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Review article

# The benefit/risk balance of subcutaneous injections as used in homeopathy and anthroposophic medicine: A narrative literature review

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ABSTRACT

*Introduction:* This review explores the benefit/risk balance of using subcutaneous injections. Overall, regulatory authorities regard that the use of injectables are only justified for acute cases and that oral products are better alternatives for both ethical and safety reasons. Conversely, Complementary & Alternative Medicine (CAM) pharmaceutical companies and doctors who prescribe injectables consider them to have additional clinical value compared with the oral route of administration (ROA), and consider the risk of the parenteral ROA as very low.
*Methods:* A narrative review was conducted. The favourable and unfavourable effects, the uncertainty of the effects and the possible mode of action of the subcutaneous ROA are described and an estimation of the benefit/risk balance is performed.
*Results:* The review demonstrates a high prescribers demand, and evidence on the existence of several favourable effects of the subcutaneous ROA (e.g., higher clinical efficacy, higher bio-availability, quicker onset of action), some unfavourable low risk effects of the subcutaneous ROA (e.g., risk related to exposure, substance and the needle) and overall a positive benefit/risk balance.
*Conclusion:* The results justify a more positive attitude from regulatory authorities towards the use of this ROA and towards ampoule prescribing doctors. However, given the small number of good studies on this topic, more research on the favourable and unfavourable effects, the uncertainties of these effects and the conceptualization of the working mechanism of the subcutaneous ROA is indicated.

## 1. Introduction

Current European standards demand medicinal products of high quality, safety and benefit. Therefore, pharmaceutical companies have to provide evidence of the benefits (e.g., efficacy/effectiveness), risks (e.g., quality, adverse events), and of the benefit/risk balance of their products. Subsequently, the European Medicines Agency (EMA) or national regulatory authorities can recommend the authorization of a medicinal product whose benefits are judged to be larger than its risks. In contrast, a medicine whose risks outweigh its benefits cannot be recommended for marketing [1].

In several pharmaceutical companies producing products used in CAM (Complementary and Alternative Medicine) practice, such as anthroposophic or homeopathic practices, one of the important types of products are the ampoules that are prescribed by doctors for parenteral administration (most often subcutaneous, sometimes intravenous).

Homeopathic and anthroposophic literature documents the use of injectables for over 100 years [2]. Today there are more than 90 million homeopathic/anthroposophic ampoules sold each year, prescribed by doctors for subcutaneous or other parenteral administration [3]. CAM pharmaceutical companies consider the subcutaneous or other parenteral ROA to have a surplus clinical value for clinical practice compared to the oral ROA [4]. In addition they consider the risk of the parenteral ROA in general very low. So overall CAM pharmaceutical companies regard the parenteral ROA to have a positive benefit/risk balance.

However, authorities in several European countries increasingly consider oral products to be better alternatives for ethical and safety reasons. Most important reason for this position is that the oral route of administration (ROA) is not intrusive and therefore has no health related risks associated with injections. In addition, it is claimed that there is currently neither a valid scientific concept of the surplus value of the subcutaneous route of administration, nor is there sufficient empirical evidence that demonstrates its clinical relevance. On the other hand, substantial evidence is also lacking for the position that ampoules prescribing doctors act unethically and expose their patients

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to unacceptable risks.

In order to acquire acceptance from the regulatory authorities for this ROA, scientific evidence has to be provided. This study therefore explores the current scientific evidence with regard to the surplus value, the risks and the benefit/risk balance of the parenteral ROA. Since the subcutaneous ROA is by far the most often used ROA compared to the intravenous ROA, this study is limited to this ROA.

## 2. Methods

A narrative review of the literature was executed on specific topics concerning the hypothesized surplus value, risks and the benefit/risk balance of this ROA. The following topics were explored:

1. With regard to the preconditions of assessing benefit/risk balances the following topics were studied:
   a. The categories and definitions of benefits and risks.
   b. The procedures to assess benefit/risk balances.
2. With regard to the hypothesized surplus value of the subcutaneous ROA the following topics were studied:
   a. The need/demand of the prescribers regarding the availability of ampoules and the reasons for this need (review of *practice-based evidence/expert knowledge*: clinically perceived surplus value of expert prescribers).
   b. The specific clinical effect of the ROA (review of the *empirical evidence from clinical research* comparing the subcutaneous and oral ROA).
   c. The mechanism of the ROA (review of the *mechanistic evidence/theoretical* added value of the subcutaneous ROA).
3. With regard to the risks and the hypothesized positive benefit/risk balance the following topics were studied:
   a. The risks and the magnitude of the risks of this ROA.
   b. The overall benefit/risk balance of this ROA.
4. With regard to the consequences of removing this ROA on the market the following topics were studied:
   a. The consequences for medicinal products in general.
   b. The consequences for anthroposophic medicinal products and homeopathic medicinal products.

### 2.1. Databases and other sources

We searched the website of EMA to study topic 1 and the databases PubMed, Google Scholar, and the Internet for topics 2–4, from the dates of their inception to May 2016. Combinations of the following search terms were used related to routes of administration (oral vs. subcutaneous), effects, safety, and two CAM specific medical systems: efficacy, effectiveness, route of administration, safety, vaccinations, oral, subcutaneous, parenteral, benefits, risks, acupuncture, immunotherapy, adverse reactions, adverse events, anthroposophy, homeopathy. Since this was a narrative review with an expected small number of relevant publications, all publications relevant for topics 1 to 4 were included in the analyses.

