists (35.0%), physicians (26.6%), family (22.4%) and friends (13.5%). Other healthcare professionals, advertisements, internet,

journals, books or recommendation by others played only a minor role with 5% or less (Figure 1).

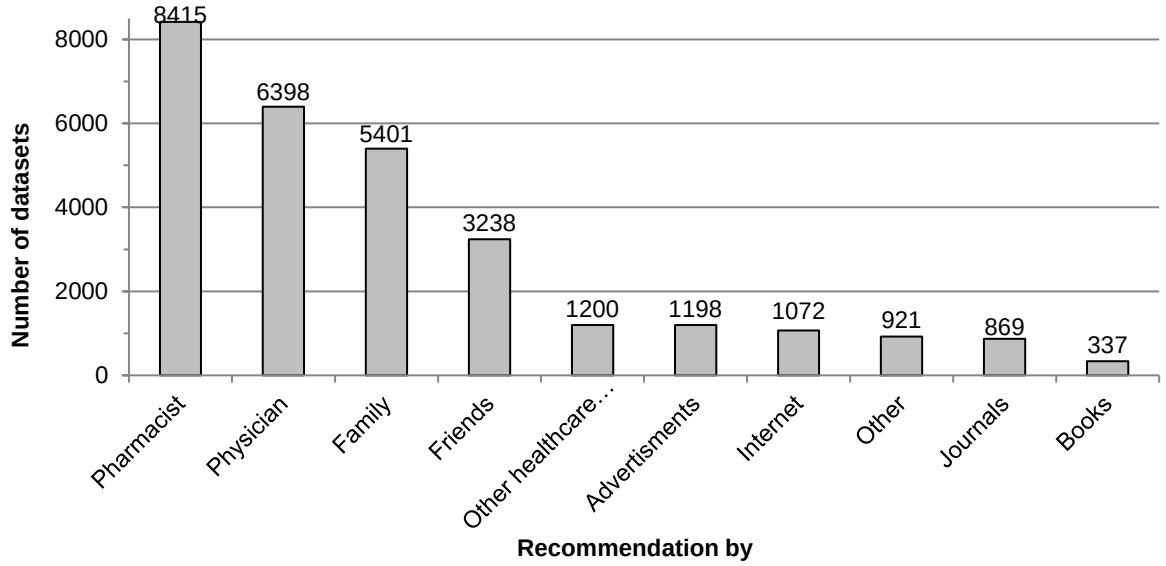

Figure 1: Recommendation of the herbal medicinal product. Data is expressed as absolute frequency of all valid datasets, whereby it was possible to give multiple answers (absolute frequency: 29049).

Besides the place of recommendation, the patients were also asked where they had bought/acquired the phytopharmaceutical product (Figure 2).

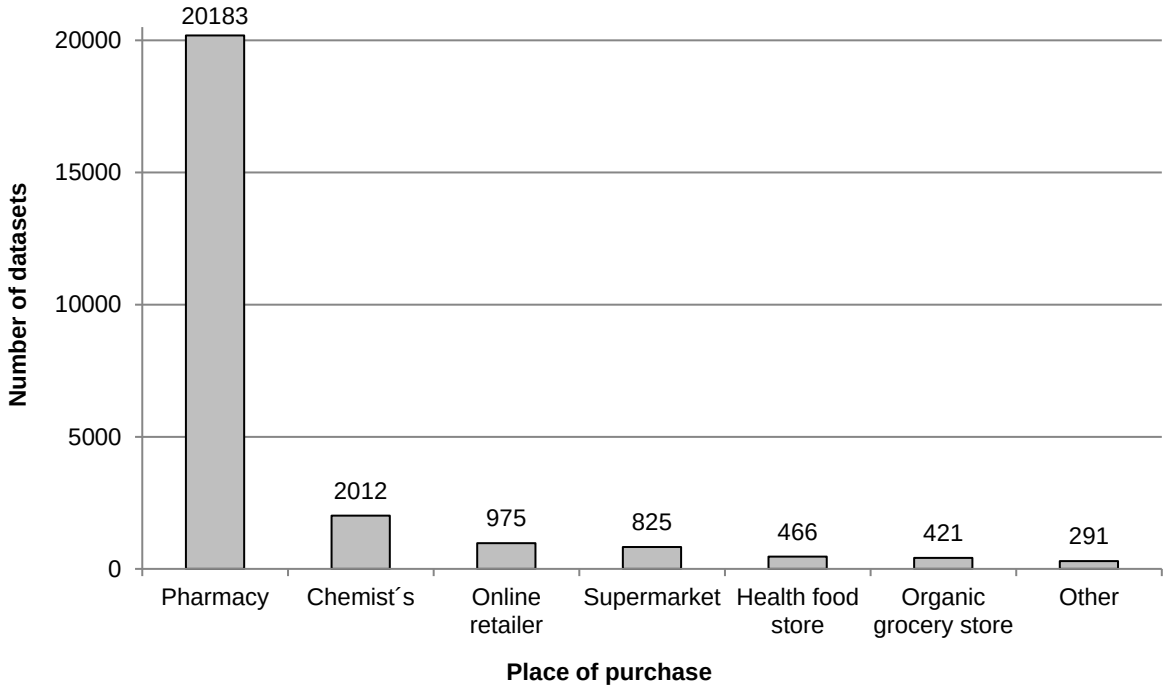

Figure 2: Place of purchase of the phytopharmaceutical. Data is expressed as absolute frequency of all valid datasets, whereby it was possible to give multiple answers (absolute frequency: 25 173).

Most of the phytopharmaceuticals were bought at pharmacies (83.9%). Chemist's shops contributed to 8.4%. Phytopharmaceuticals were also purchased from online retailers (4.1%)

or bought at the supermarket (3.4%). Health food stores and organic grocery stores contributed to the place of purchase with 1.9% and 1.7%, respectively. Other sources were documented in 1.2% of the datasets (Figure 2).

10.4 Main results

10.4.1 Conduct of the interviews

The interviews were mainly conducted in pharmacies (79.2%, 18494 valid datasets) but also in medical practices (19.8%, 4617 valid datasets). The other 226 valid datasets (1.0%) were collected elsewhere (e.g. hospital, university). For 721 datasets (3.0%), the interview location was not documented.

Of the interviewed participants, some reported the intake of more than one phytopharmaceutical product. Of those, 1233 patients generated two datasets and 181 patients generated three datasets. Thirty patients generated four datasets and five patients generated five datasets. Three patients generated six datasets and one patient produced seven datasets. In summary, 20 870 patients generated 24 058 datasets.

10.4.2 Diseases and related information

10.4.2.1 Indication

All participants were asked to give the medical indication leading to the application of the phytopharmaceutical product. Each medical indication was coded by MedDRA Lowest Level Term (LLT) or Preferred Term (PT). Table 4 summarizes LLT/PT indications reported more than 100 times, as well as the given frequency and valid percentage respectively.

Table 4: Indications (MedDRA LLT/PT) with more than 100 datasets.

Indication	Frequency	Percentage [%]
Common cold	5310	22.1
Cough	1859	7.7
Frontal sinusitis	1404	5.8
Sore throat	832	3.5
Sleep disorder	764	3.2
Cystitis	694	2.9
Bronchitis	608	2.5
Stomach complaints	562	2.3
Restlessness	513	2.1
Abdominal complaints	503	2.1
Sniffles	398	1.7
Prevention	374	1.6
Obstipation	338	1.4
Acute pain in the stomach	310	1.3
Difficulty in falling asleep	304	1.3

Dyspepsia	290	1.2
Menopause	276	1.1
Stomach ache	228	0.9
Arthralgia	214	0.9
Dysmenorrhea	214	0.9
Nausea	207	0.9
Cough with sputum	201	0.8
Diarrhoea	194	0.8
Headache	183	0.8
Forgetfulness	183	0.8
Urinary tract infection	172	0.7
Influenza	171	0.7
Infection of the respiratory tracts	169	0.7
Nervousness	143	0.6
Backache	142	0.6
Stress	141	0.6
Ache	132	0.5
Depression	127	0.5
Chesty cough	126	0.5
Feeling of fullness	125	0.5
Difficulties in concentration and attention	120	0.5
Bladder complaints	113	0.5
Wound	104	0.4
Bloated belly	101	0.4
Flatulence	100	0.4

10.4.2.2 Symptoms

With regard to the indication, symptoms were also documented. Here, the patients could give multiple answers. This was the case for 4 073 datasets (16.9%). For the remaining datasets (19 985, 83.1%), only one symptom was documented. Here, “cold/flu/fever” contributed to 47.2% of the documented symptoms in all datasets, followed by “stomach pain/digestive disorders (10.5%) and stomach/biliary problems (8.6%, Figure 3).

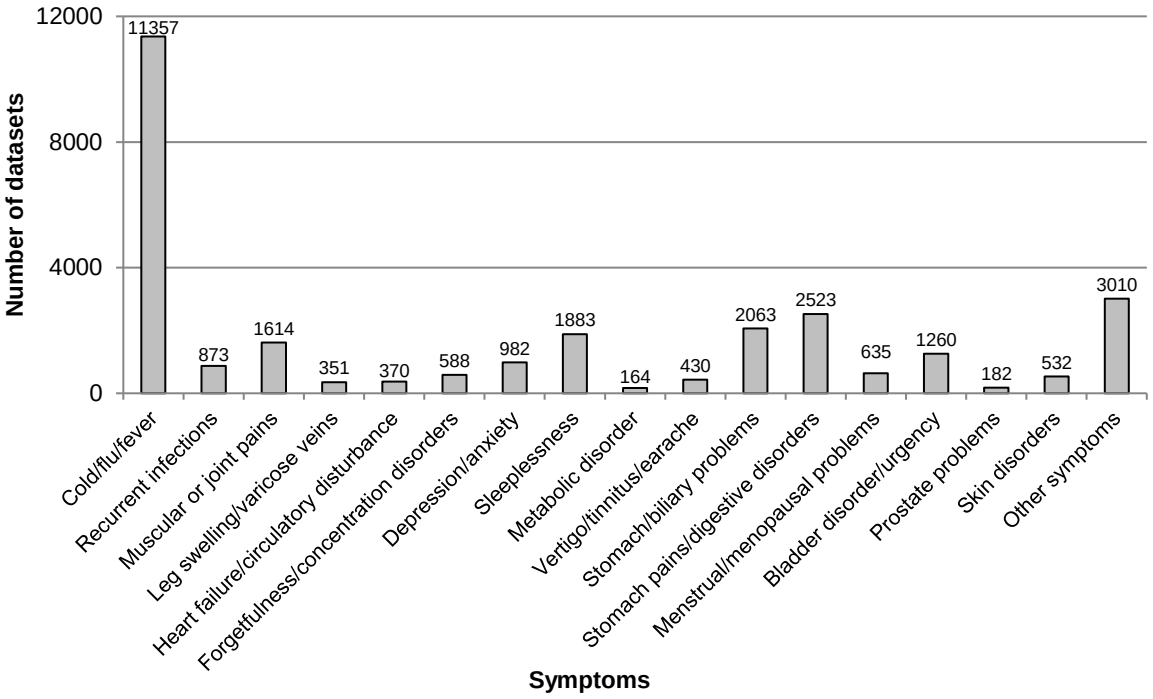

Figure 3: Frequency of reported symptoms.

In 18 234 of the valid datasets (77.6%), herbal medicines were used to treat acute symptoms. Chronic diseases were given as reason for treatment in 3644 of the datasets (15.5%). In 1628 datasets (6.9%), phytopharmaceuticals were used for preventive interventions.

10.4.2.3 Severity

Severity of symptoms was documented by an intensity scale ranging from 0 to 5 [14], with 0 representing no complaints and 5 representing the most imaginable complaints.

