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Mapping Physicians' Experiences with Medicinal Products from Whole Medical Systems: A Descriptive Analysis of the *Vademecum of Anthroposophic Medicines*

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Keywords

Anthroposophic Medicine · Clinical experience · Cross-sectional studies · Medicinal products · Practice-based evidence · Whole medical systems

Abstract

Background: Therapy in whole medical systems involves a large number of medicinal products. One source of knowledge of clinical properties of such products is the experience of therapy providers. A systematic approach to documentation, assessment, and aggregation of physicians' experiences with anthroposophic medicinal products (AMPs) has been developed: the *Vademecum of Anthroposophic Medicines*. ***Material and Methods:*** The *Vademecum* contains structured information on AMPs, including therapeutic rationale, indications, and therapy recommendations. The information is based on a 17-item questionnaire of physicians' therapy experiences, which is peer-reviewed by an interdisciplinary editorial board. We conducted a descriptive analysis of the *Vademecum*, 4th edition. ***Results:*** The *Vademecum* comprised 799 different AMPs, used for 1,773 indications, based on 2,543 questionnaires submitted by 274 physicians from 19 countries. The 799 AMPs comprised 52.6% of all AMPs marketed in Germany in 2015–2016. The 1,773 indications corresponded to 544 different ICD-10 three-digit codes, amounting to 29.3% (n = 544/1,854) of all three-digit codes. A total of 30.6% (n = 542/1,773) of indications were supported by ≥2 questionnaires. ***Conclusions:*** The current *Vademecum* covers more than half of all AMPs, used for more than one fourth of all ICD-10 three-digit codes. The *Vademecum* approach may be relevant for medicinal products from other whole medical systems.

Systematik ärztlicher Anwendungserfahrungen mit Arzneimitteln aus ganzheitlichen Therapiesystemen: Eine deskriptive Analyse des Vademecum anthroposophischer Arzneimittel

Schlüsselwörter

Anthroposophische Medizin · Klinische Erfahrung · Spezialitätenübergreifende Studien · Arzneimittel · Praxisbasierte Evidenz · Ganzheitliche Therapiesysteme

Zusammenfassung

Hintergrund: Zur Behandlung in ganzheitlichen Therapiesystemen stehen eine große Anzahl von Arzneimitteln zur Verfügung. Eine Informationsquelle über die klinische

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Anwendung solcher Arzneimittel sind die Erfahrungen der Ärzte bzw. Therapeuten. Für Arzneimittel der anthroposophischen Medizin (AM) wurde ein System zur Dokumentation, Bewertung und Zusammenstellung ärztlicher Anwendungserfahrungen entwickelt: das *Vademecum anthroposophische Arzneimittel*. ***Material und Methodik:*** Das *Vademecum* enthält strukturierte Angaben zu AM-Arzneimitteln, einschließlich therapeutischer Ratio, Indikationen und Anwendungsempfehlungen. Die Angaben basieren auf der Dokumentation ärztlicher Anwendungserfahrungen mittels 17-Punkte-Bögen, die anschließend von einer interdisziplinären Redaktionsgruppe überprüft werden. Wir stellen hier eine deskriptive Analyse des *Vademecum*, 4. Auflage, vor. ***Ergebnisse:*** Das *Vademecum* umfasst 799 unterschiedliche AM-Arzneimittel, die für 1'773 Indikationen empfohlen werden, basierend auf 2'543 Dokumentationsbögen, die von 274 Ärzten aus 19 Ländern ausgefüllt worden waren. Die 799 AM-Arzneimittel machen 52,6% aller AM-Arzneimittel aus, die in den Jahren 2015–2016 in Deutschland auf dem Markt waren. Die 1'773 Indikationen entsprechen 544 unterschiedlichen dreistelligen ICD-10-Codes, was 29,3% (n = 544/1'854) aller dreistelligen ICD-10-Codes ausmacht. Insgesamt 30,6% (n = 542/1'773) aller Indikationen basieren auf 2 oder mehr Dokumentationsbögen. ***Schlussfolgerung:*** Das heutige *Vademecum* deckt mehr als die Hälfte aller AM-Arzneimittel und mehr als ein Viertel aller dreistelligen ICD-10-Codes ab. Der *Vademecum*-Ansatz kann auch für Arzneimittel aus anderen ganzheitlichen Therapiesystemen relevant sein.

Introduction

Whole Medical Systems with Medicinal Products

Whole medical systems are complete systems of theory and practice that have evolved in different regions, cultures and time periods, mostly apart from Western, conventional medicine [1, 2]. Whole medical systems include anthroposophic medicine, ayurveda, naturopathy, traditional Chinese medicine, and unani medicine [2].

Features of whole medical systems include a tradition of use prior to the emergence of current conventional medicine, a holistic, non-reductionist ontological, epistemological and practice orientation, specific diagnostic and therapeutic typologies, and the use of a large number of medicinal products (WMPs, medicinal products from whole medical systems) of herbal, zoological or mineral origin. Because of the different typologies in whole medical systems and conventional medicine, WMPs are often used for a number of different indications according to conventional disease classification [2].