### 2.2. Analyses

The favourable and unfavourable effects and the uncertainty of the effects of the subcutaneous ROA are described and quantified, using the quantative results from the studies reviewed. An estimation of the absolute benefit/risk balance was performed, based on the input from the publications.

## 3. Results

### 3.1. Selection of studies

For choosing the *categories and definitions of benefits and risks and the procedures to assess benefit/risk balances*, we used the documents from the working group of the Committee for Medicinal Products for Human Use (CMPH) of EMA, that had worked on this topic. As a result two documents were used in this review.

**Table 1**
Overview of databases, search terms, numbers of hits and selected studies.

| Database | Search terms | Number of hits |
|---|---|---|
| PubMed | oral AND subcutaneous/injection | 47,110/11,559 |
| | oral AND subcutaneous/injection AND anthroposophic/anthroposophy | 0 |
| | oral AND subcutaneous AND homeopathic/homeopathy | 6 |
| | oral AND injection AND homeopathic/homeopathy | 9 |
| Google Scholar | oral AND subcutaneous/injection | 655,000/2.380,000 |
| | oral AND subcutaneous AND anthroposophic | 265 |
| | oral AND subcutaneous AND homeopathic/homeopathy | 3,880/3,870 |
| | oral AND injection AND anthroposophic/anthroposophy | 693/397 |
| | oral AND injection AND homeopathic/homeopathy | 10,900 |

The rest of the search strategy involved the use of multiple search terms with 'oral, subcutaneous or injection' as the basic search term. Other search terms were added alone or in combinations during the selection process: 'effects', 'safety', 'efficacy', 'effectiveness','route of administration', 'safety', 'vaccinations', 'benefits', 'risks', 'acupuncture', 'immunotherapy', 'adverse reactions', 'adverse events', 'anthroposophy or anthroposopic', 'homeopathy or homeopathic'. The search was limited by language (English).

The initial search ('oral AND subcutaneous OR injection') resulted in 11,559–2,380,000 hits in PubMed and Google Scholar (Table 1). In order to narrow down the numbers of results, one or more combinations of other search terms were used in addition. During the review process, based on the first results, it was decided to search for reviews on safety of acupuncture ("risk of the needle") and on the relationship between the extracellular matrix and subcutaneous injections ('location effects').

Then the abstracts and/or title of each publication were scanned to determine relevance to the research questions and publications and were included if they were able to provide an answer to one of the research questions. Papers retained at this stage were then read in more detail to determine their relevance to the research questions. The majority of papers were excluded at this stage as they were descriptive on use of oral and subcutaneous injections providing no answers on benefits or risks.

Finally forty-two articles were included that provided information on: practice-based evidence (4), empirical evidence from clinical studies comparing the subcutaneous and the oral routes of administration (8), working mechanisms of the subcutaneous ROA (20), risks of the subcutaneous ROA (10) (Fig. 1).

### 3.2. Categories and definitions of benefits and risks

Between 2006 and 2008 a working group of the Committee for Medicinal Products for Human Use (CMPH) of EMA worked on the topic of benefit/risk assessment aiming to improve the transparency, consistency and communication of benefit and risk assessment in CHMP reports. Based on the literature that demonstrated several different categories and definitions of benefits and risks, EMA decided to avoid the terms *benefit* and *risk*. Instead they adopted the EMA's four-fold model:

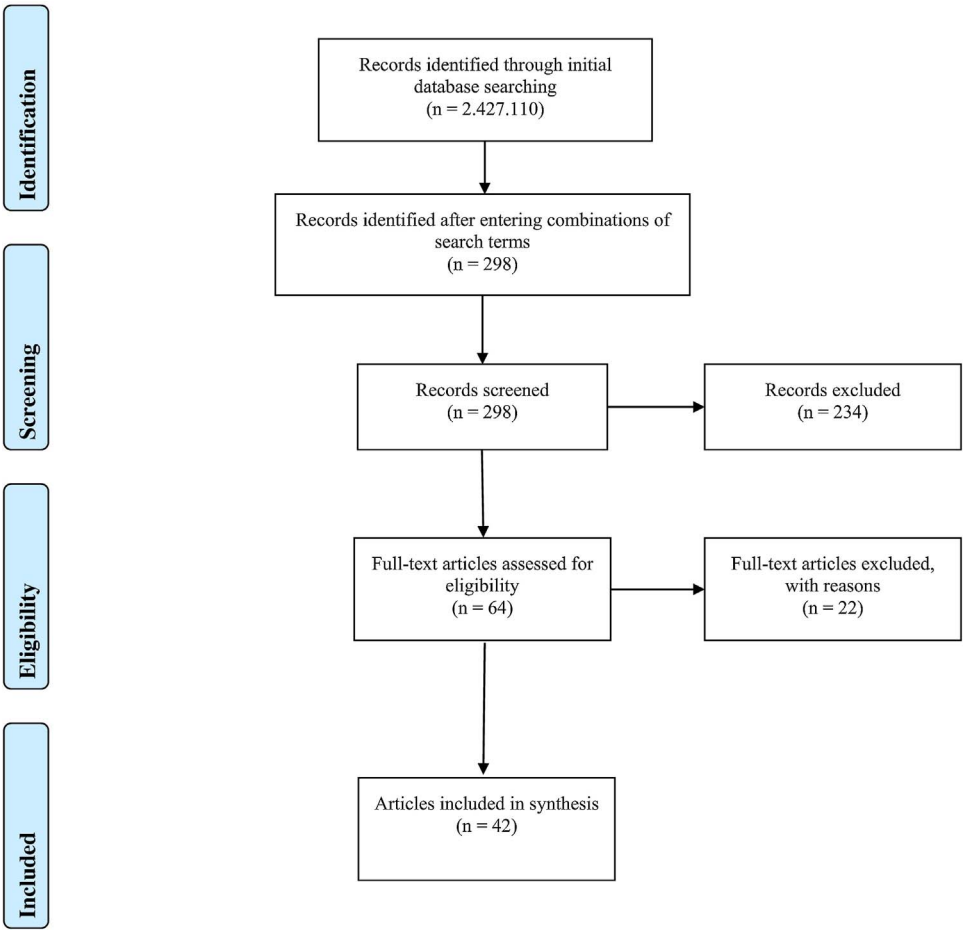


**Fig. 1.** Flow chart.

| | |
|---|---|
| **Favourable effects** | **Uncertainty of favourable effects** |
| **Unfavourable effects** | **Uncertainty of unfavourable effects** |

"*Favourable effects* are any beneficial effects for the target population (often referred to as 'benefits' or "clinical benefits") that are associated with the product. *Unfavourable effects* are any detrimental effects (often referred to as risks, harms, hazards both known and unknown) that can be attributed to the product or that are otherwise of concern for their undesirable effect on patients' health, public health or the environment. *Uncertainties about both types of effects* arise from variation, important sources of bias, methodological flaws or deficiencies (including GCP, compliance, etc.), unsettled issues, and limitation of the data set, e.g., due to sample size, study design, or duration of follow-up." …. "Within this framework, balancing benefits against risks is a matter of comparing the favourable and unfavourable effects, with an account of how that comparison is affected by consideration of the uncertainties [5], p.5".

In line with the EMA approach here this content, these definitions and this framework are used to study the benefit/risk balance of the subcutaneous ROA, although after the working group of the CMPH other departments and other organizations argued that the terms *benefit* and *risk* could not be avoided.

### 3.3. Assessment of benefit/risk balance

Since 2006 until now, the EMA has worked and will work for the next years on the topic of benefit/risk assessment. One of the projects that is finished was to judge the existing qualitative and quantitative approaches of assessing the benefit/risk balance. Although the EMA has not yet created a new and optimal benefit/risk tool, recommendations are made for assessing the benefit/risk balance. The most important recommendations are:

1. Adopt the PrOACT-URL[1] (qualitative) framework to guide the process of evaluating the benefit/risk balance.
2. Develop a quantitative model
3. Use quantitative modelling to facilitate justification of the benefit/risk assessment.

The use of the framework and the model are meant to provide a guide and to support the judgement process of the participants that assess the benefit/risk balance of a product.

In line with the EMEA approach here both a qualitative framework (qualitative studies on expert experiences) and quantitative modelling (results of empirical studies) are used to study the benefit/risk balance of the subcutaneous ROA.

[1] PrOACT-URL: Problem formulation, Objectives, Alternatives, Consequences, Trade-Offs, Uncertainties, Risk Attitude and Linked Decisions.

### 3.4. Practice-based evidence: what is the need/demand of the prescribers regarding the availability of ampoules?

Baars et al. [6] performed a survey on the professional experiences with ampoules among 2564 healthcare professionals (doctors, dentists and 'Heilpraktiker') in Europe (response rate: 64.1%) on prescribing homeopathic or anthroposophic subcutaneous injections. The results of the 1.693 responding doctors were based on an estimated number of 36 million patients treated with subcutaneous injections during an average period of 16.3 years. Most respondents considered the prescription of ampoules to be an important part of their therapeutic system. 99.5% of the doctors would like to have continued access to the option of preparations intended for administration by subcutaneous injection. 89.0% of the practitioners would be limited in providing optimum treatment for patients if these preparations were no longer available.

In general, practitioners opted for subcutaneous injections (compared to other ROA's) for the following reasons: (1) quicker effect, (2) better effect, (3) easier to dose, (4) exact location of administration, (5) combination with other therapies, (6) better compliance, and (7) if oral ingestion is not possible.

Already in 1917, Bergmann stated that this ROA is advantageous for the homeopathic remedy. Within the homeopathic therapeutic system, the advantages of the subcutaneous injections are: (1) the homeopathic substance does not have to pass through the gastrointestinal tract where it is severely altered by the gastric and intestinal juices, (2) there is no viral or microbial risk, (3) there is better patient compliance, and (4) there is improved action through injection [7].

In addition, for anthroposophic doctors the prescription of ampoules is a meaningful part of the anthroposophic medicinal system. Diagnostic procedures in anthroposophic medicine, in addition to conventional diagnostics, assesses the functional and rhythmic aspects in the morphological and physiological or biochemical systems of a human body. In particular, it considers a threefold distinction between these systems and their functioning. A good example can be found in the catabolic, the metabolic and the rhythmic systems.