The mean overall severity score was 2.77 (+1.14). No complaints (0) were documented in 3.0% of all valid datasets. In 9.3% of the datasets, the severity was rated as “1”. A severity of “2” was documented in 27.1% of all datasets. In 35.6% of the datasets, the severity was rated as “3”. A rating of “4” was documented in 18.4% of the datasets and of “5” in 6.5% of all datasets (Figure 4).

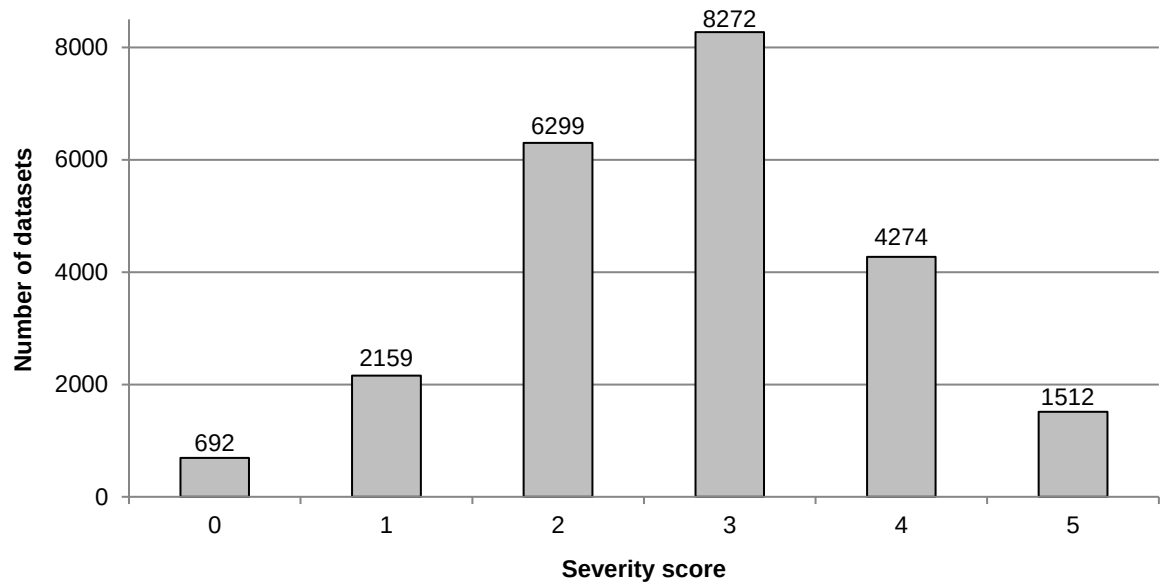

Figure 4: Symptom severity score, ranging from 0 (no symptoms) to 5 (most imaginable symptoms). Data is expressed as absolute frequency.

10.4.2.4 Duration of complaints before start of treatment

Besides the severity, the duration of the complaints before starting treatment was also documented. Before the start of treatment with herbal medicines, most participants suffered from symptoms ranging from one day to one week (38.0% of all valid datasets). In 29.6% of the datasets, the duration of complaints before starting treatment was less than one day. In contrast, in 27.3% of the datasets, patients had symptoms for a long undefined period before they started treatment with phytopharmaceuticals (Figure 5).

Figure 5: Duration of complaints before starting treatment. Data is expressed as absolute frequency.

10.4.3 Phytopharmaceuticals and their usage

After data cleansing, a total of 1 433 herbal medicinal products were identified. Besides, homeopathic substances (411 datasets, 1.7%), food supplements (349 datasets, 1.5%), or cosmetics (72 datasets, 0.3%), were also documented.

10.4.3.1 Products

The highest proportion (1453 datasets, 6.0%) attributed to a product used for gastrointestinal complaints. Followed by seven products used for upper airway infections, including common cold and cough. These add up to more than 20% (4.0%, 3.9% 3.1%, 2.9%, 2.6%, 2.3% and 2.3%, respectively) of the datasets (5069 in total).

10.4.3.2 Dosage forms

Several phytopharmaceutical products are available in different dosage forms. For example, camomile can be used as tea or tincture. Therefore, dosage forms were also inquired and documented in order to clearly differentiate the different dosage forms for one herbal medicine. Table 5 summarizes the dosage forms that were documented in more than 0.5% of all valid datasets.

Most phytopharmaceuticals were used as tea (17.4%), tablets (17.2%), drops (13.4%) or capsules (12.4%). Conversely, creams, sprays and products for inhalation played only a marginal role with 1.5% or less.

Table 5: Dosage forms of the used phytopharmaceutical products.

Dosage forms	Frequency	Percentage [%]
Tea	4 124	17.4
Tablet	4 081	17.2
Drops	3 181	13.4
Capsule	2 940	12.4
Dragée	2 605	11.0
Liquid	2 472	10.4
Ointment	1 115	4.7
Others	966	4.1
Syrup	920	3.9
Pastilles	532	2.2
Cream	362	1.5
Spray	136	0.6
Inhalation	128	0.5

10.4.3.3 Frequency and duration of treatment

Phytopharmaceuticals were predominantly used on a daily basis (77.1% of all valid datasets). In 22.9% of the valid datasets, phytopharmaceuticals were used when needed.

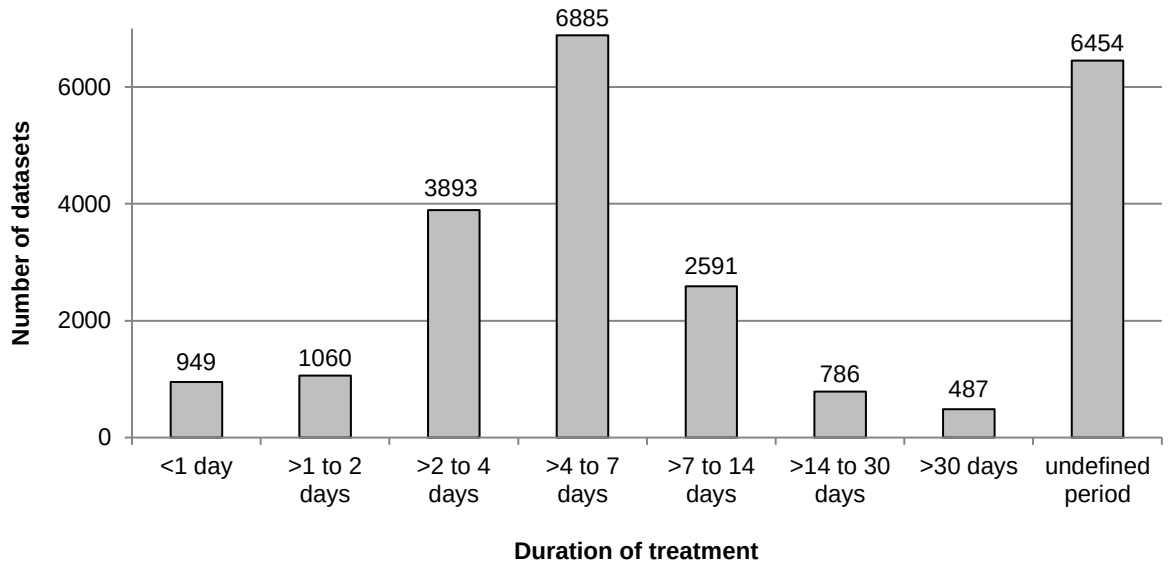

Figure 6: Duration of treatment.

Phytopharmaceuticals were mainly used for four to seven days (29.8% of all valid datasets) or for a long undefined period (27.9%). Treatment duration of less than a day was documented in 4.1% of the datasets. Treatment duration of more than one but less than two days was documented in 4.6% and of two to four days in 16.8% of the datasets, respectively. Treatment for one to two weeks was documented in 11.2% of the datasets. Treatment for two weeks up to one month was reported in 3.4% of the datasets. Treatment duration of more than a month was documented in 2.1% of all datasets (Figure 6).

10.4.3.4 Time to onset of action

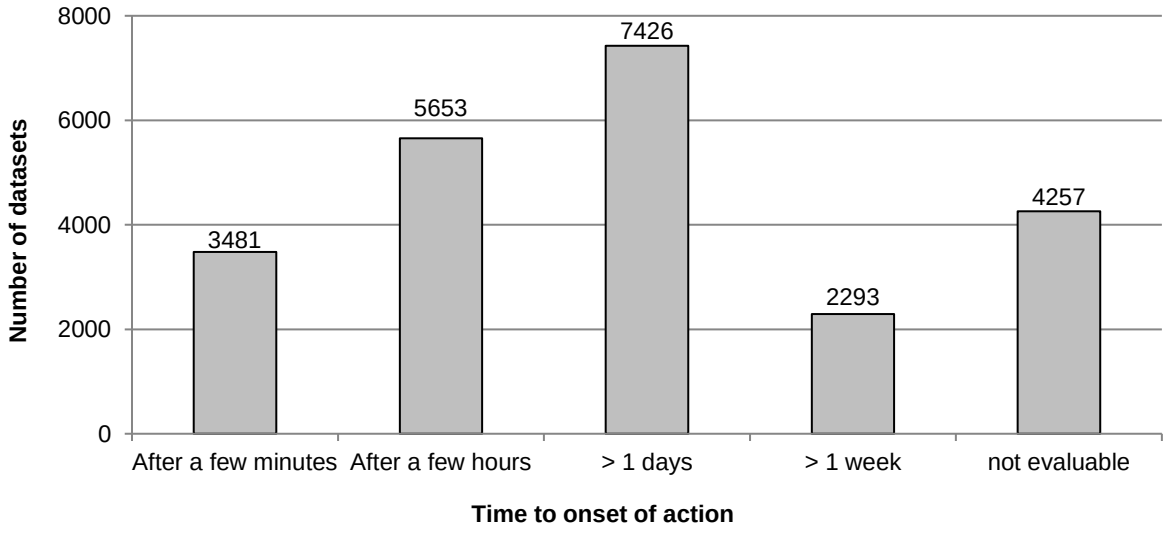

Figure 7: Time to onset of action.

In the predominant proportion of datasets, time to onset of action was documented with “more than a day” (30.9%), followed by “after a few hours” (23.5%). In 14.5% of the datasets, time to onset of action was documented with “after a few minutes” and in 9.5% of the datasets with “more than a week”. In 17.7% of the datasets, onset of action could not be specified by the patient (Figure 7).

10.4.4 Concomitant diseases and medication

10.4.4.1 Concomitant diseases

In 9 330 (38.8%) of the valid datasets (23 544), patients stated concomitant diseases (Figure 8). Of those, 54.6% reported one concomitant disease (correlating to 21.2% of all datasets) and 45.4% reported two or more concomitant diseases (17.6% of all datasets). Predominantly, hypertension was stated as concomitant disease (29.8% of all datasets stating concomitant diseases and 11.6% of all datasets), followed by metabolic disorders (20.8% and 8.1%) and asthma/hay fever (11.5% and 4.5%). Other diseases comprised 22.3% of all datasets stating concomitant diseases and 8.7% of all datasets. The most stated “other” disease was hypothyroidism with 294 datasets (3.2% of all datasets stating concomitant diseases and 1.2% of all datasets).