Experiential Literature on Medicinal Products from Whole Medical Systems

Historically, the experiences with WMPs have been summarized in texts (often titled "handbook," "materia medica," "pharmacopoeia," "vademecum," or similar) describing indications, contraindications, therapy recommendations, etc. From the second part of the 20th century onwards, clinical studies have been performed for a number of WMPs. Nonetheless, because of the large number of WMPs and indications, it is not feasible to conduct clinical studies for each indication for each WMP [2]. Therefore, for a large proportion of WMPs, the requirements for obtaining regular marketing authorization (including effect documentation in controlled clinical trials) cannot be met. However, a number of countries have established separate regulatory provisions for some types of WMPs, making use of other types of evidence, including experiential reports, in order to demonstrate at least some plausibility for effects (e.g., Canada [3], Switzerland [4], the European Union [5]).

Much of the experiential literature on WMPs has limitations: therapy recommendations based on the experience of one or a few therapy providers; limited data on how the experiences came about (e.g., what kind of setting, how many patients were treated over what time period); lack of information on how the experiences were aggregated and assessed (e.g., review of medical case records or global recollection from memory).

It should be possible to improve the quality of the experiential literature by a more systematic approach, e.g. incorporating experiences from several therapy providers from different settings and regions, using detailed systematic description of the experiences as well as transparent procedures for data collection and more explicit criteria for the assessment. In this paper we present a quantitative descriptive analysis of one such systematic approach to the therapy experiences with medicinal products from AM.

AM and Anthroposophic Medicinal Products

AM is an integrative whole medical system, founded in Central Europe in the early 1920s by Rudolf Steiner and Ita Wegman [6]. In contrast to most whole medical systems, AM was developed within conventional, Western medicine and is provided by estimated 19,000 physicians in inpatient hospitals and outpatient settings around the world [7]. Physicians are trained in AM according to an international, standardized curriculum but they also use contemporary disease classification systems alongside with AM diagnostic typologies. Medicinal products from AM (AMPs) are manufactured according to specific AM procedures or homoeopathic procedures (involving successive 1:10 dilutions labelled D1, D2, etc.) according to Good Manufacturing Practice and national drug regula-

Table 1. Classification of anthroposophic medicinal product (AMP) groups and individual AMPs

Level	Description
7	AMPs with identical type of starting material or manufacturing procedures
6	AMPs with similar starting materials and manufacturing procedures
5	AMPs with identical starting material but different manufacturing procedures
4	AMPs with identical manufacturer and starting material, but with different dosage forms
3	AMP, including different concentration and pack sizes
2	Specific concentration of an AMP
1	Specific concentration and pack size of an AMP

tions [8]. The available evidence suggests that AMPs are generally well tolerated, with infrequent adverse reactions of mostly mild to moderate severity [9, 10].

AMP therapy is used in virtually all medical fields [6] and involves well over 1,000 products, often used in different combinations [11–15]. Accordingly, for AMP therapy there are several thousand therapy options. Clinical studies have mainly been conducted for mistletoe AMPs and approximately 50 other AMPs [9].

Vademecum of Anthroposophic Medicines

The *Vademecum of Anthroposophic Medicines* [15] (from Latin: *vade mecum* – "walk with me," henceforth abbreviated *Vademecum*) is essentially a collection of structured information about a large number of AMPs, including therapeutic rationale, indications, recommendations for use, and literature references. The *Vademecum* is based on a structured documentation of therapy experiences of several hundred physicians, which is peer-reviewed and processed by an interdisciplinary editorial board (qualifications and demographics of participating physicians and board members are presented in the Results section). The project is independent of AMP manufacturers.

The *Vademecum* originated in an international survey among AM physicians in 2006–2007 and was first published in German in 2008. Since then revised editions and translations (English, Spanish, French, Italian) have appeared; the current 4th German edition was published in 2017 [15]. (In addition, there exists an online Vademecum External Applications in Anthroposophic Nursing, http://www.pflege-vademecum.de, which is not dealt with in this paper.)

The primary target group for the *Vademecum* are physicians prescribing AMPs. The *Vademecum* is published in printed and electronic editions, with information structured according to AMP groups. These groups are pragmatically defined by the *Vademecum* editorial board, whereby each AMP group may include one or several different AMPs with identical or similar starting materials, manufacturing processes or dosage forms, corresponding to the levels 2–6 in Table 1. The information text on each AMP group includes the following items (some items are not provided for all AMPs or indications):

- For each AMP group: name with synonyms, composition, dosage forms, manufacturers, therapeutic rationale according to AM, regulatory approved indications in Germany, literature references
- For each indication of each AMP group: name of indication, typical symptoms, dosage recommendation, onset of action, therapy duration, adjunctive or differential therapy, contraindications, adverse reactions, strength of recommendation, name of the reporting physicians

The information in the *Vademecum* is compiled by a collaboration between the editorial board and reporting physicians: all AM physicians from any country are eligible for participation. For the preparation of new editions, reporting physicians are asked to submit two types of questionnaires, each referring to one indication for one AMP group:

For AMP groups and indications that have not been published in previous *Vademecum* editions, physicians document their therapy experiences in a "new report questionnaire" consisting of 17 items, covering the following topics:

- AMP group: name, manufacturers, country of manufacture
- Description of indication, typical symptoms and findings, triggers and causes, age and gender, constitution type, other relevant modalities
- Dosage: general, for adults and for children
- Time until the effect can be expected or time after which ineffectiveness must be assumed if no effect is registered, first symptoms to improve, average treatment duration
- Adverse reactions, adjunctive and differential therapies
- Approximate number of cases successfully treated in this way, how certain is the physician about the effectiveness of this product
- Additional literature

Each submitted new report is peer reviewed by the editorial board, resulting in either acceptance of the report, request to the reporting physician for clarification, completion of the questionnaire responses, or rejection of the report.