"Here, anthroposophic medicine distinguishes between organs or organ systems, which are related to the nerve-sense system (catabolic function) and organs or organ systems which are connected to the regeneration system (metabolic function). A third distinctive system, the rhythmic functions in the body, or cardiovascular/respiratory system, is oriented to balance the divergent activities and functions (polarities) of the nerve-sense (catabolic) and regeneration (metabolic) systems and to facilitate a harmonic functioning of the three systems in the human body.

With this concept, illness is not only regarded as a malfunction of one single organ but is perceived as an imbalance between and within different organ systems, including the question as to whether the rhythmic system is fulfilling its task to balance and harmonise properly [8], p. 26 (Fig. 2).

Against this conceptual background, anthroposophic medicine uses a broad variety of anthroposophic medicinal products from minerals, animals and different parts of plants in a variety of routes of application and various concentrations or potencies according to the disease, part of the body and body function affected and to the age and condition of the patient [9]. The subcutaneous ROA is thus within this medical system, not only used for the reasons given above [if appropriate], but is also a specific 'clinical tool' that is used to influence a specific target part of the human being, the rhythmic system directly [8].

It can be concluded that there is, both coming from the extensive amount of clinical experience with subcutaneous injections and from the background of the homeopathic and anthroposophic therapeutic systems, a large demand of the prescribers regarding the availability of this ROA for use in clinical practice.

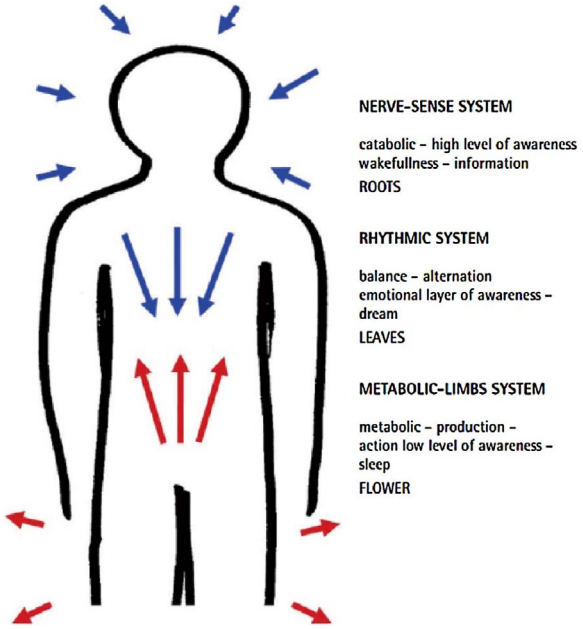


**Fig. 2.** The threefoldness of the human being.

### 3.5. Empirical evidence from clinical studies comparing the subcutaneous and the oral routes of administration

The comparison of the effects of the subcutaneous and the oral ROAs is a very small research domain, without studies referring to AMPs or HOMPs. However, in the field of conventional medicine, there is evidence that the subcutaneous ROA is associated with higher clinical efficacy, but more withdrawal due to toxicity in metothrexate (MTX) treatment, based on a systematic review of 38 publications [10]. Braun et al. [11] performed a six-month, multicenter, randomized, double-blind, controlled, phase IV trial studying the clinical efficacy and safety of subcutaneous versus oral administration of MTX in patients with active rheumatoid arthritis. The subcutaneous administration (SC) was significantly more effective than oral administration of the same MTX dosage. There was no difference in tolerability. The bioavailability of oral MTX was lower than that of SC MTX but was associated with higher variability. Wilson et al. [12] also found a higher bioavailability (a relative per oral bioavailability of 86% in comparison to subcutaneous). Lau et al. [13] studied the pharmacokinetics and bioavailability of midazolam after intravenous, subcutaneous (SC), intraperitoneal (IP) and oral administration (PO) under a chronic food-limited regimen in food-limited rats. The mean absolute bioavailability was route-dependent: 39.3% (SC), 19.2% (IP) and 4.6% (PO). Tfelt-Hansen [14] studied the efficacy and adverse events of subcutaneous, oral, and intranasal sumatriptan used for migraine treatment, by executing a systematic review on 30 trials, based on numbers needed to treat. Subcutaneous sumatriptan was significantly more efficacious than oral sumatriptan, but caused more adverse events than oral sumatriptan. Subcutaneous sumatriptan was the form with the quickest onset of action. Intranasal sumatriptan had the same efficacy as oral sumatriptan and a quicker onset of action than the oral form, but with a limited therapeutic effect for the first 30 min after administration.

Murillo et al. [15] studied the modulation of the cellular immune response after oral or subcutaneous immunisation with microparticles containing *Brucellaovis* antigens in BALB/c mice. An antigenic extract (HS) from *Brucellaovis* was encapsulated in either poly-ϵ-caprolactone (PEC) or poly-lactic-co-glycolic acid 75:25 (PLGA) microparticles containing β-cyclodextrin and Pluronic F-68® as stabilising agents. HS–PEC elicited a Th1 response although of low intensity. In contrast, subcutaneous immunisation with HS–PEC induced high IFN-γ and IL-2

release as part of a Th1 response.

Some studies provide evidence that the subcutaneous and the oral ROA provide different effects. The subcutaneous route is used for many protein drugs because such drugs would be digested in the digestive tract if they were taken orally [16]. Edwards et al. [17] compared the oral and subcutaneous routes of administration of cocaine HCl in female Wistar rats for food and water consumption, locomotor activity, stereotypic behaviors, plasma drug concentrations and injection site pathology. Subcutaneous administration was associated with a sensitization to the effects of cocaine on locomotion and stereotypy, higher blood levels than oral administration at the same dose, and severe dermal lesions. Oral cocaine was also associated with behavioral sensitization. However, unlike the SC route, oral cocaine was characterized by dose-related increases in locomotion and stereotypy in the absence of gastrointestinal pathology.