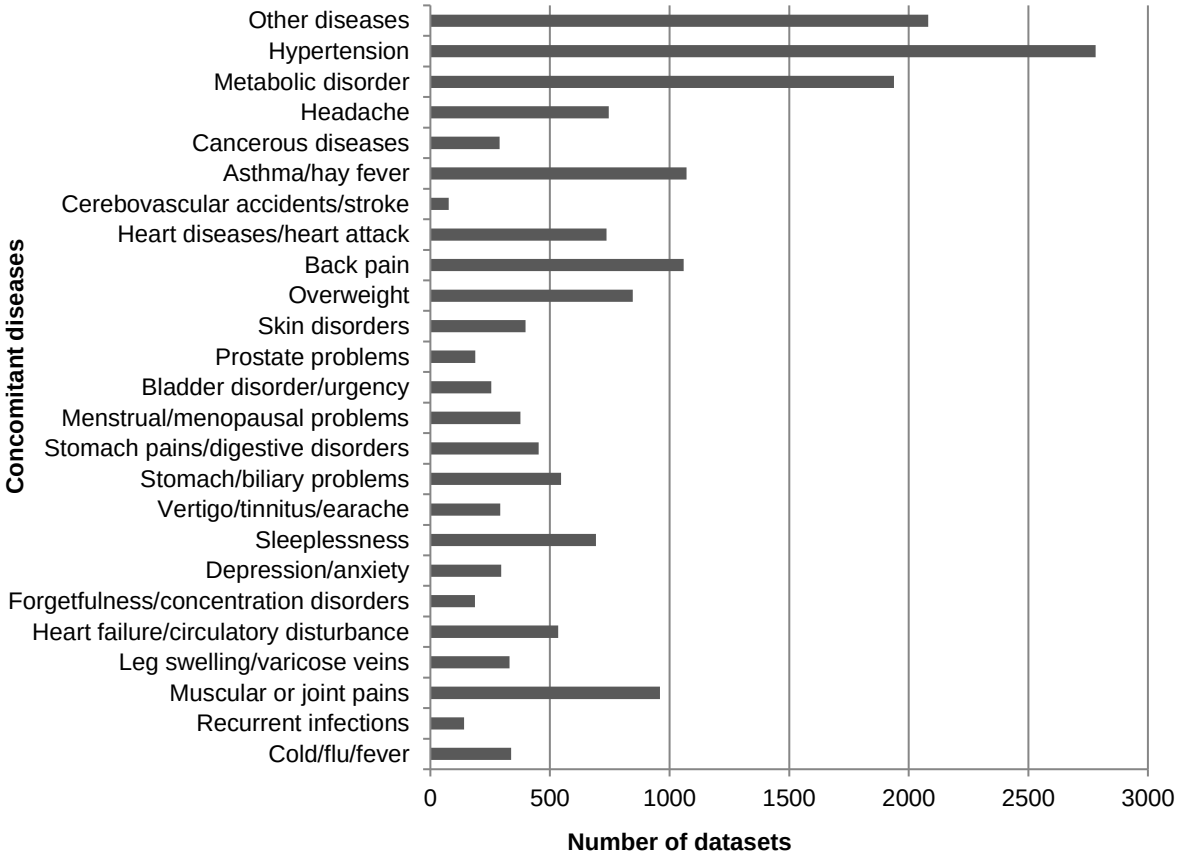

Figure 8: Number of datasets with concomitant diseases.

10.4.4.2 Concomitant medication

Despite of concomitant diseases, concomitant medications were also documented in the questionnaire. Here, 47.3% of all valid datasets (23 460) contained concomitant medications. Of those, 546 datasets (4.9%) stated L-Thyroxin as concomitant medication (2.3% of all datasets), followed by Ibuprofen (472 datasets, 4.3% and 2.3%) and the “pill” (290 datasets, 2.6% and 1.2%). Antibiotics comprised 1.9% (214 datasets) of all datasets stating concomitant medications (0.9% of all datasets) and 1.8% (0.8%) stated hypertension drugs (203 datasets). In 238 of the datasets, patients did not give any information on the concomitant medication (“Keine Angabe”, translates as “no details provided”).

10.5 Other analyses

10.5.1 Subgroup analyses regarding efficacy (CGI-E)

To further analyze the efficacy of the phytopharmaceutical products, subgroup analyses with correlation to the CGI-E were performed.

10.5.1.1 CGI-E in correlation to ‘Recommendation by’

Of the 8415 phytopharmaceuticals that were recommended by pharmacists, 49.3% showed a marked and 38.5% a moderate therapeutic effect. Minimal or unchanged improvement was reported in 9.0% or 3.2% of the datasets, respectively (Figure 9). For the same phytopharmaceuticals recommended by pharmacists, 91.7% of the datasets were rated without any or no significant (6.9%) side effects (Figure 11). In 1.1% of the datasets significant impairment or worse (0.4%) were reported (Figure 11). Phytopharmaceuticals that were recommended by pharmacists had a mean CGI-E score of 3.20.

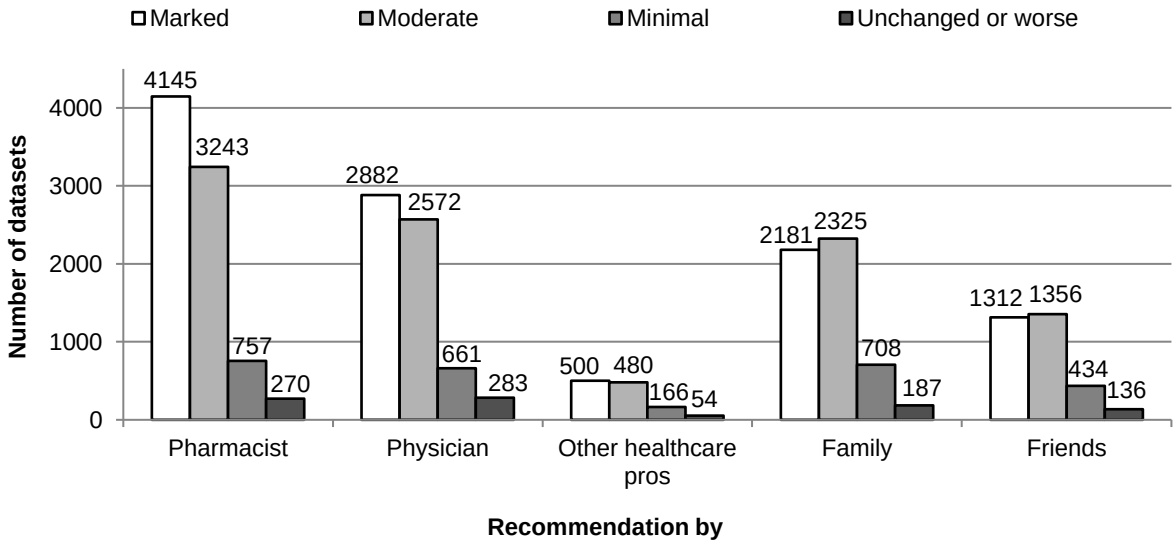

Figure 9: Therapeutic effect according to CGI-E correlated to the recommendation of phytopharmaceuticals. Depicted are absolute numbers of datasets recommended by pharmacists, physicians, other healthcare professionals, family and friends.

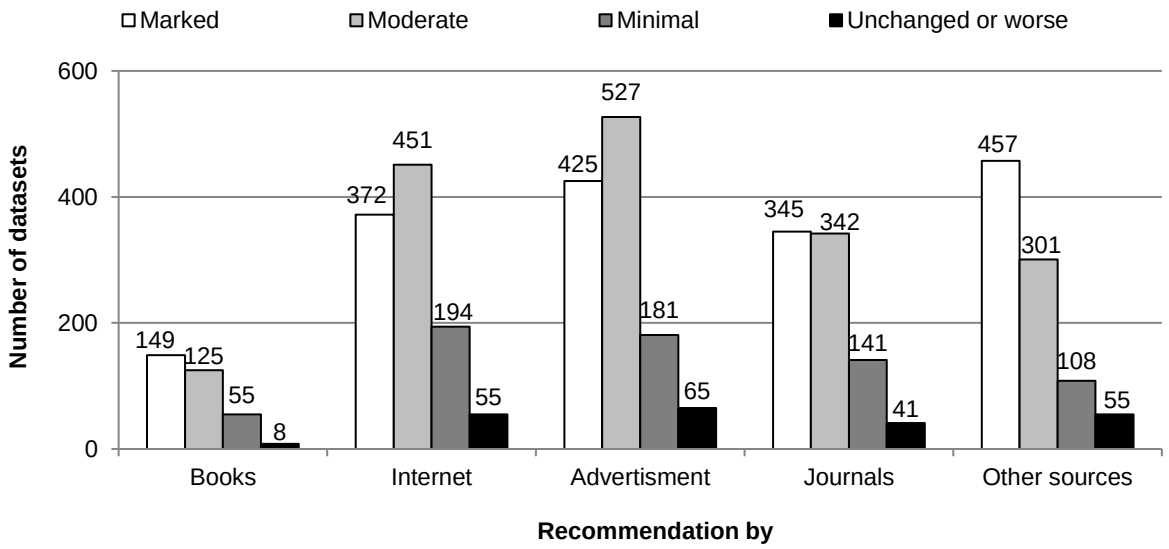

Figure 10: Therapeutic effect according to CGI-E correlated to the recommendation of phytopharmaceuticals. Depicted are absolute numbers of datasets recommended by books, internet, advertisement, journals or other sources.

Recommendation by journals, internet or advertisement played a minor role with half the number of datasets compared to recommendation by pharmacists, physicians, family and friends (Figure 10). Recommendation by pharmacists, physicians or other sources led to largest proportion to marked therapeutic effects. While the proportion of moderate therapeutic effects predominate the datasets recommended by family, friends, advertisement or books (Figure 9 and Figure 10).

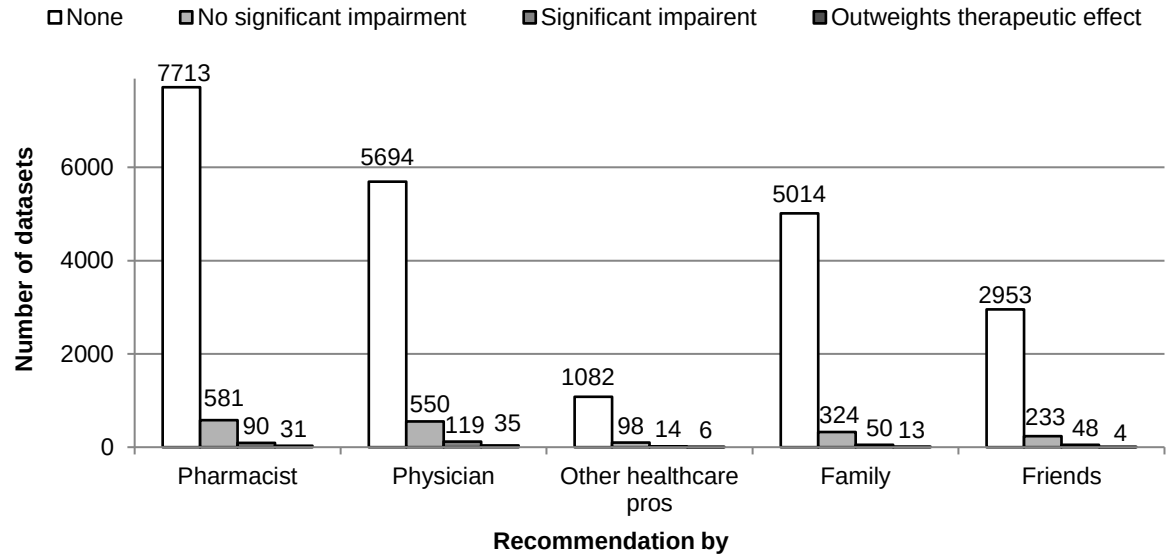

Figure 11: Side effects according to CGI-E correlated to the recommendation of phytopharmaceuticals. Depicted are absolute number of datasets recommended by pharmacists, physicians, other healthcare professionals, family and friends.