The contents of the accepted new reports are enhanced by therapy experiences of the editorial board members and, if necessary, by a narrative literature review. If the editorial board concludes that the experiential evidence is sufficient for inclusion of the new AMP group and/or

new indication into the next *Vademecum* edition, an information text is written in a consensual process among board members. If the evidence is deemed insufficient, the data are stored in the project database and may be used for subsequent revisions.

For each indication, the strength of recommendation is classified by the editorial board in a consensus process into one of three categories [16]:

- "Well-established, standard AMP therapy" ("both with respect to breadth of application and evidence of effectiveness")
- "Normal indications" ("sufficiently broadly anchored in the observations of experienced, qualified colleagues and therefore suitable for publication")
- "Indications requiring further experience and review" ("because current published medical knowledge is not yet adequate")

For indications that have been previously published, physicians are encouraged to submit "feedback questionnaires" with confirmation of perceived effectiveness of the AMP for the indications in question, reports of non-effectiveness or additional information. This feedback is assessed by the editorial board and, if accepted, incorporated into subsequent Vademecum editions, including the name of the reporting physician.

In the 4th German edition [15], the information on the AMP group of mistletoe (*Viscum album*) products, which are used for cancer and other indications [17], has been expanded into a section of 303 pages, including additional subsections on botany, manufacturing procedures, protocols for specific indications, and overview of clinical trials.

Context for and Aim of the Present Analysis

There is a need for an adequate framework for registration and marketing authorization of AMPs in Europe and worldwide. With regard to this need, the European Scientific Cooperative on Anthroposophic Medicinal Products (ESCAMP – http://www.escamp.org/) was founded. One of the tasks of ESCAMP is to compile and publish research syntheses of the available scientific documentation on the pharmaceutical quality, safety, and efficacy/effectiveness of the entire group of AMPs.

The aim of this analysis is to provide a quantitative description of the *Vademecum*, including the number of AMPs and indications (absolute and relative to all AMPs on the market and all indications for AMP treatment, respectively) and the amount of experiential evidence per indication.

Materials and Methods

Object of the Analysis

The object of this descriptive quantitative analysis was the *Vademecum*, 4th German edition [15] (henceforth "*Vademecum*").

Main Research Questions

- Quantitative description of participating physicians, new report questionnaires, AMPs and their pharmaceutical properties, indications for AMP therapy, safety
- Relative frequencies of AMPs in the *Vademecum* versus AMPs on the market, indications in the *Vademecum* versus all indications in medicine

Variables Analysed

- Participating physicians: gender, country, number of years since medical licensing, specialist qualification, and (only available for editorial board members) setting
- New report questionnaires: country of reporting physician
- Feedback questionnaires: impact on editorial assessment (confirmation of perceived effectiveness of the AMP for the indication in question, addition of critical comments)
- Pharmaceutical properties of AMPs: starting materials, concentration of active substances, route of administration
- Regulatory status of AMPs marketed in Germany: marketing authorization or registration with or without indication
- Indications: classification, strength of recommendation according to the assessment of the *Vademecum* editorial board ("well-established, standard AMP therapy"/"normal indications"/"indications requiring further experience and review")
- Therapy experiences and recommendations: therapeutic action, onset of action (time until the effect can be expected), therapy duration, adjunctive therapy, adverse reactions, contraindications
- Literature references: type and language of reference

Definitions and Classification

The term "AMP groups" in this paper corresponds to the terms "Medicines" and "Arzneimittel" in the English and German *Vademecum* editions, respectively.

AMPs were defined according to the German Medicines Act [18]. For practical purposes, all medicinal products marketed in Germany by the manufacturers Abnoba (Pforzheim, Germany), Helixor (Rosenfeld, Germany), Wala (Bad Boll, Germany), and Weleda (Arlesheim, Switzerland) were classified as AMPs.

AMPs on the German market in the period 2015–2016 were defined as AMPs listed at least once in the pharmaceutical catalogues published by the AMP manufacturers in the years 2015 and 2016.

For AMPs, the main unit of analysis was each product with a separate registration or marketing authorization, corresponding to AMPs with a separate entry in the pharmaceutical catalogues of the respective manufacturers. This category includes different potencies and pack sizes of otherwise identical AMPs (level 3 in Table 1). Accordingly, AMPs listed together within a separate entry but marketed in different concentrations or pack sizes were grouped together.

For individual AMPs and AMP groups, generic terms were used; for AMPs with more than one starting material, all starting materials were listed.

The term "indication" in this paper refers to indications described in the *Vademecum* and does not imply that the respective product is approved for the "indication" in Germany or any other country.

