Title page

How to handle Homeopathic Aggravation – Risk Assessment in Homeopathic Practice

Wie homöopathische Verschlimmerung behandlen – Risikobewertung in der homöopathischen Praxis

Short Title: Homeopathic aggravation and risk assessment

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Summary

Even though homeopathy is regarded by many as a harmless intervention, homeopathic practice, may not be entirely risk free. Homeopathic aggravation, a concept unique for homeopathy, may impose a particular risk as it allows the health status of the patients to deteriorate before there is an possible improvement. Risk in homeopathy can be divided into direct and indirect risk. Direct risk includes traditional adverse effects of an intervention and indirect risk is related to adverse effect of the treatment context, for example the practitioner. Available data suggest that the risk profile of homeopathic remedies is minor, however, there is a potential for indirect risk related to homeopathic practice. In that respect it is imperative to distinguish homeopathic aggravations from adverse effects. In a general risk evaluation of the homeopathic treatment it may be useful to assess the patients symptoms in accordance with the natural course of disease and evaluate any deviation from the normal curve as a possible adverse effect of the treatment. It is imperative that during the education in homeopathy, more emphasis is placed on patient safety and that the students are trained to identify serious and red flag situations.

Schlüsselwörter

Zusammenfassung

Obwohl Homöopathie prinzipiell als risikofreie Therapieform gilt, ist die klinische Praxis nicht generelle ohne Risiko. Die sog. „homöopathische Erstverschlimmerung“ bezeichnet eine initiale Verschlechterung des Zustands der Patienten, gefolgt von einer Verbesserung. Risiko im Zusammenhang mit Homöopathie kann man nach direktem und indirektem Risiko unterteilen. Direktes Risiko bezeichnet dabei die direkten unerwünschten Effekte (adverse effects) des homöopathischen Arzneimittels, während indirektes Risiko eine potenzielle Gefährdung des Patienten durch die klinische Praxis, also z.B. den Behandler beschreibt. Die Datenlage legt nahe, dass das direkte Risiko verbnden mit homöopathischen Arzneimitteln gering ist, dass jedoch ein indirektes Risiko durch die Behandlungspraxis besteht. Vor diesem Hintergrund ist es grundsätzlich wichtig klar zwischen einer „homöopathische Erstverschlimmerung“ und unerwünschten Effekten (adverse effects) zu unterscheiden. Im Hinblick auf eine bestmögliche Risikoabschätzung kann es sinnvoll sein, der natürlichen Verlaub der Erkrankung und evtl. Abweichungen davon in die Risikobewertung mit einfliessen zu lassen. Unserer Ansicht nach ist es von fundamentalere Wichtigkeit, in der

Homöopathieausbildung besonderen Wert auf die Einschätzung von Patientsicherheit und Behandlungsrisiko, sowie die Identifikation von „red flag“ Situationen legen.

Background

Historically, risk and patient safety have been considered essential in the treatment of disease and since the time of Hippocrates and the dictum to do no harm has been imperative (1). With the dramatic advance of the medical profession over the last fifty years, the topic has received considerable attention, in particular with the introduction of “The Nuremberg Code” (2), and the Helsinki declaration (1964/2004) in medical research.

A severe example from homeopathic treatment in which the ethical dictum to do no harm was heavily violated, was a case where a 9 month old baby was admitted to hospital after homeopathic treatment (3). She had been given several homeopathic remedies to treat atopic dermatitis. The child developed Bullous Pemphigoid during the treatment period, which lasted for five months. When the infant was finally admitted to hospital, its condition was life threatening. This severe situation occurred because the homeopath interpreted the worsening of symptoms as homeopathic aggravations and continued treatment instead of referring to conventional care.

This case illustrates that even though homeopathy is regarded by many as a non-effective and harmless intervention, homeopathic practice, even though many patients utilize it with high satisfaction (4, 5), may not be entirely risk free.

Homeopathic aggravation

According to homeopathic philosophy, homeopathic aggravation is a “temporary worsening of existing symptoms following the administration of a correctly chosen homeopathic prescription”. In homeopathic theory, homeopathic aggravation is generally seen as a favorable response to treatment and is expected to be followed by an improvement (6-8). George Vithoulkas describes initial aggravation as the optimal reaction to be expected from a correct, constitutional remedy (9). Therefore, in homeopathic theory, a temporary deterioration of the patient’s health status as part of the therapeutic process is widely accepted.

The available literature assessing the occurrence of homeopathic aggravation in clinical practice remains unclear. Some authors estimate that 75% of all chronic cases demonstrate appreciable aggravation of their symptoms during homeopathic treatment (8, 10). Other authors report a lower frequency of 10-20% in clinical practice (11). In a systematic review of homeopathic

aggravations, Grabia and Ernst found, that four included trials reported 40 cases of aggravation in the placebo groups and 63 cases in the homeopathy groups. The authors concluded that although the included Randomized Controlled Trials (RCT) mentioned the phenomenon of homeopathic aggravations, the evidence was not strong enough to provide support for the existence of aggravations. In conclusion, even though the physiological and pathophysiological basis of homeopathic aggravation remains unclear, the described worsening of symptoms and deterioration of the patients' health status during homeopathic intervention appears to be frequent. Thus, relevant with regard to patient safety as the concept allows an increase of symptoms as a part of a healing process. In clinical practice, the practitioner must decide whether deteriorations of the patient's symptoms are homeopathic aggravations or adverse effects.