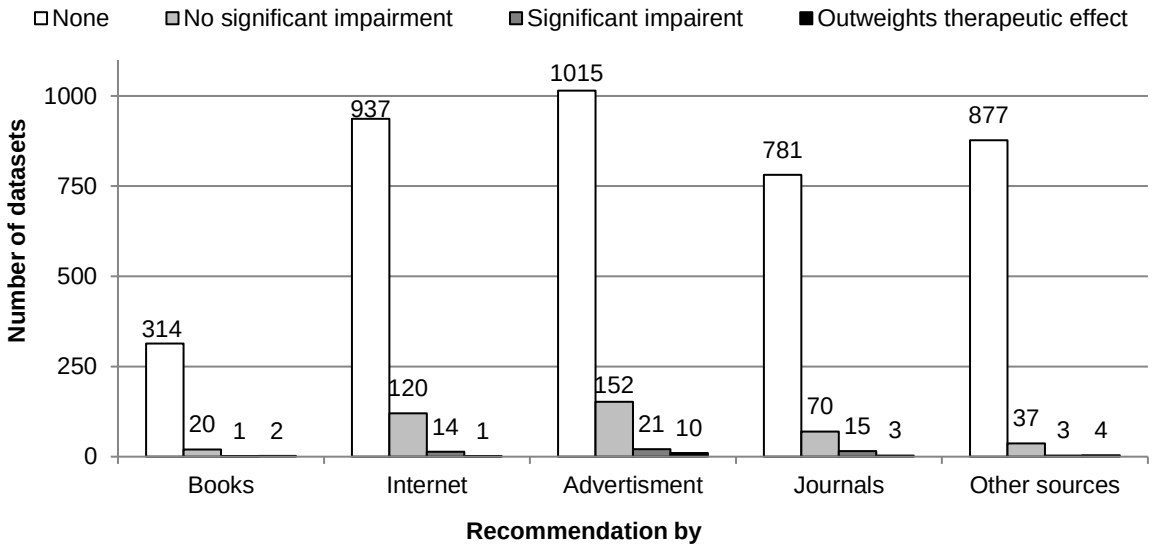

Figure 12: Side effects according to CGI-E correlated to the recommendation of phytopharmaceuticals. Depicted are absolute numbers of datasets recommended by books, internet, advertisement, journals or other sources.

The greatest proportion of datasets without any side effects was recommended by books (93.2%), family members (92.8%), or other sources (95.2%, Figure 12). Of the 6398 phytopharmaceuticals that were recommended by physicians, 89.0% showed no side effects and 8.6% no significant impairment through side effects (Figure 11). Fewer datasets without side effects were only recommended by advertisement (84.7%) and internet (87.4%).

10.5.1.2 CGI-E in correlation to the place of purchase

As shown in section 10.3.2, more than 80% of the datasets stated “pharmacy” as the place of purchase (Figure 13). Most of these datasets (46.4% and 39.2%) documented a marked or moderate efficacy, respectively. Only a small proportion of these datasets described only minimal effects (10.2%), or unchanged or worse conditions (4.1%). Regarding the other places of purchase (with frequencies < 1 000 for each category) the different efficacy stages were similarly distributed. However, for these places of purchase (organic grocery store, chemists, online-retailer, health food store and supermarket), the difference between datasets with only a minimal or no efficacy compared to datasets with a marked or moderate efficacy was less pronounced compared to pharmacies.

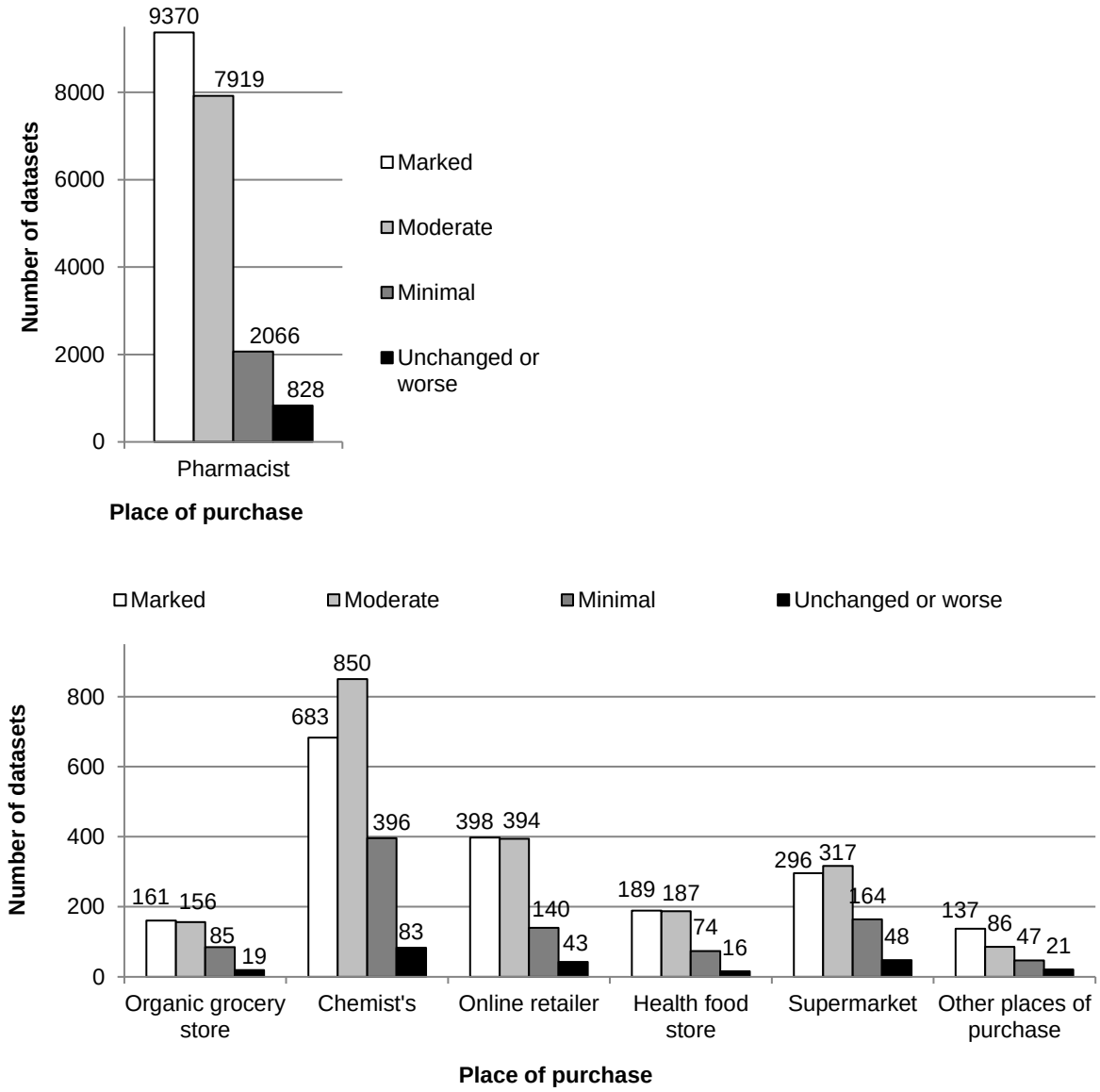

Figure 13: Place of purchase correlating to the therapeutic effect (CGI-E). Data is expressed as absolute numbers of datasets.

Interestingly, the highest proportion of datasets without side effects was for supermarkets as place of purchase. For pharmacies, 91.1% of the datasets stated no side effects. 'No significant impairment' was highest in datasets with health food stores as sources of supply (10.9%). The proportion of datasets stating significant impairment or 'outweigh the therapeutic effect' was evenly distributed throughout the places of purchase (ranging from 1.0% to 1.8% and from 0% to 0.4%, respectively).

10.5.1.3 CGI-E in correlation to indication

Since different indications probably go in line with different efficacy and safety, the CGI-E was correlated to the indication (coded according to MedDRA LLT) stated in the datasets.

In this study, common cold was the most frequently stated indication according to MedDRA LLT and was chosen as an example for the correlation (Table 6). As an example, for a more or less chronic indication, sleeping disorders (5th most stated indication according to MedDRA LLT) was chosen for the correlation with CGI-E (Table 7).

Of the 5310 datasets with common cold as indication, 2374 datasets (44.7%) were rated with a well-marked therapeutic effect. Of the datasets with excellent/well marked efficacy, 27 (1.1%) were associated with significant impairment and in 3 cases (0.1%) the side effects outweighed the excellent therapeutic effect. In the datasets stating marked improvement, the therapeutic effect was associated with significant impairment in 1.5% or 'outweigh the therapeutic effect' in 0.3% of the corresponding datasets, respectively. The proportion of datasets impaired through side effects further increased with decreasing therapeutic effect: Regarding datasets with minimal improvement, 1.3% reported a superimposition of the therapeutic effect through side effects. Of the datasets with unchanged or even worsened symptoms, 5.4% side effects further outbalanced the already poor effects.

Table 6: The CGI-E for all valid datasets with indication common cold. Data is expressed as absolute frequency and percentage of all valid datasets.

Therapeutic effects Frequency (Percentage)	Absence of side effects	No significant impairment through side effects	Significant impairment through side effects	Side effects outweigh the therapeutic effect
Excellent – well-marked	2210 (41.6%)	134 (2.5%)	27 (0.5%)	3 (0.1%)
Moderate – marked improvement	1979 (37.3%)	133 (2.5%)	32 (0.6%)	6 (0.1%)
Minimal – slight improvement	555 (10.5%)	25 (0.5%)	11 (0.2%)	8 (0.2%)
Unchanged – worse	164 (3.1%)	5 (0.1%)	8 (0.2%)	10 (0.2%)

As an example, for a more or less chronic disease, the indication 'sleeping disorders' was analyzed with regard to the CGI-E.

Of the 764 datasets with sleeping disorders as indication, 310 datasets (40.6%) were rated with a well-marked therapeutic effect. Of the datasets with excellent/well marked efficacy, 2 (0.6%) were associated with significant impairment. Side effects that outweighed the excellent therapeutic effect were not documented. In the datasets stating marked improvement, the therapeutic effect was associated with significant impairment in 2%. Again, 'outweigh the therapeutic effect' did not occur. Regarding datasets with minimal improvement, 1.8% reported

a significant impairment of the therapeutic effect and 0.9% a superimposition through side effects. Of the datasets with unchanged symptoms, neither a significant impairment, nor a superimposition of the therapeutic effect occurred because of side effects. For unchanged or worse conditions, side effects outweighed the therapeutic effect in 6% of the corresponding datasets.

Table 7: The CGI-E for all valid datasets with indication sleeping disorders. Data is expressed as absolute frequency and percentage of all valid datasets.

Therapeutic effects Frequency (Percentage)	Absence of side effects	No significant impairment through side effects	Significant impairment through side effects	Side effects outweigh the therapeutic effect
Excellent – well-marked	292 (38.2%)	16 (2.1%)	2 (0.3%)	0 (0.0%)
Moderate – marked improvement	250 (32.7%)	39 (5.1%)	6 (0.8%)	0 (0.0%)
Minimal – slight improvement	94 (12.3%)	13 (1.7%)	2 (0.3%)	1 (0.1%)
Unchanged – worse	43 (5.6%)	3 (0.4%)	0 (0.0%)	3 (0.4%)

10.5.1.4 CGI-E correlated to symptoms

Correlation of the CGI-E with the number of symptoms revealed no difference in therapeutic effects, whether one symptom (19 985 datasets) or two and more symptoms (4 073 datasets) were reported. A marked effect was experienced by the patients in 45.2% of the datasets with one symptom and in 42.9% of the datasets with two or more symptoms. Moderate improvement was seen in 38.9% datasets with one symptom and in 41.1% datasets with two and more symptoms. Datasets with minimal or worse therapeutic effect displayed the same proportion for one or two and more symptoms.

No side effects according to CGI-E were reported in 91.5% of the datasets with one symptom and 89.8% of the datasets with two or more symptoms. Proportion of datasets with no significant impairment was slightly increased from 6.8% with one symptom to 8.3% with two or more symptoms. Proportion of significant impairment or worse was similar for one or two and more symptoms.