Data Collection and Preparation

Two variables pertaining to the participating physicians (number of years since medical licensing, specialist qualification) were not documented in the *Vademecum* project. As a substitute, corresponding data were extracted from the database of the Association of Anthroposophic Physicians in Germany (GAÄD). From

this database, number of years since medical licensing was available for 43.8% (n = 116/265) of all physicians and for 66.3% (n = 110/166) of physicians from Germany. Specialist qualification was available for 74.3% (n = 197/265) of all physicians and for 78.3% (n = 130/166) of physicians from Germany. Missing data were not replaced.

All other data were extracted from the *Vademecum* database (Interleave GmbH, Munich, Germany), using SQL queries. The *Vademecum* database contains all texts and data in the *Vademecum* since the first edition from 2008; for the variables analysed in this paper, there were no missing data.

The AMP groups of the *Vademecum* were coded as level 3 AMPs (Table 1) by checking with the ESCAMP database of AMPs (ESCAMP e.V., Freiburg, Germany). The ESCAMP database contains, amongst others, detailed pharmaceutical data for all AMPs marketed in Germany since 2000.

Pharmaceutical properties of AMPs were classified according to the *Anthroposophic Pharmaceutical Codex* (APC 4.1 [8]). For analysis of starting materials of mineral origin, the categories 2.1 and 2.4 in the APC were grouped together.

Indications were coded according to the International Classification of Diseases, 10th revision (ICD-10). Adverse reactions were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0, MedDRA MSSO, McLean, VA, USA).

The variables "onset of action" and "therapy duration" were documented in free text and categorized for analysis. For both variables, a proportion of responses was given as ranges (e.g., 1–3 days). For the analyses the maximum time period was used.

For calculation of the concentration or decimal potency of AMPs with more than one active substance, the substance with the lowest potency was used. For AMPs of the group Iscucin, which are potentized in successive 1:20 dilution, the corresponding decimal potency (1:10 dilution) was used.

Data Analysis

Data analysis was performed using IBM SPSS Statistics 25® (International Business Machines Corp., Armonk, NY, USA). Analysis was descriptive without hypothesis testing. The relative frequencies of AMPs in the *Vademecum* versus AMPs on the German market were analysed in subgroups according to marketing status in Germany (all 2 subgroups), route of administration (3 most frequent subgroups) and origin of starting material (3 most frequent subgroups).

Results

Overview

The *Vademecum* comprised 625 different AMP groups used for 1,773 different indications, based on a total of 2,543 new report questionnaires submitted by 274 physicians. The 1,773 indications were supplemented with a total of 19,328 citations of 2,389 different literature references.

Participating Physicians and New Report Questionnaires

Of the 274 participating physicians, 264 submitted questionnaires individually, while 10 physicians from Milan, Italy, submitted questionnaires collectively. In the present analysis, the latter 10 physicians were counted as one, resulting in n = 265 physicians. These were working in Germany (62.6%, n = 166/265), Switzerland (13.6%, n = 36), the Netherlands (6.0%, n = 16), Austria (3.8%, n = 10), Italy (3.8%, n = 10), France (2.3%, n = 6), Sweden (1.9%, n = 5), or other countries (6.0%, n = 16), altogether in 19 different countries. A total of 65.3% (n = 173/264) of physicians were men and 34.3% (n = 91) were women. Physicians had a mean 33.5 years (standard deviation [SD] 9.9, median 33.0 years, interquartile range [IQR] 26–40 years, range 10–66 years, n = 116 physicians evaluable for this item) of experience since their medical licensing and were qualified as family physicians (54.8%, n = 108 of 197 evaluable physicians), internists (15.7%, n = 31), paediatricians (10.2%, n = 20), gynaecologists (5.6%, n = 11), neurologists (2.5%, n = 5), or another of 8 different specialties (11.2%, n = 22).

The editorial board preparing the 4th edition of the *Vademecum* consisted of 10 physicians (8 male, 2 female, all 10 were also participating physicians) from 4 countries (Austria, Brazil, Switzerland, Germany) with specialist qualification in family medicine (n = 2), paediatrics (n = 2), obstetrics and gynaecology (n = 1), internal medicine (n = 6), haematology and oncology [2]. Their medical work was or had been mainly in inpatient hospitals (n = 4) and outpatient settings (n = 6).

The 2,543 new report questionnaires were submitted from: Germany (63.7% of reports, n = 1,619/2,543), Switzerland (12.8%, n = 325), Italy (9.7%, n = 246), Austria (6.5%, n = 166), the Netherlands (2.0%, n = 51), or from other countries (5.3%, n = 136).

Each physician submitted 1–4 new report questionnaires (66.4% of physicians, n = 176/265), 5–9 questionnaires (17.0%, n = 45), 10–19 questionnaires (8.3%, n = 22) or ≥20 questionnaires (8.3%, n = 22) with a median of 3 questionnaires per physician (IQR 1–7, mean 9.6, range 1–231 questionnaires).

AMP Groups and AMPs

Of the 625 AMP groups, 23.0% (n = 144) had a description of the therapeutic action.

A total of 97.3% (n = 608/625) of AMP groups were marketed in at least one country, 1.6% (n = 10) were available as magistral prescription, and 1.1% (n = 7) were not AMPs according to the definition (see Methods section) (other medicinal products: n = 3, body care products: n = 4).