Risk assessment and patient safety

Operationally and methodologically, risk is generally defined as a compound measurement of the probability of an event and the magnitude of the potential negative outcome of that event (12). Risk can be assessed from a variety of perspectives. In medical science, risk can be divided into direct and indirect risk (13, 14), as illustrated in figure 1.

Figure 1

Direct risk is caused by the treatment itself and linked directly to the intervention. This dimension includes traditional adverse effects of an intervention, such as bleeding in response to acupuncture needling or the adverse effect of an herb, as well as risk connected to self-management advice from the practitioner (15). Indirect risk is related to adverse effect of the treatment context, for example the CAM practitioner, rather than the intervention. A patient may be harmed by a care context, which prevents the patient from receiving the best possible treatment relevant to her or his health needs. For example patients who seeks a CAM practitioner for their health complaints which may be effectively treated by conventional medicine (e.g. cancer), and the CAM practitioner, often unwittingly, causes a delay of conventional treatment (15). Another example is care in conventional or CAM setting, which is experienced as disrespectful and thus causes the patient to delay appropriate care. In this present paper, adverse effect is understood as all diseases or unwanted and/or harmful reactions resulting from a medication or an intervention, regardless of their relation to the actual treatment (16).

Risk in medicine

It is likely that most simple "direct risks" (at least on a theoretical basis) are related to the intervention, e.g., such as harm caused by pharmacological products, medical treatments and procedures. Several terms are used to describe direct risk, such as adverse event, adverse reactions, and side effects (17). The term "Adverse effect" covers, a broad spectrum of potential risks and thus includes more sources of risk than merely those related to drugs and includes indirect risk sources since the term encompasses all unwanted effects, without making assumptions about their mechanisms (18) (table1).

Table 1: Descriptors of risk grouped according to sources and concepts of risk

The homeopathic intervention is a complex treatment situation that consists of in-depth consultations often reaching beyond the bodily complaints meaning that it also includes psychological problems in the assessment. Moreover, it is generally also combined with lifestyle advice. Consequently, a broader definition of risk is needed. Therefore, the term "adverse effect" that encompasses all unwanted effects, without making assumptions about their mechanisms is suitable for complex treatment situations like homeopathy.

Risk in homeopathy

Adverse effects of homeopathic remedies have been investigated by Dantas and Rampes (19). They stated that there was a rate of 9% for adverse effects in patients using homeopathic remedies in contrast to 6% in the placebo group. A meta–analysis (11) of 3,437 patients in 25 placebo-controlled RCTs, reported 33 cases of adverse effects for patients treated with homeopathy and 97 for patients treated with placebo. Data from observational studies and surveys (20) reveal that reported adverse effects from homeopathic treatment fluctuates between 2% (5) and 11% (21). Cases of adverse effects related to homeopathic practice have been reported in the literature (3, 22, 23). A systematic review of case reports published in 2012 (24) reported that among the 38 primary cases included, 30 pertained to direct adverse effects of homeopathic remedies and another eight were related to adverse effects caused by substituting homeopathy for conventional medicine.

Homeopathic remedies are mostly considered harmless in terms of safety concerns. Homeopathic remedies undergo a process of a stepwise dilution and vigorous shaking, until the content of the substance to be diluted is very low or non-existent in the solvent (alcohol, milk, sugar, or other) (7, 25). A direct pharmacological effect is therefore impossible for remedies of high dilutions. However, not all homeopathic remedies are of high dilutions and remedies in

low dilutions may cause harm if administrated too frequently over a long period of time (26). Moreover, remedies of low dilutions are pharmacologically active and therefore associated with direct risk. In addition, these remedies may impose indirect risk that is linked to clinical practice and the concept of homeopathic aggravation. Remedies of high dilutions, however, does not have a pharmacological effect and a direct toxicological risk from these remedies is impossible. The risk related to the remedies of high dilutions is therefore indirect and related to homeopathic practice as illustrated in figure 1b.

Figure 1b: Pharmacological model in association with direct and indirect risk in homeopathy.

How to distinguish between homeopathic aggravation and adverse effects

According to homeopathic theory, homeopathic aggravation is an independent concept from adverse effect and worsening of the symptoms is accepted to a certain degree and monitored as a part of the healing process. Since homeopathic aggravation is tolerant towards worsening of the patients' symptoms, it is important that homeopathic practitioners increase their awareness of adverse effects. It is important with regard to patient safety, that homeopaths do not ignore signs of serious adverse effects (red flag situations) and thus provoke a dangerous situation for the patients. Consequences of overlooking serious symptoms are demonstrated in the case presented previously (3) and in a systematic review recently published (24).