Summarizing the results, we can conclude that there is evidence for some pharmaceutical treatments in some diseases that the subcutaneous ROA compared to the oral ROA is associated with: (1) higher clinical efficacy, (2) higher bio-availability, (3) equal or higher risk of dose-related toxicity, (4) quicker onset of action; and (5) different effects.

### 3.6. Mechanistic evidence

Based on the literature, the following categories of (possible) working mechanisms of the subcutaneous ROA can be distinguished: (1) mechanical effects, (2) substance effects, (3) location effects, (4) time effects, and (5) placebo effect. For each of the five mechanistic categories we summarize the evidence.

#### 3.6.1. Mechanical effects

Three types of mechanical effects are described in the scientific literature: needle, technique and volume effects. The needle effect is hypothesized to be the result of specific mechanical changes due to the application of a needle into the body [18,19]. The technique effect is thought to be the effect of the mechanical changes due to the turning of a needle when the needle is already in the body [20]. The last hypothesized mechanical effect is the mechanical changes due to an increase in volume of fluid, especially in the extracellular matrix (ECM) [21].

#### 3.6.2. Substance effect

Two types of possible substance effects related to the ROA are described in the scientific literature: biochemical effects and the ‘absence of devitalization’ effects.

The biochemical effect concerns the fact that parenteral ROA’s surpass digestion especially in the intestinal tract and the liver. The oral and parenteral administration of the same substance may therefore result in different plasma metabolite concentration-time profiles and different plasma metabolites [16]. The subcutaneous route is used for many protein drugs because such drugs would be digested in the digestive tract if they were taken orally [16].

The liver is usually assumed to be the major site of first-pass metabolism of a drug administered orally, but other potential sites are the gastrointestinal tract, blood, vascular endothelium, lungs, and the arm from which venous samples are taken. Bioavailability, defined as the ratio of the areas under the blood concentration-time curves, after extra- and intravascular drug administration (corrected for dosage if necessary), is often used as a measure of the extent of first-pass metabolism. When several sites of first-pass metabolism are in series, the bioavailability is the product of the fractions of drug entering the tissue that escape loss at each site. The four primary systems that affect the first pass effect of a drug are the enzymes of the gastrointestinal lumen, gut wall enzymes, bacterial enzymes, and hepatic enzymes. One major therapeutic implication of extensive first-pass metabolism is that much larger oral doses than intravenous doses are required to achieve equivalent plasma concentrations. Drugs that undergo extensive first-pass metabolism may thus produce different plasma metabolite concentration-time profiles after oral and parenteral administration [16].

Another effect of first-pass metabolism is that it can change the biochemical properties of substances. This effect is for example exploited for beneficial purposes. Some prodrugs, for example codeine (methylmorphine, inactive) are converted from an inactive form to the pharmacologically active form (morphine proper) by first pass metabolism (in this case, desmethylation).

In anthroposophic medicine (AM) it is conceptualized that all substances from living beings (plants, animals and human beings) contain higher order organization formative forces that are responsible for the organization of organic material elements. These organizations are destroyed, devitalized or detached from the material elements during physiological digestion. So, in addition to the biochemical effects there is also, according to the AM therapy system, a de-vitilization effect on substances that follow the oral ROA. The subcutaneous ROA therefore leads to an absence of the de-vitalization in the digestive tract/liver, etcetera, with as a result (compared to the same substance that follows the oral ROA) another (more vital) substance with other effects [8,22].

#### 3.6.3. Location effects

Three possible location effects are described in the scientific literature: physiological target, acupuncture points, and extracellular matrix effects.

#### 3.6.4. Physiological target

The first effect is the effect of applying a substance near or on the exact physiological target. The rationale of this approach is that it is hypothesized to provide a fast treatment effect, since the pharmacological substance is (per)acute in the target area of the body [23].

A second effect is hypothesized to be a specific target location effect: the so-called acupuncture points used in Traditional Chinese Medicine (TCM). Based on a review of 29 RCTs, Vickers et al. [24] demonstrate specific effects of acupuncture in the treatment of chronic pain. Significant differences between true and sham acupuncture indicate that acupuncture is more than a placebo. There is some positive evidence for an association between both acupuncture points and acupuncture meridians and lower electric impedance and higher capacitance [23]. Collagenous bands, represented by increased ultrasound echogenicity, are significantly associated with lower electrical impedance and may account for reduced impedances previously reported at acupuncture meridians [25]. Well-documented and reproducible effects on the peripheral, central, and autonomic nervous systems have been demonstrated for both manual and electrical stimulation with acupuncture needles in humans and animals. The relevance of these mechanisms to pain reduction, peripheral anti-inflammation, cardiovascular, gastrointestinal, and endocrine regulation are summarized by Longhurst et al. [26]. Another model that has received a substantial amount of attention is the “trigger-point” muscle stimulation model. Acupuncture needle manipulation can be used to stimulate hyperirritable foci at neuromuscular junctions causing a specific “twitch response” that can alter extracellular inflammatory mediators surrounding the trigger point, suggesting that this mechanism may be related to local pain reduction [26]. Finally, there is the connective-tissue stimulation model, that was based on the observation that manual stimulation with acupuncture needles causes highly specific mechanical stimulation of subcutaneous loose connective tissue. Fibroblasts within the loose connective tissue respond to this mechanical stimulation with active cytoskeletal remodeling that may have important downstream effects within connective tissue. Although the relationship between these connective-tissue responses and clinical effects remains unknown, the intriguing overlap between acupuncture meridians and connective tissue suggests a possible relevance of this connective-tissue model to some poorly understood Traditional Chinese Medicine concepts, such as propagation of effects along acupuncture meridians [26]. The reviewed evidence