Of the 608 AMP groups marketed in at least one country, n = 586 (96.4%) were marketed in Germany, corresponding to 799 different AMPs (level 3 in Table 1). All following results in this section refer to these 799 AMPs.

Of the 799 AMPs, 63.2% (n = 505/799) had a marketing authorization or registration with indication while 36.8% (n = 294) were marketed without indication. With a few exceptions, these two categories correspond to

Table 2. Concentration of anthroposophic medicinal products (AMPs)[1]

Concentration	Number	Percent
Concentrated form[2]	180	10.7
Mother tincture	56	3.3
D1	39	2.3
D2	117	7.0
D3	168	10.0
D4	87	5.2
D5	124	7.4
D6	235	14.0
D7–D11	232	13.8
D12–D15	210	12.5
D16–D30	229	13.6
D40–D60	6	0.4
Total AMPs	1,683	100.0

[1] AMPs of level 2 in Table 1. For AMPs with more than one active substance, the highest concentration or lowest potency is used.
[2] Neither potentized nor mother tincture.

Table 4. Anthroposophic medicinal product (AMP) groups with at least 10 indications each

	AMP group	Indications	
		n	%
1	*Viscum album*	85	4.8
2	Argentum metallicum praeparatum	17	1.0
3	*Onopordum/Hyoscyamus/Primula*	14	0.8
4	Aurum metallicum praeparatum	13	0.7
5	*Formica*	12	0.7
6	Arandisite	11	0.6
7	*Belladonna*	11	0.6
8	Mercurius vivus naturalis	11	0.6
9	Quartz	11	0.6
10	*Aesculus/Equisetum/Solum*	11	0.6
11	Stibium metallicum praeparatum	11	0.6
12	*Arnica* (planta tota)	10	0.6
13	Ferrum sulfuricum/Mel/Vinum/Quartz	10	0.6
14	Phosphorus	10	0.6
15	*Plantago/Primula/Hyoscyamus*	10	0.6
	All other AMP groups	1,526	86.1
	Total indications	1,773	100.0

AMPs manufactured according to an anthroposophic or homoeopathic procedure, respectively.

Starting material for the AMPs was a single parent substance according to APC 4.1 (49.7%, *n* = 397/799), a mixture of several parent substances (40.8%, *n* = 326), a composition (6.5%, *n* = 52), and other (0.5%, *n* = 4). Of the 397 AMPs with a single parental substance as starting material, the origin of the substance was mineral (25.7%, *n* = 102/397), botanical (42.6%, *n* = 169), zoological (23.7%, *n* = 94), or it was a starting material having undergone special treatment (8.1%, *n* = 32).

Table 3. Route of administration of anthroposophic medicinal products (AMPs) marketed in Germany

Route of administration	AMPs in *Vademecum*	
	n	%
Parenteral (injections)	352	44.1
Oral	326	40.8
Cutaneous	81	10.1
Rectal	15	1.9
Ophthalmic	14	1.8
Nasal	4	0.5
Oromucosal	4	0.5
Vaginal	2	0.3
Auricular	1	0.1
Total	799	100.0

The 799 different "level 3" AMPs (AMPs of different concentrations, potencies grouped together: level 3 in Table 1) corresponded to n = 1,683 different "level 2" AMPs (each concentration or potency counted separately: level 2 in Table 1). For each of these 1,683 AMPs, the substance with the highest concentration was in concentrated form or a mother tincture in 14.0% (*n* = 236/1,683) of AMPs, a D1–D3 potency in 19.3% (*n* = 324) and in a ≥D4 potency in 66.7% (*n* = 1,123) (further details in Table 2).

The most frequent routes of administration of the AMPs were parenteral (i.e., injection, 44.1%, *n* = 352/799), oral (40.8%, *n* = 326), and cutaneous (10.1%, *n* = 81) (Table 3).

Indications

Of the 625 AMP groups in the *Vademecum*, 0.2% (*n* = 1/624) had no indication, 42.6% (*n* = 266) had 1 indication, 19.2% (*n* = 120) had 2 indications, 13.6% (*n* = 85) had 3 indications, 7.0% (*n* = 44) had 4 indications, and 17.4% (*n* = 109) had ≥5 indications, with a total of 1,773 indications (median 2 indications per AMP; IQR 1–3, mean 2.8, SD 4.0, range 0–85 indications); AMPs with ≥10 indications are listed in Table 4.

The indications were based on an assessment by the *Vademecum* editorial board plus new report questionnaires. A total of 5.2% (*n* = 92/1,773) of indications had no new report questionnaire, 64.2% (*n* = 1,139) had 1 questionnaire, 18.4% (*n* = 326) had 2 questionnaires, and 12.2% (*n* = 216) had ≥3 questionnaires, with a mean of 1.43 questionnaires per indication (SD 0.92, median 1, IQR 1–2, range 0–7 questionnaires).