Beside the number of symptoms, the patients were asked to indicate if the phytopharmaceutical product was used for acute or chronic symptoms or for preventive interventions. The mean CGI-E score was 2.88 for chronic ailments, 3.05 in case of preventive interventions and 3.15 for treatment of acute symptoms.

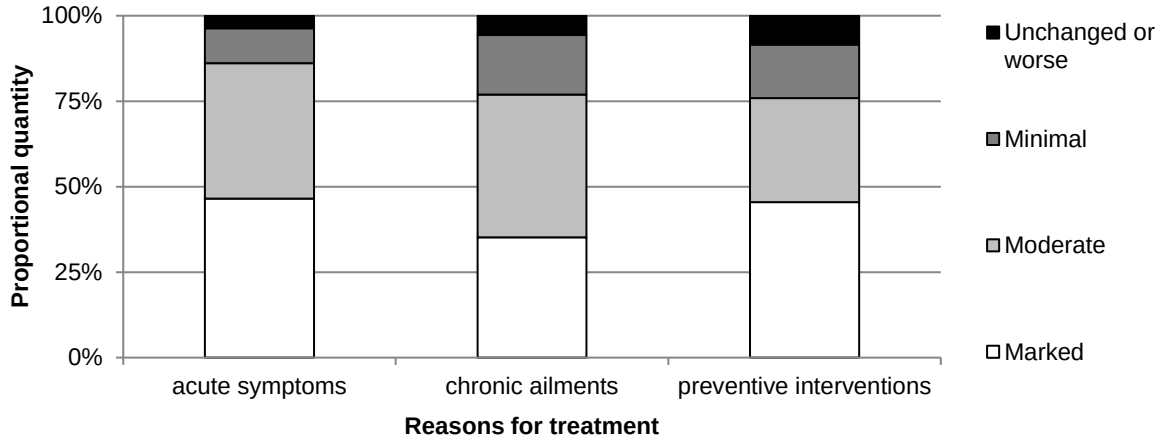

Figure 14: Therapeutic effect according to CGI-E correlated to the reason for treatment.

When correlating the CGI-E with the reason for treatment, chronic ailments had the lowest marked efficacy (35.2%) in comparison to acute symptoms (46.5%) and preventive interventions (45.5%, Figure 14). In contrast, the proportion of a moderate therapeutic effect was lowest (30.4%) in case of preventive interventions and highest for chronic ailments (41.8%). Interestingly, preventive interventions had the highest proportion of unchanged or worsened conditions (8.4%) in contrast to chronic (5.6%) or acute (3.7%) symptoms.

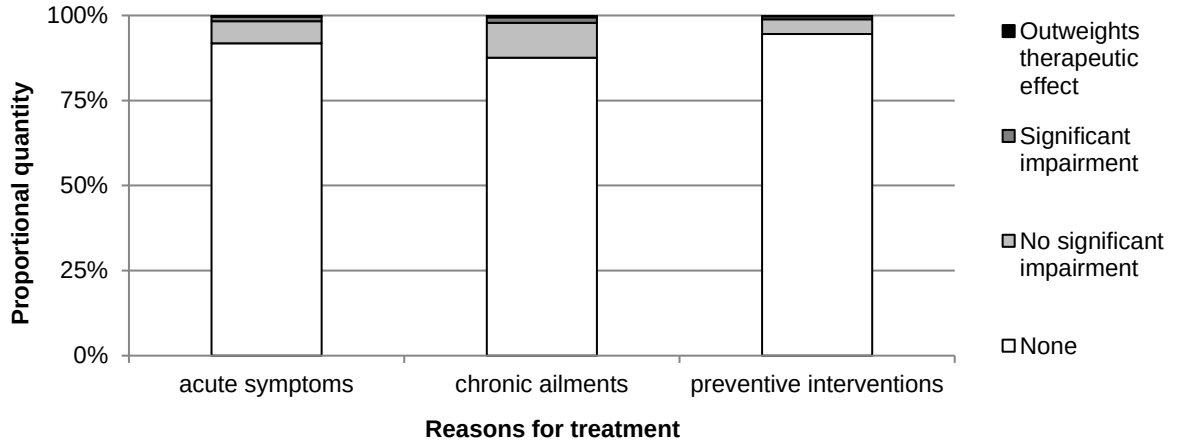

Figure 15: Side effects according to CGI-E correlated to the reason for treatment.

Regarding side effects in correlation to the reason for treatment, preventive interventions showed the best outcome: 94.5% of the valid datasets stated no side effects and 4.4% stated no significant impairment. Only 0.8% stated a significant impairment and in even less datasets (0.3%), side effects outweighed the therapeutic effect. Chronic ailments displayed the smallest proportion of datasets with no side effects (87.6%), whereas the proportion of datasets with no significant impairment (10.2%), significant impairment (1.6%) and 'outweigh the therapeutic effect' were highest (0.5%) compared to other reasons for treatment (Figure 15).

10.5.1.5 CGI-E in correlation to severity

Most patients rated the severity of their disease with a severity score of 3 (Figure 4). Correlation of the severity score to the therapeutic effect according to CGI-E constituted no difference. A mean severity score of 2.79 ± 1.16 was yielded for marked therapeutic effects, 2.76 ± 1.07 for moderate effect, 2.66 ± 1.21 with minimal therapeutic effects and in case of unchanged or worse situation slightly higher with a mean of 2.92 ± 1.41.

In contrast, correlating side effects according to CGI-E with the mean severity score showed that the severity score increased with decreasing CGI-E score (Figure 16). With no side effects reported, the mean severity score was 2.75 ± 1.15 and further increased when impairment was reported: In datasets with no significant side effects the mean severity score was 2.87 ± 1.01 and 3.12 ± 1.05 for 'significant impairment'. Where side effects outweighed the therapeutic effect, the corresponding symptoms were rated with a mean severity score of 3.40 ± 1.03.

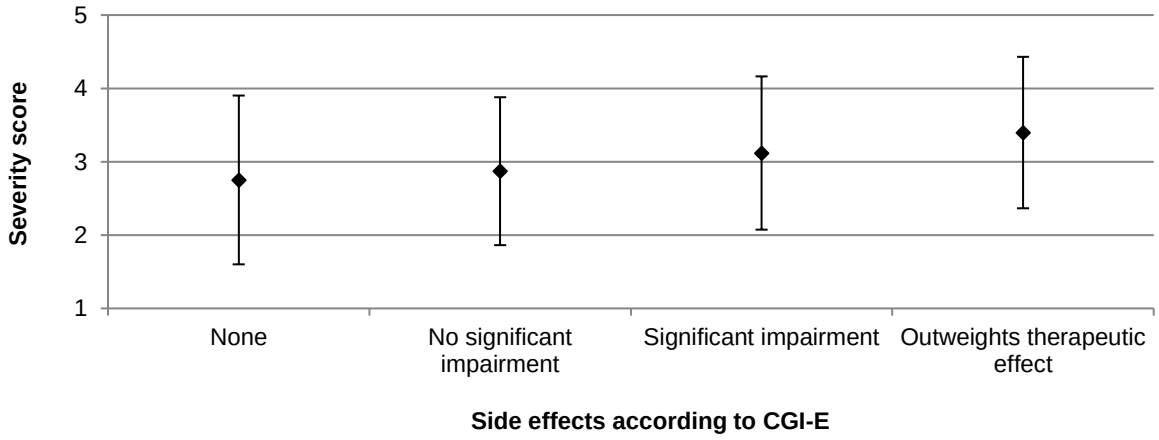

Figure 16: Side effects according to CGI-E correlated to the symptom severity score. Data is shown as mean ± SD.

10.5.1.6 CGI-E in correlation to the onset of action

A good efficacy is closely related to a quick onset of action. Therefore, the time to onset of action was correlated to the CGI-E.

The absolute number of datasets increased with increasing time to onset of action up until one week (Figure 7): from 3481 and 5653 datasets with an onset of action after a few minutes and after a few hours, respectively, to 7426 datasets with an onset of action after more than one day. Then, only 2293 datasets documented an onset of action after more than one week.

For example, datasets with an onset of action after more than one day showed that most patients experienced a marked (37.1%) or moderate (42.1%) therapeutic effect. A minimal effect was reported for 7.2% and an unchanged/worse situation was reported in 0.4% of the datasets with an onset of action after more than one day.

Regarding side effects, 91.2% of the datasets with an onset of action after more than one day stated no side effects. No significant side effects were documented in 7.4% of the datasets.

Significant impairment or ‘outweigh the therapeutic effect’ was reported in 1.2% and 0.2% of these datasets, respectively.

When comparing the proportional quantities of this correlation, the datasets showed that an increased time to onset of action was correlated to a reduction in marked efficacy: from 61% for an onset of action after a few minutes to 36% after an onset of action after more than a week. Whereas moderate and minimal effects increased with increasing time to onset of action: from 33% (after a few minutes) to 50% (after more than a week) and from 0.6% (after a few minutes) to 13% (after more than a week), respectively. Unchanged/worsened conditions were similar throughout all times until onset of action (Figure 17).

With increasing time to onset of action, the proportion of datasets without any side effects decreased (from 93.8% after a few minutes to 87.7% after more than one week), whereas the proportion of datasets with side effects increased from 4.7% after a few minutes to 10.7% after more than one week. Significant interferences because of side effects or strong side effects, which outweigh the therapeutic effect, were similarly distributed throughout the time until onset of action (Figure 18).

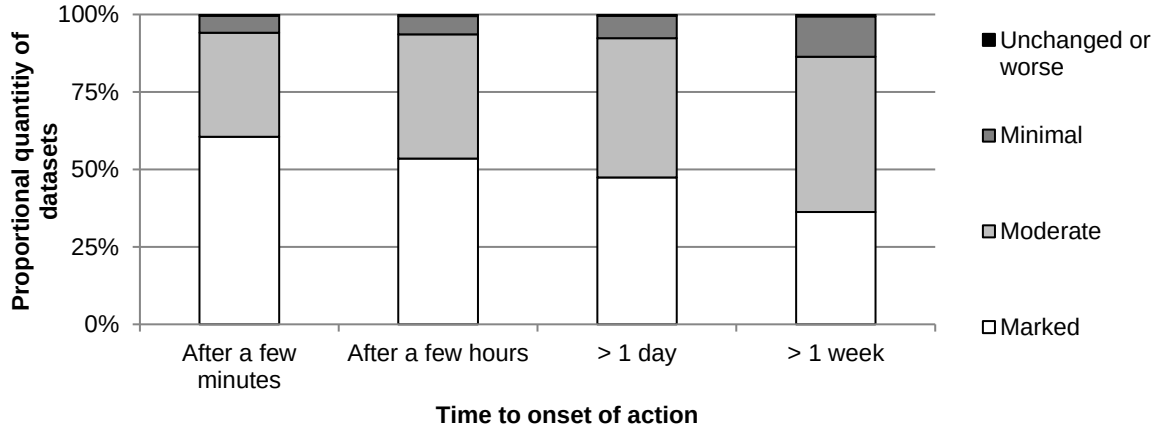

Figure 17: Therapeutic effect according to CGI-E correlated to the onset of action depicted as proportional quantity of datasets.