supports the view that the human body's fascia network may be the physical substrate represented by the meridians of TCM. Specifically, this hypothesis is supported by anatomical observations of body scan data demonstrating that the fascia network resembles the theoretical meridian system in salient ways, as well as physiological, histological, and clinical observations [27].

A third location effect concerns the biochemical and mechanical effects on the extracellular matrix (ECM). "The ECM is a three-dimensional network composed of proteins and polysaccharides that fills up the extracellular space in an organism. Within the ECM reside specialized, indigenous and adaptive cells called fibroblasts that mediate the dynamic process of ECM turnover, regulated via the activity of matrix proteolytic enzymes and the effect of a broad range of cytokines and other biochemical factors. It proved to be essential for its physiology that a cell interacts with the surrounding ECM, mediated through the attachment of ECM ligands to cell surface receptors, primarily integrins. Through their stimulation from either the inside or the outside of the cell, they can convert extracellular signals to intracellular signals and the other way around. This bidirectional communication between the cell and the ECM influences a wide range of cell processes, such as differentiation, survival, proliferation, migration, gene expression and actin organization. …. Mechanical signals have given several researchers a lead for formulating a few very intriguing hypotheses that envision a role for the ECM as a *body-wide signaling network*. Not only is the ECM found in all multicellular organisms, but also it is widely distributed throughout the body, connecting all cells to its network. Furthermore, the ECM has now been ascribed a commonly accepted functional role in addition to its conventional role as an inert scaffold that maintains tissue integrity. The ECM could constitute a possible network of fibroblasts, or engage in charge transfer, filtering that contributes to tissue memory, body-wide plasticity or it could be viewed as a sensory organ. All these hypotheses still lack enough experimental evidence for their confirmation. Considering it to be a bodywide signaling network automatically raises the question of how to manipulate the ECM. The ideas about chemical (nutrition, tissue engineering) and mechanical manipulation (acupuncture) of the ECM are just as speculative as the assumptions on which they are based, but nevertheless interesting to consider [28], p. 2."

The complex interactions of cells with the extracellular matrix (ECM) play crucial roles in mediating and regulating many processes, including cell adhesion, migration, and signaling during morphogenesis, developmental patterning, tissue homeostasis, wound healing, and tumorigenesis, stem cell niches, function-specific activities, cell migration and cell death occurring in the cell is a result of all incoming signals from neighboring cells and ECM, and genetic diseases. Many of these interactions involve transmembrane integrin receptors. Integrins cluster in specific cell–matrix adhesions to provide dynamic links between extracellular and intracellular environments by bi-directional signaling and by organizing the ECM and intracellular cytoskeletal and signaling molecules [21,29,30]. The subcutaneous ROA directly influences the ECM, both biochemically and mechanically.

#### 3.6.5. Time effect

The parenteral ROA's provide faster effects than the oral ROA [14].

#### 3.6.6. Placebo effect

A last location effect is the placebo-effect that is associated with the parenteral ROA. A placebo intervention can be defined as an intervention which has no direct pharmacological, biochemical or physical mechanism of action according to the current standard of knowledge. It can take the form of a placebo medication or of a diagnostic or therapeutic sham procedure [31]. Placebo responses can have several psychological or neurobiological mechanisms [32] and can be initiated and maintained by for example positive expectations, beliefs, change in emotions and motivation and classical conditioning [33,34].

Several studies demonstrate that the intravenous or subcutaneous ROA of drugs has larger placebo response rates than the oral ROA [35,36]. However, a review on placebo effects demonstrates that the absolute magnitude of placebo interventions is small and do not have important clinical effects in general. Only in certain settings placebo interventions can influence patient-reported outcomes, especially with regard to the treatment of pain and nausea [37].

## 4. The risks of the subcutaneous ROA

### 4.1. Estimation of the overall risk

Homeopathic and anthroposophic medicinal products (HOMPs and AMPs) were introduced in the end of the 18th century and the 1920s [38], respectively. Most HOMPs and AMPs have been developed and marketed until the 1950s. Since then there has not been any report on fatalities or malformations associated with these products.

The results of a study on the professional experiences of 1.693 doctors in Europe prescribing homeopathic or anthroposophic products for subcutaneous injection suggests, that these injectables have a very low risk profile [6]. In total 90.1% of the practitioners responded that they had never (57.4%) or very rarely (32.6%) observed adverse effects directly due to the injections. 9.9% of the practitioners indicated that they had rarely (6.4%) or only occasionally (3.5%) observed adverse effects due directly to a subcutaneous injection. In total there were 32 types of adverse effects reported due to a subcutaneous injection. For each report the practitioners were asked to assess the associated risk on a scale of 1 to 5 (1 = none, 2 = little, 3 = some, 4 = high, 5 = very high). Of these 32 types, 29 are transient and harmless and, only three reactions were reported with a mean risk higher than 'little': anaphylactic reaction (2.33), feverish symptoms (2.67), and aversion/anxiety against injections (2.50). Only one reaction was reported with a risk greater than 'high': asthma (4,00).