In addition to the new report questionnaires, 7.8% (*n* = 136/1,733) of indications had been commented on in feedback questionnaires (127 indications had 1 questionnaire, 8 indications had 2, and 1 indication had 3 feedback questionnaires), leading to (a) confirmation of perceived effectiveness of the AMP for the indication in question

Table 5. Indications: ICD-10 diagnosis chapters

ICD-10 chapter	Number	Percent
J00–J99 Diseases of the respiratory system	254	11.4
M00–M99 Diseases of the musculoskeletal system and connective tissue	232	10.4
F00–F99 Mental and behavioural disorders	219	9.9
K00–K93 Diseases of the digestive system	190	8.5
R00–R99 Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	181	8.1
N00–N99 Diseases of the genitourinary system	160	7.2
L00–L99 Diseases of the skin and subcutaneous tissue	152	6.8
I00–I99 Diseases of the circulatory system	141	6.3
C00–D48 Neoplasms	128	5.8
G00–G99 Diseases of the nervous system	114	5.1
A00–B99 Certain infectious and parasitic diseases	96	4.3
S00–T98 Injury, poisoning, and certain other consequences of external causes	91	4.1
H60–H95 Diseases of the ear and mastoid process	57	2.6
O00–O99 Pregnancy, childbirth, and the puerperium	53	2.4
E00–E90 Endocrine, nutritional, and metabolic diseases	53	2.4
H00–H59 Diseases of the eye and adnexa	44	2.0
D50–D89 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	23	1.0
P00–P96 Certain conditions originating in the perinatal period	14	0.6
Q00–Q99 Congenital malformations, deformations, and chromosomal abnormalities	14	0.6
Z00–Z99 Factors influencing health status and contact with health services	7	0.3
V01–Y98 External causes of morbidity and mortality	0	0.0
U00–U85 Codes for special purposes	0	0.0
Total ICD-10 diagnoses	2,223	100.0

(n = 131 indications), (b) addition of critical comments such as lack of effectiveness in some cases (n = 3 indications), or both (n = 2 indications).

The level of evidence for the 1,773 indications was classified by the *Vademecum* editorial board as "well-established, standard AMP therapy" (10.9%, n = 193/1,773 indications), "normal indications" (80.4%, n = 1,426), and "indications requiring further experience and review" (8.7%, n = 154).

Coding the 1,773 indications according to ICD-10, 80.4% of indications (n = 1,425/1,773) corresponded to one ICD-10 code, 13.6% (n = 241) of indications had 2 codes, 4.1% (n = 72) had 3 codes, 1.6% (n = 28) had 4–6 codes, and 0.4% (n = 7) were uncodable, resulting in a total of 2,223 ICD-10 three-digit codes, thereof 544 different codes:

- The most frequent ICD-10 diagnosis chapters were J00–J99 respiratory disorders (11.4%, n = 254/2,223 diagnoses), M00–M99 musculoskeletal disorders (10.4%, n = 232), and F00–F99 mental and behavioural disorders (9.9%, n = 219) (Table 5)
- The most frequent ICD-10 diagnosis blocks were F40–F48 neurotic, stress-related and somatoform disorders (4.5%, n = 101/2,223), J30–J39 other diseases of upper respiratory tract (3.7%, n = 83), N80–N98 non-inflammatory disorders of female genital tract (3.7%, n = 83), C00–C75 malignant neoplasms (3.5%, n = 77), and L20–L30 dermatitis and eczema (3.5%, n = 77)

Table 6. Indications: ICD-10 three-digit codes

ICD-10 code	Number	Percent
J45 Asthma	33	1.5
L20 Atopic dermatitis	33	1.5
F32 Depressive episode	31	1.4
L30 Other dermatitis	29	1.3
F41 Other anxiety disorders	28	1.3
J32 Chronic sinusitis	28	1.3
G47 Sleep disorders	26	1.2
N94 Pain and other conditions associated with female genital organs and menstrual cycle	25	1.1
I10 Essential (primary) hypertension	24	1.1
R53 Malaise and fatigue	23	1.0
M54 Dorsalgia	23	1.0
R10 Abdominal and pelvic pain	20	0.9
T88 Other complications of surgical and medical care, not elsewhere classified	20	0.9
C50 Malignant neoplasm of breast	20	0.9
F45 Somatoform disorders	20	0.9
J18 Pneumonia, organism unspecified	20	0.9
All other ICD-10 diagnoses	1,820	81.9
Total ICD-10 diagnoses	2,223	100.0

- The most frequent ICD-10 three-digit codes were J45 asthma (1.5%, n = 33/2,230 diagnoses), L20 atopic dermatitis (1.5%, n = 33), and F32 depressive episode (1.4%, n = 31) (Table 6)

Table 7. Anthroposophic medicinal products (AMPs) in *Vademecum* versus AMPs in Germany

AMPs	In *Vademecum*	Marketed in Germany 2015–2016	In *Vademecum*/ in Germany, %
All types	799	1,519	52.6
Marketed			
With indication	505	857	58.9
Without indication	294	661	44.5
Route of administration[1]			
Parenteral (injections)	352	744	47.3
Oral	326	532	61.3
Cutaneous	81	160	50.6
Origin of starting material[1, 2]			
Mineral	102	144	70.8
Botanical	169	352	48.0
Zoological	94	263	35.7

[1] Three most common categories. [2] Analysis restricted to AMPs with one starting material.