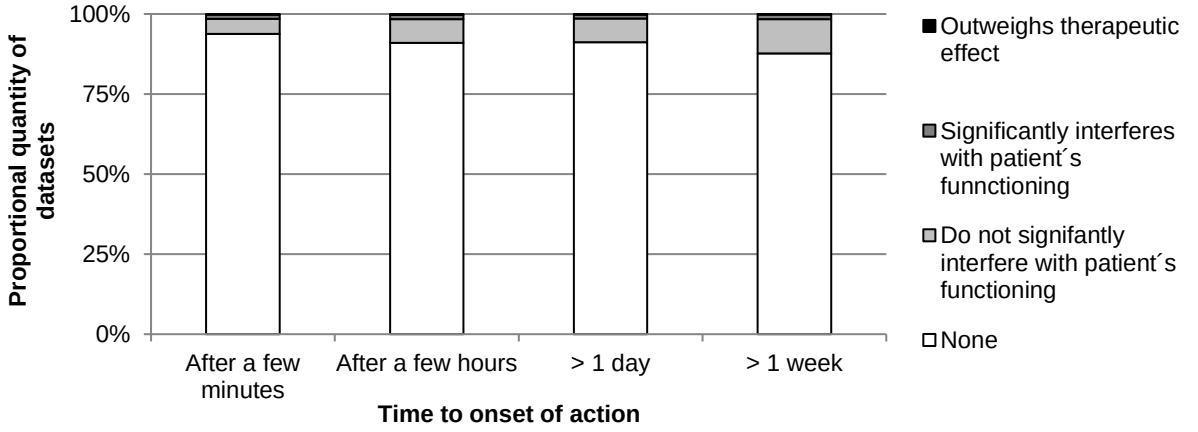

Figure 18: Side effects according to CGI-E correlated to the onset of action depicted as proportional quantity of datasets.

10.5.1.7 CGI-E correlated to concomitant diseases and concomitant medication

Correlation of the CGI-E with concomitant diseases showed that marked therapeutic effects slightly decreased with an increasing number of concomitant diseases. Without concomitant diseases 45.8% datasets were rated with marked therapeutic effect while with one co-existing disease 45.1% datasets showed marked effects. With two or more concomitant diseases, 41.2% stated a marked therapeutic effect. Moderate therapeutic effects increased with the number of concomitant diseases, from 38.7% without to 39.9% with one and 40.5% with two or more concomitant diseases. While unchanged or worse effects were reported more frequent no matter if one or two other concomitant diseases were stated.

The proportion of datasets with no side effects according to CGI-E slightly decreased with an increasing number of concomitant diseases: from 91.9% with no concomitant disease to 90.7% with one and 89.4% with two or more concomitant diseases. With an increasing number of concomitant diseases, the not significant side effects increased from 6.7% with none to 7.1% with one and 8.3% with two or more concomitant diseases. Significant impairment was reported by the same proportion of datasets as soon as one concomitant disease exists: 1.0% datasets without concomitant disease, 1.7% datasets with one and 1.8% datasets with two or more concomitant diseases. The proportion of datasets that stated 'outweigh the therapeutic effect' was similar with (both 0.5%) or without (0.4%) concomitant diseases.

In datasets with no concomitant disease a mean CGI-E score of 3.13 was reached. With one concomitant disease the mean CGI-E score decreased to 3.10 and to 3.01 when two or more concomitant diseases were reported.

Intake of concomitant medication was reported for 11 090 datasets (46.1%) and was correlated to the therapeutic and side effects according to CGI-E. A marked therapeutic effect was reported in 46.3% of all datasets without documented concomitant medication and in 42.5% of all datasets with concomitant medication. The proportion of datasets with moderate therapeutic effect increased from 38.4% without to 40.7% with concomitant medication. Also, the proportion of minimal effects slightly increased (11.4% without to 12.1% with, respectively). The proportion of datasets with unchanged or worse conditions after phytopharmaceutical treatment increased from 4.0% without to 4.7% with concomitant medication.

Regarding the side effects according to CGI-E, the proportion of datasets with 'outweigh the therapeutic effect' or significant impairment was similar with or without concomitant medication (0.4% both). 'No significant impairment' slightly increased from 6.8% of the datasets without concomitant medication to 7.5% with intake of concomitant medication. The proportion of datasets without any side effects slightly decreased from 91.7% without to 90.5% with concomitant medication.

10.5.2 Subgroup analyses regarding recommendation and source of supply (secondary endpoints)

10.5.2.1 Place of purchase in correlation to dosage forms

In pharmacies, all dosage forms were represented. The proportions of drops (15.0%), tea (11.4%), tablets (19.2%), capsules (13.0%) and liquid (11.0%) were more or less evenly distributed. Ointment (4.9%), syrup (4.2%) and other dosage forms (3.4%) constituted almost 5% each, while and cream (1.6%), inhalation (0.5%), spray (0.6%) and suppositories (0.2%) comprised the smallest proportions of dosage forms recommended by pharmacists (Figure 19).

An analogous distribution was also seen for recommendation by online retailers which are mainly internet pharmacies. Here, the fraction of tablets (21.6%) and capsules (19.6%) was slightly larger while the fraction of syrup (1.7%) and dragées (7.6%) was lower.

In contrast, tea was the main phytopharmaceutical product purchased in organic grocery stores (70.6%), supermarkets (76.5%), health food stores (53.3%) and at the chemists (53.7%). Furthermore, phytopharmaceuticals for inhalation, sprays or suppositories were not bought at all in organic grocery stores, whereas creams, globules and suppositories were not purchased in supermarkets (0% each).

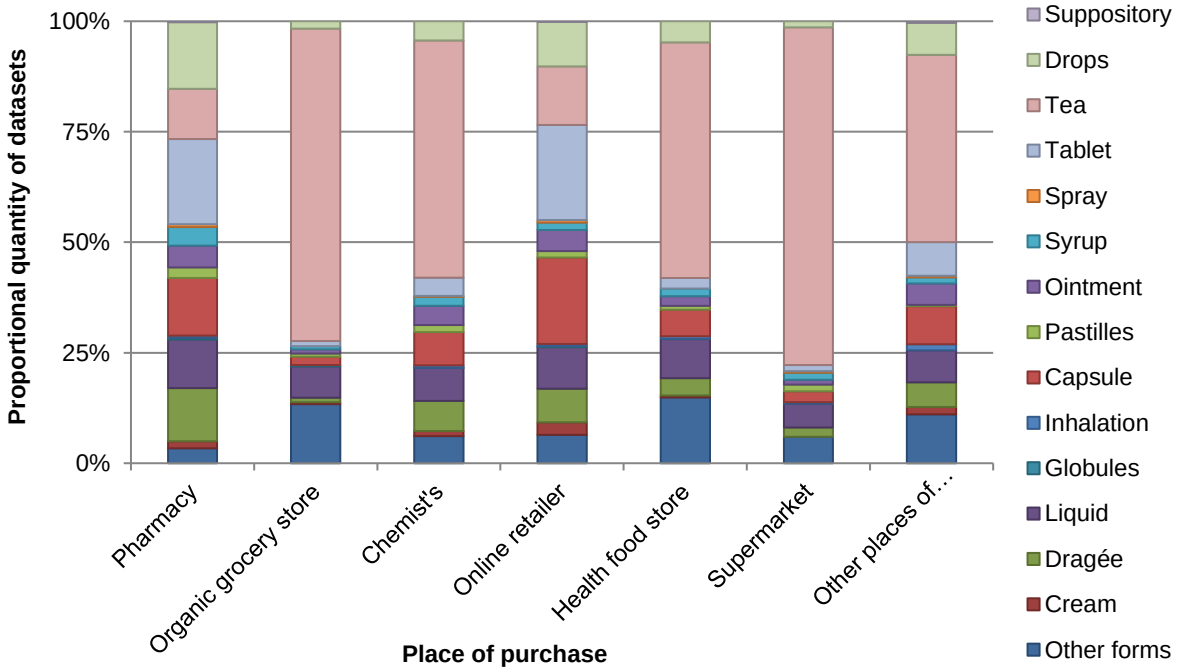

Figure 19: Dosage forms correlated to the place of purchase.

10.5.2.2 Way of recommendation correlated to indication

The four most frequently reported medical indications were common cold (5 310 datasets, 21.1%), cough (1 859 datasets, 7.7%), frontal sinusitis (1 404 datasets, 5.8%) and sore throat (832 datasets, 3.5%; please refer also to Table 4).

Correlation to the way of recommendation revealed that phytopharmaceuticals to treat these acute symptoms were mainly recommended by pharmacists (Figure 20). Phytopharmaceuticals to treat common cold (27.6%) and sore throat (33.5%) were recommended second most by family members. While for cough and frontal sinusitis, the second most recommendations were made by physicians (25.9% and 36.3%, respectively, Figure 20). Recommendation by books, the internet, advertisement or journals played only a marginal role to cure these acute symptoms.

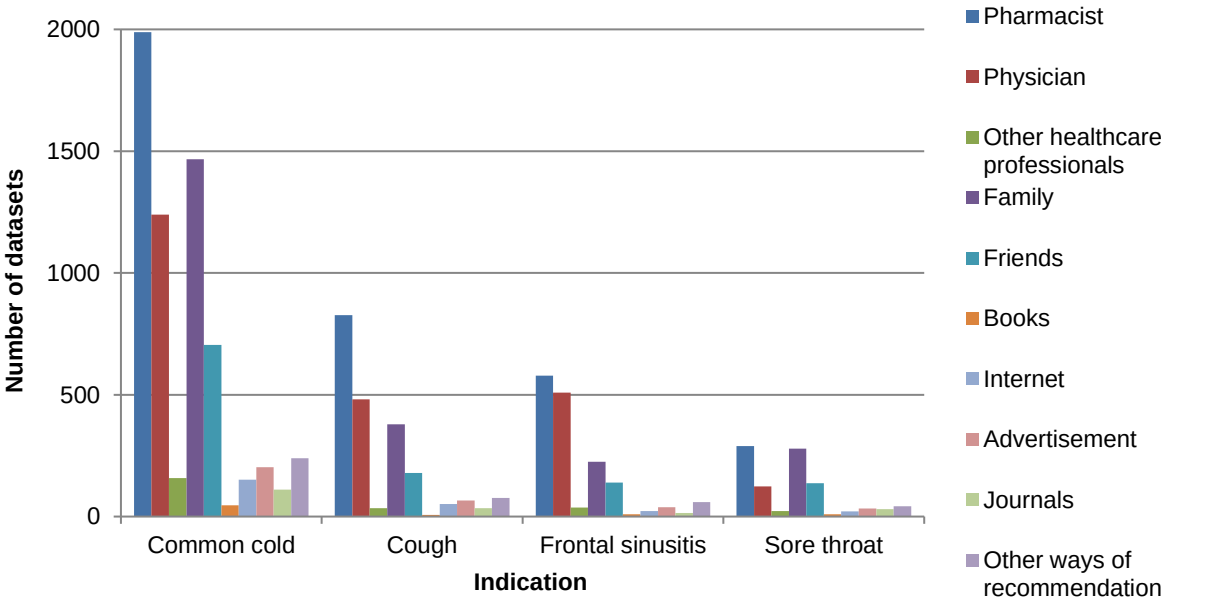

Figure 20: Four most frequently reported acute symptoms correlated to the way of recommendation depicted as absolute number of datasets.

In contrast, phytopharmaceuticals used for prevention were mainly recommended by family members (Figure 21). Additionally, the fraction of recommendation by books (5.1%), internet (6.1%), advertisements (4.3%) and journals (8.3%) was larger in case of prevention compared to other indications. For treatment of menopausal problems or depression, which are more of a chronic nature, the physician was the predominant and pharmacists the second most way of recommendation (Figure 21). Generally, books, internet, advertisements and journals played only minor roles in recommending phytopharmaceutical products.