Alvarellos et al. [39] demonstrated in a case-series of nine patients suffering from a high level of pain after breast cancer therapy despite use of postoperative treatment with conventional analgesics, that there were no side-effects of subcutaneous injections with Traumeel. Huber et al. [40] studied the effectiveness of subcutaneous injections of a cartilage preparation in osteoarthritis of the knee in a randomized, placebo controlled phase II study with 89 patients. Severe side effects did not occur, minor side effects in 2 patients (1 in each group) were related to the subcutaneous injection.

Jong et al. [3] examined the safety status of anthroposophic and homeopathic solutions for injection through a systematic evaluation of the reported Adverse Drug Reactions (ADRs). ADRs were extracted from the pharmacovigilance databases of eight German manufacturers. Analysed ADRs included case reports in humans only, (spontaneous) case reports from post-marketing surveillance, literature and clinical/safety trials. Between 2000–2009, in total 303 million ampoules for injection were sold and 486 case reports were identified, corresponding to a total number of 1180 ADRs. Of all case reports, 71.8% (349/486) included ADRs that were already known (listed, e.g., stated in package leaflet) and 9.5% (46/486) of the reports were classified as serious. The most frequently reported ADRs were pruritus, followed by angioedema, diarrhoea and erythema. A total of 27.3% (322/1180) were localized reactions such as erythema, pain, swelling and inflammation of the application or injection site. The overall incidence of ADRs associated with injections was less than 4 per 1 million sold ampoules and classified as very rare.

EvaMed is a German prospective observational study with 38 AM physicians [41], a prospective pharmacovigilance study with special trained doctors in pharmacovigilance to avoid underreporting of adverse drug reactions and to evaluate the safety of CAM-drugs. It is one of the biggest pharmacovigilance networks to evaluate the safety of anthroposophic drugs and other CAM-drugs covering a time span of more than 10 years. Eligible for this analysis were patients of physicians in the EvaMed network, with (1) at least one prescription of an AMP

documented in the period 1 Jan 2001 to 31 Dec 2010, and (2) followed by at least one visit to the EvaMed physician in the period 2 Jan 2001 to 31 Dec 2011. The results demonstrate a very low incidence of ADRs associated with injections: 27 ADRs in 16,378 prescriptions (=0.165% ADRs/prescription), only one of which was serious [41–44]. Another study on CAM-drugs used in hospitals also demonstrated only three non-serious ADRs (local redness) as a result of subcutaneous injections [45].

This systematic evaluation demonstrated that the rate of reported ADRs associated with anthroposophic and homeopathic solutions for injection is very low. Most reported ADRs were known and one quarter consisted of local reactions. These findings suggest an excellent safety profile of solutions for injection as therapeutically applied in anthroposophic medicine and homeopathy, where the overall incidence of ADRs was very rare.

### 4.2. Estimation of the specific risks

Three main types of specific risks are described. The first risk is the *risk related to exposure*. This means that when this ROA is unprofessionally handled, used by an untrained person, there is an increased chance of overdose. This has specifically been described in the literature with regard to drug abuse. The second risk is *hazard related to substance*. This includes both dose-dependent risks and local reaction risk (e.g., local redness, erythema, edema, and itching) [6]. The third risk is the *risk of the 'needle'*. This includes: (1) hygiene risks (infection) due to needle sharing or abscessed infections of injection sites are caused by lack of hygiene and a lack of aseptic technique; (2) local destruction risks, for example: scarring of the peripheral veins, bleeding (destruction of small blood vessels), nerve puncture, brain damage (as a result of too deep needling at the skull base, pneumothorax (due to deep needling inside the lung or into the upper chest, penetrating into the pleural cavity); kidney damage (due to deep needling to the lower part of back); haemopericardium; and (3) other undesired effects, for example: anxiety (dizziness as a result of fear for the needle), pregnancy termination (according to a research, it has been demonstrated that inserting needles into acupuncture points can stimulate oxytocin and adrenocorticotropic hormone (ACTH) production), low blood pressure (acupuncture can also result in temporary low blood pressure and this may cause the patient to faint), rashes (some people may be allergic to metals and this can ultimately result in allergic symptoms such as rashes) [46].

Since acupuncture is a manipulation of a needle in the subcutaneous region without applying a substance, documentation of adverse reactions to acupuncture can provide important information on the risks of the subcutaneous ROA. In a systematic review of adverse events on acupuncture based on more than million treatments, 715 significant or serious adverse events have been reported in association with acupuncture. About 80% of these cases were due to trauma or infection, in approximately equal numbers. There were 12 primary reports of deaths, and 39 secondary reports. According to the evidence from 12 prospective studies which surveyed more than a million treatments, the estimated risk of a serious adverse event with acupuncture is very low: 0.05 per 10,000 treatments, and 0.55 per 10,000 individual patients [47].

### 4.3. Control of the risks

Nurses, doctors and patients perform subcutaneous injections. Currently the scientific basis for technical performance, the technique of applying subcutaneous injections optimally, is weak [48]. Given the described risks of the subcutaneous ROA, (more) control of the risks of the subcutaneous ROA in healthcare must be sought in: training of nurses, doctors and patients based on available evidence on technical performance including hygiene measures and information of the (low) risks related to the substance administered, the needle and other undesired risks.