Onset of Action and Therapy Duration

Onset of action was indicated for 67.3% (n = 1,194/1,773) of indications and categorized as: <1 h or "immediately" in 12.6% (n = 151/1,194 of indications), 1–23 h in 10.0% (n = 119), 1–6 days in 25.9% (n = 309), 7–27 days in 24.5% (n = 292), ≥28 days in 15.1% (n = 180), "rapid" (German *rasch*) or similar in 7.7% (n = 92), "slow" in 1.0% (n = 12), and not categorizable in 3.3% (n = 39).

Therapy duration was indicated for 65.1% (n = 1,555/1,173) of indications and was categorized as: "single application" in 0.3% (n = 4/1,155) of indications, <7 days in 9.9% (n = 114), 1–5 weeks in 27.3% (n = 315), 6 weeks to 3 months in 16.2% (n = 187), >3 months in 37.1% (n = 429), and not categorizable in 9.2% (n = 106).

Recommendations for Adjunctive Therapy

Recommendations for adjunctive therapy, e.g. with other AMPs or non-medication anthroposophic medical treatment were given for 43.9% (n = 778/1,773) of indications.

Adverse Reactions and Contraindications

Adverse reactions were documented for 10.2% (n = 64/625) of AMP groups, with a total of 116 free text entries of adverse reactions, corresponding to 152 MedDRA codes. Most frequent MedDRA high-level group terms for adverse reactions were administration site reactions (30.3%, n = 46/152), general system disorders, not elsewhere classified (14.5%, n = 22), epidermal and dermal conditions (7.9%, n = 12), allergic conditions (7.2%, n = 11), and body temperature conditions (7.2%, n = 11). Most frequent MedDRA system organ classes were general disorders and administration site conditions (52.0%, n = 79/152), psychiatric disorders (9.9%, n = 15), skin and subcutaneous tissue disorders (9.9%, n = 15), gastrointestinal disorders (7.9%, n = 12), and immune system disorders (7.2%, n = 11).

In addition to adverse reactions, the physicians documented contraindications to 5 AMP groups (this item was not specifically mentioned in the questionnaire).

Literature References

The *Vademecum* database comprised a total of 3,568 different literature references, thereof 56.2% (n = 2,005/3,568) journal articles, 37.9% (n = 1,353) book chapters, 4.8% (n = 172) books, and 1.1% (n = 38) Internet sources. Of the 2,005 journal article references, 66.2% (n = 1,327) were from *Der Merkurstab (Journal of Anthroposophic Medicine)* (from 1946 to the present, current German name used since 1988). The references were in German (89.9%, n = 3,207/3,568) or English (10.1%, n = 361) language.

In the digital version of the *Vademecum*, a list of literature references is included for each AMP group. Of the 625 AMP groups, 2.6% (n = 16/625) had no reference, 4.8% (n = 30) had 1–4 references, 14.1% (n = 88) had 5–9, 30.1% (n = 188) had 10–19, 34.2% (n = 214) had 20–49, 9.6% (n = 60) had 50–99, and 4.6% (n = 29) had ≥100 references, with a median of 19 references per AMP group (IQR 10–34, range 0–1,320, mean 30.9 references).

AMPs and Indications in the Vademecum: *Relative Frequencies*

The number of AMPs in the *Vademecum* marketed in Germany (n = 799) amounted to 52.6% (n = 799/1,519) of all AMPs marketed in Germany in 2015–2016. Among 8 selected AMP subgroups (marketing status [2 subgroups], origin of starting material [3 subgroups], route of administration [3 subgroups]), this proportion ranged from 35.7% (AMPs with 1 starting material of zoological origin, n = 94/263 AMPs) to 70.8% (AMPs with 1 starting material of mineral origin, n = 102/144) (Table 7).

The number of indications in the *Vademecum*, coded as ICD-10 diagnoses, was compared to all regularly used diagnoses in the ICD-10 classification system. For this analysis, the chapter U00–U85 codes for special purposes was excluded. The *Vademecum* had diagnoses in 95.2% (n = 20/21) of ICD-10 diagnosis chapters and 75.9% (n = 161/219) of ICD-10 diagnosis blocks, and the *Vademecum* ICD-10 three-digit codes amounted to 26.6% (n = 544/2,042) of all three-digit codes (Table 7).

Discussion

Overall Results

In this first comprehensive quantitative description of the *Vademecum*, the AMP groups listed amounted to 53% of all AMPs on the German market in 2015–2016. The indications for the AMPs amounted to 27% of all three-digit ICD-10 codes. Indications were based on new report questionnaires submitted by 274 physicians from 19 different countries plus assessment by the editorial team; 31% of indications were supported by 2 or more new reports.

Strengths and Limitations

Compared to much other experiential literature on WMPs, the *Vademecum* has a number of strengths, including a systematic, detailed and transparent documentation of clinical experiences, the broad international participation of experienced physicians, critical peer review of all reports, and independence of industry. Moreover, in addition to therapy recommendations, the *Vademecum* also provides readers with a comprehensive literature list for each AMP group. With regard to external validity, because of the high number of participating physicians from a range of countries, the information in the *Vademecum* can be assumed to be representative for the experiences of AMP prescribers.