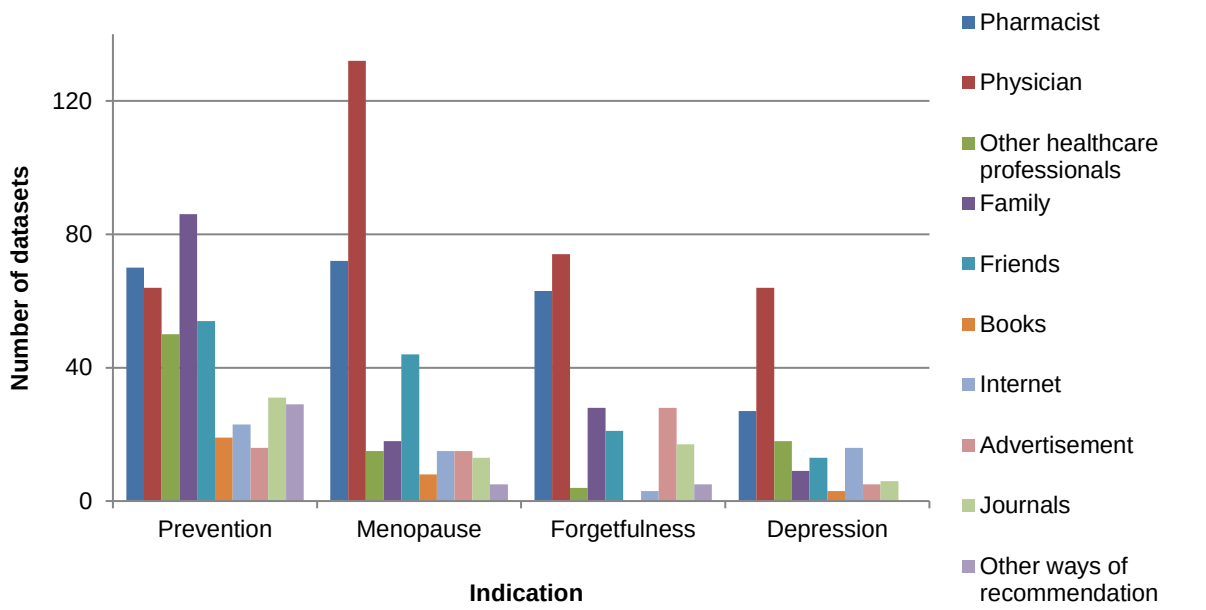

Figure 21: Four medical indications illustrative for chronic ailments and preventive interventions, correlated to the way of recommendation depicted as absolute number of datasets.

10.5.2.3 Way of recommendation in correlation to severity

The way of recommendation was not influenced by the severity of symptoms (Figure 22). Similar to the overall mean severity score (Figure 4), symptom severity was mainly rated as '3'. The highest mean severity score (ranging from 0 to 5) was 2.94 for recommendations by a physician. The lowest mean rating (2.51) correlated to the recommendation by books.

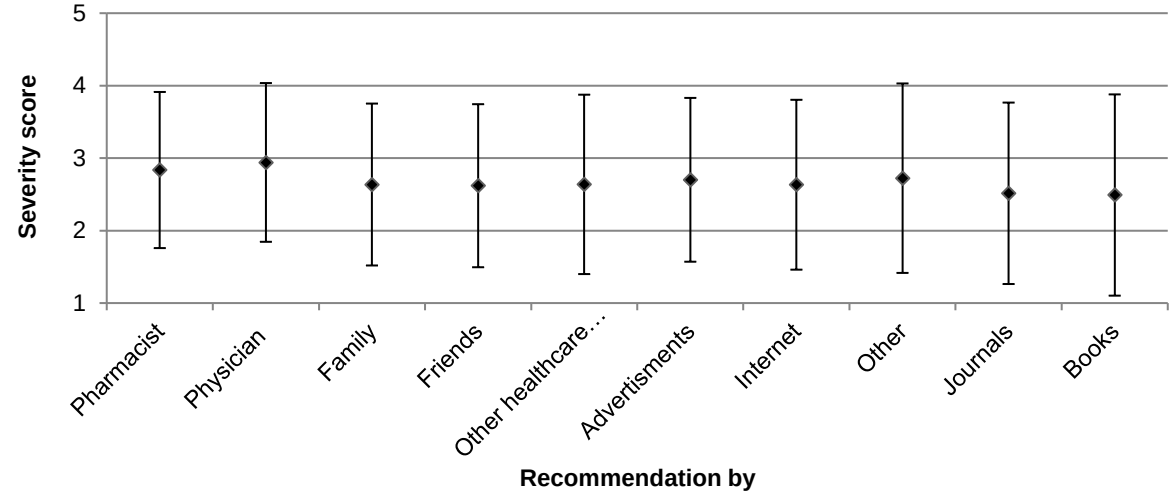

Figure 22: Symptom severity score correlated to the way of recommendation. Data is expressed as mean severity score (ranging from 0 to 5) ± SD.

10.5.2.4 Way of recommendation correlated to onset of action

Since the patient's subjective experience with phytopharmaceuticals was the main focus, we analyzed if the onset of action met the expectations of the patients concerning the way of

recommendation – e.g. that products, that were recommended by a physician would therefore have a shorter onset of action in comparison to e.g. the supermarket (Figure 23).

Patients were asked to give the time to onset of action and this was correlated to the way of recommendation.

Phytopharmaceuticals recommended by pharmacists exhibited an onset of action after a few minutes (17.0%), after a few hours (31.3%), after more than one day (41.3%) or after more than one week (10.3%). Products recommended by physicians displayed the smallest proportion with an onset of action after a few minutes (12.0%) and after a few hours (27.9%). An onset of action after more than one day (42.5%) or after more than one week (17.6%) was more characteristic for recommendations by physicians. Recommendation by other healthcare professionals and the internet displayed a similar distribution: fractions of phytopharmaceuticals with an onset of action of up to a few hours contributed to less than 50%. The largest proportions of phytopharmaceuticals with a quick onset of action of a few minutes were recommended by family (22.7%) or other sources (27.4%).

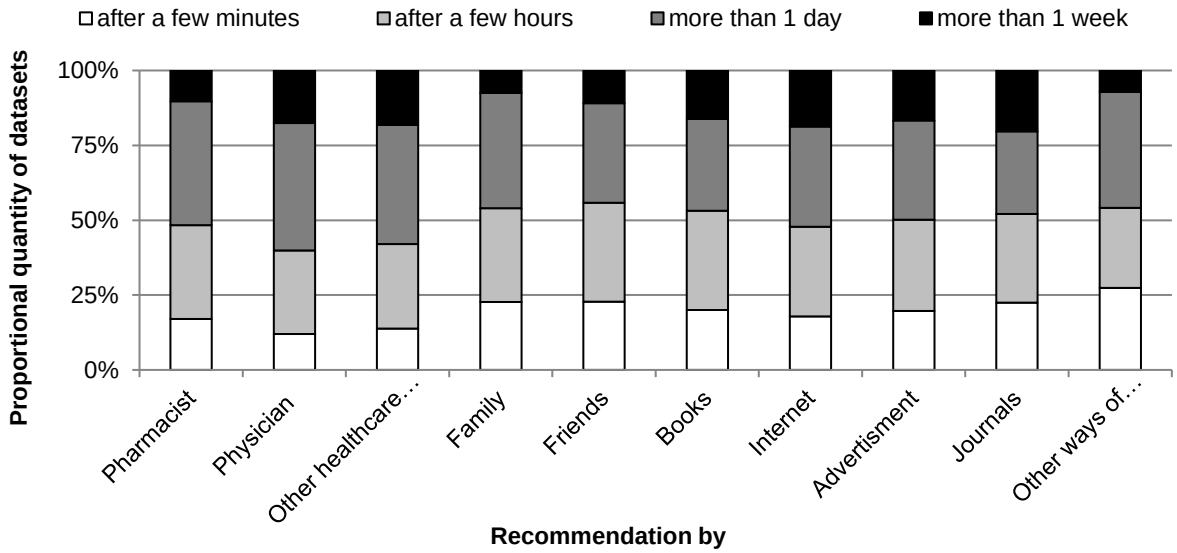

Figure 23: Time to onset of action correlated to the way of recommendation depicted as proportional quantity of datasets.

10.6 Adverse events/adverse reactions

Adverse events, as defined by the European Medicines Agency, were not documented [15].

Adverse reactions (as experienced by the user) were only documented, when the patients had to consult a physician because of the adverse reaction. Of the 20 870 interviewed patients, 172 patients (0.7%) experienced adverse reactions for which they consulted a physician. Of the 172 documented adverse reactions, 142 (82.5%) occurred during daily use. When adverse reactions to clustered age, the proportion of adverse reactions increased with increasing age, resulting in 15 adverse reactions (1.1%) for patients over 75 years. The highest number of

adverse reactions occurred in patients aged between 31 and 50 years (50 documented adverse reactions in 6766 patients, 0.7%).

10.6.1 Adverse reactions in correlation to the CGI-E

In addition to the CGI-E index, side effects were documented by asking for if the patients had to consult a physician because of the experienced adverse reaction. From the 20 870 interviewed patients, 172 datasets (0.7%) documented adverse reaction which were analyzed in correlation to the therapeutic (CGI-E): the mean CGI-E score constituted 1.18 ± 0.90, while the mean CGI-E score constituted 3.11 ± 0.93 for datasets without adverse reactions.

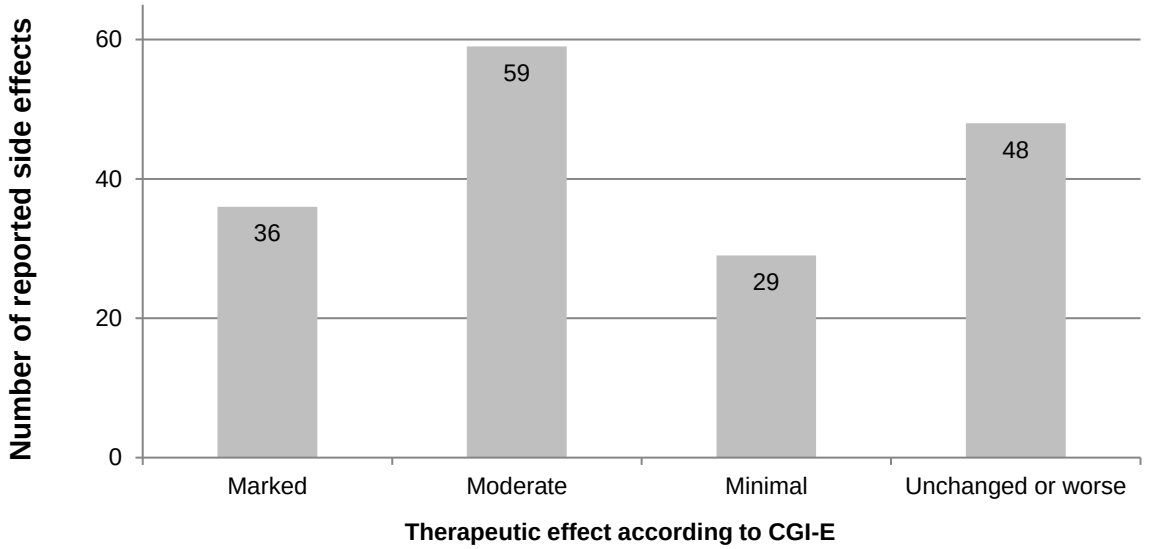

Figure 24: Therapeutic effect according to CGI-E correlated to reported AEs depicted as absolute number of datasets.

Although the patients had to consult a physician because of the experienced adverse reactions, a marked therapeutic effect was documented in 20.9% of the datasets with reported adverse reactions. Despite the experienced adverse reactions, a moderate effect was stated in 34.2% of these datasets and even 16.8% datasets reported a minimal therapeutic effect. Unchanged or worse conditions were documented in 27.8% of the 172 datasets with reported adverse reactions (Figure 24).