## 5. The overall balance of favourable and unfavourable effects of injectables

According to the *professional judgement* of CAM professionals prescribing injectables there is a large therapeutic benefit of injectables and a very low risk of adverse effects due to the form of administration (see also pp. 10 and 18). So according to the present practice-based evidence of the professionals based on clinical expertise in the field of injectables prescribing doctors, there is a large positive benefit/risk balance with regard to the subcutaneous ROA. However, there is some methodological uncertainty with regard to these results, since the data is based on expert knowledge, with for example the possibility of recall bias.

With regard to the evidence from *comparative studies* comparing the oral and the subcutaneous ROA there is evidence for some pharmaceutical treatments in some diseases that the subcutaneous ROA compared to the oral ROA is associated with: (1) higher clinical efficacy, (2) higher bio-availability, (3) quicker onset of action; (4) different effects, and (5) lower risk of long-term co-morbidity and mortality. There is equal or higher risk of toxicity. However, this is dose-related. So according to the limited evidence available coming from comparative studies comparing the oral and the subcutaneous ROA, there is a positive benefit/risk balance with regard to the subcutaneous ROA, especially when the dose-related risk of toxicity is sufficiently controlled.

With regard to the evidence from *mechanistic studies* there is some evidence for the following mechanisms of the subcutaneous ROA: (1) mechanical effects, (2) substance effects, (3) location effects, (4) time effects, and (5) placebo effect.

With regard to the evidence on the *risks of the subcutaneous ROA*, the analysis of expert knowledge of injectables prescribing professionals, the evidence from comparative studies comparing the oral and the subcutaneous ROA, the evidence from mechanistic studies, the systematic evaluation of the reported ADRs extracted from the pharmacovigilance databases of eight German manufacturers, and the analysis of specific risks demonstrated a very low risk profile of the subcutaneous ROA.

## 6. The consequences of removing the subcutaneous ROA of the market

There is a current trend in the policies of regulatory authorities towards removing the subcutaneous ROA more and more of the market in favor of the oral ROA. They regard the subcutaneous ROA only justified in acute cases and consider oral products to be better alternatives for ethical and safety reasons [6].

However, the results of this review provide both clinical and mechanistic evidence on other effects than time effects ('acute cases') only and demonstrate that the risks of this ROA are very small, especially when handled professionally. Given the estimated overall positive benefit/risk balance, healthcare professionals in general would be severely limited in providing optimum treatment for patients if this ROA was no longer available. This is even more the case for anthroposophic and homeopathic prescribing healthcare professionals, since this ROA is additionally an important clinical tool as part of the anthroposophic and homeopathic medical systems.

## 7. Discussion

For ethical and safety reasons drug regulatory authorities in several European countries increasingly consider oral products to be better alternatives than subcutaneous injections. Due to a lack of evidence, regulatory authorities regard the use of injectables overall only justified in acute cases. In order to acquire acceptance from the regulatory authorities for the subcutaneous ROA, scientific evidence on the positive benefit/risk balance has to be provided. This study therefore explored

the current scientific evidence with regard to the surplus value and the benefit/risk balance of the subcutaneous ROA.

Besides the overall result of the weighing of the favourable and unfavourable effects, one of the interesting results comes from comparing the clinical experience and the scientific results. The clinical experiences of prescribing doctors with regard to the higher clinical efficacy/better effect, quicker effect and quicker onset of action and the different effects of the subcutaneous ROA are supported by epidemiological studies. At the other hand it is not clear how large the placebo effect contributes to the total effect of this ROA, according to findings from research on conventional research [49], acupuncture research [50], and research on placebo interventions [51].

The major limitation of the study is the small amount of (good) studies and good evidence on this topic. As a result, for some aspects of this ROA only limited empirical evidence and/or evidence of low quality is available, with uncertainty about the effects as a result.

The results of this review have consequences for the conceptualization of the working mechanism, further research on the effects, use in clinical practice, and regulatory attitudes towards the subcutaneous ROA. Since the favourable effects are more than only a time effect (that is the main reason for the indication ‘acute cases’), a broader conceptualization of the working mechanism is needed that encompasses and integrates the whole of mechanical, location, substance, time and placebo effects. For that, much more fundamental and clinical research is needed on both the mechanistic working mechanisms and the comparison of the oral and subcutaneous ROAs. Since all the available evidence demonstrates a large benefit/risk ratio and a very low risk profile of the subcutaneous ROA, especially when the most important risks are sufficiently controlled, there is no need to limit the use of this ROA to the indication ‘acute cases’.

## 8. Conclusions

1. This narrative review of the literature demonstrates several favourable clinical and mechanistic effects of the subcutaneous ROA in general, some unfavourable effects of the subcutaneous ROA and overall a positive benefit/risk balance, with good controllable risks.
2. With regard to the marketing authorization of this ROA, the overall positive benefit/risk balance in combination with the large preference of prescribing doctors justifies a positive attitude from the regulatory authorities towards the use of this ROA. The current evidence also does not support the position that ampoules prescribing doctors act unethically and expose their patients to unacceptable risks.
3. More high quality evidence on the effects of the subcutaneous ROA is needed.

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