On the other hand, compared to clinical studies, all experiential literature including the *Vademecum* has a fundamental design limitation in the retrospective overall assessment of the AMP therapy option, instead of prospective documentation of consecutive patients with the possibility of control groups. In spite of the detailed documentation structure of the *Vademecum*, the retrospective overall assessments can be biased in several ways (e.g., imprecise or selective memory, biased overall assessments) [19]. However, due to prohibitive costs, it is not feasible to conduct clinical studies for more than a fraction of all AMPs and indications. Accordingly, for a large proportion of AMPs, clinical documentation will have to rely on other types of evidence such as experiential literature including the *Vademecum*.

Interpretation and Comparison to Other Studies

Nearly all *Vademecum* indications (99.6%) could be coded as one or several diagnoses of the ICD-10 system, and these indications amounted to 29% of all ICD-10 three-digit codes. This reflects the strong conceptual and practical integration of AM with conventional medicine, with AMP therapy used in most medical specialties. AM involves various typologies [Baars et al., submitted 2019] but these complement rather than replace conventional medical nosology. In contrast, only one fourth of AMP groups in the *Vademecum* had a description of the therapeutic action according to AM; in this respect there seems to be room for improvement. Also, less than one third of indications were supported by at least 2 new reports; an increased number of new reports per indication would give more support of plausibility for the information.

The most frequent route of administration of AMPs (44%) was parenteral, reflecting the high importance of injections in AMP therapy [20].

For almost one third of indications, the onset of action of the AMP was described as "rapid" or within 24 h. Such a rapid onset of action (and time period after which ineffectiveness can be assumed if no effect is registered) can be used by clinicians to monitor therapy and could be investigated further in clinical studies [21].

At the other end of the time horizon, for more than one third of indications the therapy duration exceeded 3 months, which is often needed in AMP therapy for chronic diseases [23].

Adverse reactions were reported for 10% of AMP groups. In comparison, in the EvaMed pharmacovigilance study of more than 300,000 AMP prescriptions to more than 40,000 patients, medically confirmed adverse reactions occurred to 5% of AMPs [10]. The higher frequency of adverse reactions in the *Vademecum* compared to EvaMed could be related to a longer observation time (lifetime experience of *Vademecum* physicians vs. follow-up of mean 27 months in EvaMed).

Implications and Future Developments

The *Vademecum* has been developed as a guidance tool for physicians prescribing AMPs, and the results of this analysis can serve as feedback to the *Vademecum* project.

In addition, the *Vademecum* can be used as a source of experiential evidence for scientific and regulatory assessment of AMPs. ESCAMP is developing a scientific basis for an appropriate regulatory framework for AMPs, and the results of this analysis can yield background information for scenario analyses with alternative regulatory models: "If a certain set of criteria is applied for experiential evidence, what proportion of AMPs and indications would fulfil these criteria in the current *Vademecum*?" and "What would need to be added, in

order to increase this proportion by a certain degree?" Furthermore, for specific AMPs or AMP groups, the effort and benefit of added experiential evidence in the *Vademecum* project can be weighed against other approaches to increase the evidence base, such as high-quality case reports [22, 24], registry and real-world data studies, and clinical trials.

Notably, if the *Vademecum* is to be used for regulatory purposes, certain technical limitations of the present version should be overcome. This issue has been discussed at length elsewhere [19], and corresponding work to improve future editions has started.

This quantitative description of the *Vademecum* documentation system for therapy experiences of AM physicians with AMPs may also be useful for similar projects for other WMPs. In Germany, such a project has been launched (Hufeland-Vademecum, http://www.hufeland-gesellschaft.de/vademecum.html). The *Vademecum* approach may also be relevant for screening programmes for medicinal plants as potential drugs for specific diseases [25].

Conclusions

This analysis of the *Vademecum of Anthroposophic Medicines* shows that it is possible to document, critically assess, and aggregate experiential evidence among a large group of therapy providers for a large number of WMPs in a systematic and transparent way. The *Vademecum* has a potential for scientific and regulatory assessment of AMPs, and the *Vademecum* approach may be relevant for WMPs from other whole medical systems and for screening programmes for medicinal plants as potential drugs for specific diseases.

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Statement of Ethics

This analysis does not include any data on treatment of individual patients, hence no ethical approval was necessary. Data were derived from sources publicly available for a small charge (*Vademecum*, 4th edition [15]). The publication was prepared according to the STROBE guidelines for cross-sectional observational studies [26].

Disclosure Statement

H.J.H. is member of the GAÄD and is scientific director and president of ESCAMP. G.S. and A.G. are members of ESCAMP. J.M. is secretary of GAÄD. G.S. is member of the Extended Board of the GAÄD, member of the Commission C of the Federal Institute of Drugs and Medical Devices (BfArM), and deputy head of the Medical Section at the Goetheanum.

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Author Contributions

G.S. is co-founder and co-manager of the *Vademecum* project. J.M. is responsible for the *Vademecum* database, extracted data for analysis, had access to all data, and is guarantor. H.J.H. and A.G. wrote the analysis plan. A.G. and J.M. analysed data. H.J.H. was principal author. All authors participated in critical revision of the manuscript and approved the final paper.

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