Regarding side effects according to CGI-E, 29 datasets (16.9%) reported no side effects, although patients consulted a physician because of the experienced adverse reactions. Insignificant side effects despite of adverse reactions were documented for 34 datasets (19.8%). This increased further to 64 datasets (37.2%) that documented a significant impairment through side effects. For 45 datasets (26.2%) with adverse reactions, side effects outweighed the therapeutic effect.

10.6.2 Adverse reactions in correlation to concomitant diseases and medication

Correlation of reported adverse reactions (as experienced by the users) with concomitant diseases was performed to evaluate if adverse reactions occurred predominantly when patients suffered simultaneously from concomitant diseases. Concomitant diseases were reported in 9 166 of 23 104 valid datasets (39.6%). Of those, 94 datasets (1.0%) stated adverse reactions for which the patients had to consult a physician. In contrast, no concomitant disease was stated in 13 938 datasets (60.3%), of those 78 (0.6%) reported adverse reactions.

Concomitant medication was reported in 10 902 (47.4%) of all valid datasets (23 023). Of those, 85 datasets (0.8%) reported adverse reactions. No concomitant medication was indicated in 12 121 (52.6%) of all valid datasets (23 023), of those 85 (0.7%) reported adverse reactions.

11. Discussion

11.1.1 Key results

For the PhytoVIS study, 20 870 patients were questioned, resulting in 24 058 valid datasets. More than 2/3 of the participants were female (67.3%). Of those, 1.5% were pregnant and 1.0% were lactating. Regarding age distribution, the highest proportion (29.2%) of participants was between 31 and 50 years old, followed by 25.5% aged between 18 and 30 years. Of note, data from infants (0-23 months, 1.3%) and toddlers (2-5 years, 2.2%) was also collected by questioning their parents. Older people (>75 years) accounted for 5.7% of the participants.

Regarding the primary outcome, more than 40% (41.9%) of the datasets showed an excellent therapeutic effect without any side effects. No therapeutic effect was documented in 4.3% of all valid datasets. Of those, 9.3% (corresponds to 0.6% of all datasets) also documented side effects.

Secondary outcomes were recommendation of the product and place of purchase: The products were mainly recommended by pharmacists (35.0%), physicians (26.6%) and family members (22.4%). The products were predominantly purchased in pharmacies (83.9%). Other places of purchase played only a minor role. Of the 1 433 used products, the highest proportion (6.0%) attributed to a product used for gastrointestinal complaints, followed by 4.0%, 3.9% and 3.1% for single products used for upper airway infections, incl. common cold and cough.

The indication, for which the herbal medicinal products were used, were coded using MedDRA LLT or PT. Common colds attributed to more than 1/3 of all indications (common cold: 22.1%, cough: 7.7%, frontal sinusitis: 5.8%, sore throat: 3.5%). In 77.6% of all datasets, phytopharmaceuticals were used because of acute symptoms. This was paralleled by a duration of complaints (before start of treatment) ranging from one day to one week for 38.0% of all datasets. The onset of action after using the phytopharmaceuticals was mainly after more than one day (30.9% of all datasets). In 17.7% of the datasets, the onset of action was not evaluable.

Concomitant diseases and medications were reported in 38.8% and 46.1% of all datasets.

Hypertension was the most stated concomitant disease (17.6%), whereas L-Thyroxin was the most stated concomitant medication (2.3%).

Subgroup analyses for the primary and secondary endpoints showed no statistically significant or clinically relevant differences, but only tendencies.

In this study, adverse reactions were only documented if the patients had to consult a physician because of it. This was the case for 172 of the 20 780 patients (0.7%). As expected, the CGI-E was lower for datasets with a documented adverse reaction (1.18 ± 0.90) than in datasets without adverse reactions (3.11 ± 0.93).

11.1.2 Limitations

Observational research is more prone to bias and confounders than RCTs [16]. This is also the case for the study presented here: The site Cologne was expected to contribute to more than half of the study data, which was expected to result in location bias. This effect was – at least in part – balanced by the participation of other sites throughout Germany (universities of Frankfurt, Kiel and Mainz). Furthermore, since the students autonomously chose the sites for conducting the interviews, several students performed the internship in their home town, leading to a more widespread distribution of interview locations.

Since students of human medicine or pharmacy acted as interviewers, the different focus in their education could have also led to bias. In a preceding pilot study, which was conducted from July 2012 to October 2013 and gained nearly 2 000 data sets, this interference was not seen (unpublished data).

In the observational plan, pharmacies were predefined as the primary location for conducting the interviews. This could lead to location bias and to a shift towards pharmacies as sales locations. Here more than 80% of the phytopharmaceuticals were purchased in pharmacies that could be due to the pre-selection of sites. Bias could have been also generated through the selection of patients. To avoid this, the students were particularly trained on the defined procedure for surveying the patients: The students were instructed not to be selective and to approach the next available patient for the interview. But the willingness of the patient to participate may also bias the results of the study, especially with regard to having time for the interview. This 'having time' stands for many other components of the patient's actual situation and might also depend on the location of the interview place (e.g. busy place downtown, rural) and of its nature (pharmacy, physician's practice). This aspect may also expand to the gender of the interviewees: Since more than 2/3 of the interviewed patients were female, we hypothesize that men are more pressed for time then women and are therefore more reluctant to participate in the interview. This could result in the disbalanced gender distribution observed here.

11.1.3 Interpretation

Two thirds of the participants were female. Furthermore, of those, 1.5% were pregnant and 1.0% were lactating, representing very vulnerable groups, which are normally excluded from clinical studies. In contrast to RCTs, also age or gender was not restricted in this study.

Most of the participants were 31 to 50 years old. This could at least in part be due to the heterogeneous cluster chosen for this study: While this cluster covers 19 years, all other clusters (18 years and older) cover nine to 14 years. With other clustering, age distribution could have shifted in both directions.

Analysis of the CGI-E revealed that most of the patients experienced a moderate or excellent efficacy without any side effects. As expected, the severity of side effects increased with

decreasing efficacy. When correlating the CGI-E with the reason for treatment (acute symptoms, chronic, ailments, prevention), phytopharmaceuticals used for chronic ailments had to lowest CGI-E. Interestingly, phytopharmaceuticals used for prevention had the most datasets with unchanged or worse conditions. Here, patients are often without any symptoms and therefore there is nothing to improve. While acute symptoms had the highest ratio of a marked efficacy, chronic ailments had the highest proportion of moderate and minimal efficacy. This could be due to the nature of acute symptoms, which are relatively easy to cure, whereas chronic ailments are often more severe. As expected, phytopharmaceuticals used for preventive interventions had the best outcome regarding side effects, whereas chronic ailments had the poorest outcome.

Side effects according to CGI-E also increased with increasing severity. While the severity score was 2.75 for datasets without side effects, side effects that outweighed the therapeutic effect had an underlying severity score of 3.40: The phytopharmaceutical products could have difficulties in counteracting the symptoms. This is related to the onset of action, where the CGI-E decreased with increasing time to onset of action. While efficacy decreased, side effects increased with increasing time to onset auf action.

The CGI-E also decreased with an increasing number of concomitant diseases. Symptoms from concomitant diseases can outweigh the good efficacy of a phytopharmaceutical product and the patients experience the product as less effective. In the study presented here, we could not detect differences between patients with or without concomitant diseases.

Phytopharmaceuticals were mainly recommended by pharmacists and physicians, showing that many patients sought professional advice before usage. This correlates to the priority place of purchase: the large majority of phytopharmaceuticals were purchased in pharmacies. However, since the observational plan specified pharmacies as the primary location for conducting the interviews, this could be due to location bias. Interestingly, when correlating dosage forms with the place of purchase, teas were mainly bought in the supermarket and organic grocery stores, but not in pharmacies or via online retailers. Conversely, tablets were mainly bought in pharmacies and via online retailers, but only to a small extent at supermarkets or organic grocery stores. Teas, like chamomile or tea mixtures for e.g. cough are also sold in supermarkets. Although these teas have no drug quality, they are often much cheaper than the medicinal teas sold in pharmacies. In our opinion, this results in the preference of the supermarket by the patients for purchasing teas.

Correlating the CGI-E with the way of recommendation revealed that there were no statistical or clinical differences in the CGI-E with regard to the way of recommendation. This was also the case for the CGI-E correlated to the place of purchase. Though, when comparing the CGI-E categories ‘marked’ and ‘moderate with ‘minimal’ and ‘unchanged or worse’ the difference for pharmacies was about 4 times greater than for the other places of purchase (about 2 times),

showing a tendency towards a better efficacy for phytopharmaceuticals bought at pharmacies. Regarding side effects, no differences (statistically or clinically) were detected. However, the best outcome regarding side effects was for supermarkets as places of purchase. This could be due to the fact that teas – which are most likely not perceived to cause side effects – were primarily bought at supermarkets (76.5%).

Generally speaking, the correlation between the way of recommendation and severity showed that the severity was highest for patients who consulted physicians (2.94) or pharmacists (2.84). This could be because the level of suffering is high and therefore patients tend to seek professional advice for their illness. However, here again, the differences were neither statistically nor clinically relevant. On this basis, the patients could also have high expectations regarding the onset of action of the recommended products. However, the correlation of the way of recommendation with the onset of action showed that this was not the case. Actually, a quick onset of action (‘after a few minutes’ and ‘after a few hours’) was lowest for recommendations made by a physician. This could be because the severity of the underlying disease was highest for this kind of recommendation.

The proportion of adverse reactions, for which patients had to consult a physician, was very low with 172 reported adverse reactions. The majority of adverse reactions occurred during daily use. By daily usage, it is more likely that adverse reactions occur in contrast to usage when needed. As expected, the mean CGI-E of datasets that reported an adverse reaction was considerably but not significantly lower than for datasets without adverse reactions. Interestingly, more than half of the datasets stated a marked or moderate efficacy despite the adverse reactions. This goes in line with the documented side effects: For several datasets, no side effects were documented although patients consulted a physician because of an adverse reaction. However, more than 60% of the patients with a documented adverse reaction had at least significant side effects.

As presumed, the proportion of adverse reactions increased with increasing age: While 0.6% of the patients aged 18 to 30 years old experienced an adverse reaction, the proportion of adverse reactions increased to 1.1% for patients aged 75 and older. If this was due to concomitant diseases or medications – which are common in the elderly - was also analysed. Here, the proportion of adverse reactions in datasets with concomitant diseases was 1.7-fold higher than in datasets without documented concomitant diseases. Interestingly, no differences were detected regarding datasets with or without documented concomitant medications.

11.1.4 Generalization

The PhytoVIS study shows that phytopharmaceuticals are used by the broad public, including pregnant/lactating women, toddlers, children and senior citizens over 75 years.

The patients experienced the phytopharmaceuticals as very effective and with no or only minor side effects. Fortunately, phytopharmaceuticals were primarily recommended by pharmacists and physicians, showing that patients seek professional advice before purchasing a herbal medicinal product. Overall, phytopharmaceuticals were mainly bought in pharmacies, but common products like tea were primarily bought in supermarkets and organic grocery stores. Phytopharmaceuticals are often considered safer in comparison to conventional pharmaceuticals. This could tempt the patients to overdose or to combine the phytopharmaceuticals with other (conventional) medications. This was not seen here: Patients with concomitant diseases and/or concomitant medications showed no differences compared to patients without these issues. Thus, the number of adverse reactions was very low, further demonstrating the good safety of herbal medicinal products.

12. Other information

Not applicable.

13. Conclusions

In conclusion, PhytoVIS is a reliable tool to acquire data on the modes of use of phytopharmaceuticals by the broad public. Because of the high number of data sets, even vulnerable groups like pregnant/lactating women, toddlers, or old people can be investigated. Most patients experienced the used products as highly effective with no or only minor side effects.

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15. Appendices

15.1 List of stand-alone documents

Not applicable.

15.2 Additional information

Not applicable.