Our research group has developed criteria which describes homeopathic aggravation and thus distinguish homeopathic aggravation from adverse effects. They include i) an increase in the patient's existing symptoms, ii) and/or a feeling of well-being that emerges 1-3 days after taking the remedy, iii) headache and/or fatigue may accompany these symptoms. If the worsening of symptoms continues for 14 days without a feeling of well-being, the symptoms are defined as adverse effects (27, 28). These criteria will firstly, and most relevant, enhance patient safety, and secondly, they will allow the comparison of safety data across studies, since there is to date no uniform definition of homeopathic aggravation vs. adverse effect.

The concept of homeopathic aggravation: Potential explanations unrelated to homeopathic theory and a general risk evaluation

The natural history of disease

The natural history of a disease is a theory about the diseases' normal course in the absence of an intervention. The central question for studies of prevention and treatments is whether the use of a particular preventive or treatment measure can change the natural history of the disease in

a favorable direction, by reducing or preventing clinical manifestations, complications or death (29). The natural history of disease refers to a description of the uninterrupted progression of a disease in an individual from the moment of exposure to causal agents until recovery. Knowledge of the natural history of disease is important for disease prevention and control. Moreover, the natural history of disease is one of the major elements of descriptive epidemiology (29).

If a patient who is visiting a homeopath experiences worsening of the symptoms, the homeopath must evaluate the situation. If the patient sees the homeopath during a point in time, when the symptoms are close to peak, he or she will experience an initial worsening of symptoms, followed by an improvement. Therefore, homeopathic aggravations may be understood as the "natural history of disease" as the patients will experience a worsening of the symptoms, even if they simultaneously experience a feeling of well-being (increase in energy or improved sleep). If the worsening of these symptoms lasts for more than three days, and the patients feel worse, and there are no signs of well-being, it is likely that the disease is more severe than anticipated. Consequently, the curve will peak at a much later stage or just continue on and on. For example catching a cold is normally an event that occurs once or twice during the winter season and many patients seek the help from a homeopath, especially if this is a recurring event. If the symptoms of a cold persist and the patient develops fatigue and weakness, the homeopath should be concerned and closely follow the patient on a daily basis. These symptoms are unacceptable and the patient should be referred to conventional care if no signs of improvement appear. If it turns out that the patient is then diagnosed with pneumonia, the cold was "the top of an iceberg". The cold represented superficial symptoms, while a far more serious disease that was developing underneath. In order to ensure patient safety in such cases, it is important that the homeopath follows the patient carefully by assessing the symptoms frequently, and refers the patient to conventional care, if no therapeutic improvements appear.

In the theory of diseases, "the iceberg model" is a metaphor emphasizing that for virtually every health problem, the number of known cases of disease is outweighed by those that remain undiscovered (30) , much as the unseen part of an iceberg is much larger than the part that is visible above the water (31).

Another, even more serious example is a patient with cough, shortness of breath and breast pain who visits a homeopath and is later diagnosed with lung carcinoma. Therefore, the iceberg model suggests that an awareness of potentially serious differential diagnoses is mandatory for a practicing homeopath, so the patient is transferred immediately to conventional care, if the

first sign of a "red flag" situation occur. An awareness and alertness for red flag situations should always be present when observing and monitoring patients' symptoms.

Nocebo effect

Homeopathic remedies may impose risk known as the nocebo effect (32). Nocebo effects are defined as the development of negative effects that are attributed to a medication, albeit the drug itself does not cause the provocation of these symptoms (14, 32). The development of adverse effects after placebo intake has been reported for medical conditions such as depression (33) and cancer (34). Nocebo effects are estimated to account for 72% of drop-outs in drug groups of fibromyalgia trials (35). Observations from clinical trials indicate that patients' expectations play an important role in the development of nocebo effects. If patients were informed about potential adverse effects of a specific drug, they reported more symptoms than patients who were given limited information about potential adverse effects (36). Moreover, it seems that Pavlovian conditioning and associative learning may activate the development of nocebo effects, although there is weaker evidence for their involvement in nocebo effects compared to their role in developing placebo responses. A frequently cited clinical example for the conditioning of adverse effects is the development of anticipation nausea in patients undergoing chemotherapy (32).

The available data suggest (21, 37) that patients experienced homeopathic aggravations rather often during treatment. A possible explanation for such a high occurrence may be that many homeopaths inform their patients that homeopathic aggravations might occur during treatment. Health care providers should be aware that all interactions with the patients have the potential to result in expectations. Consequently, the information that patients receive prior to treatment

Conclusion

The risk profile of the homeopathic remedies is minor, however, there is a potential for indirect risk related to homeopathic practice. In that respect it is imperative to distinguish homeopathic aggravations from adverse effects as homeopathic aggravation may impose a particular risk on patients. Homeopaths may believe that homeopathy is free of risk and does not cause adverse effects. This attitude among homeopaths underlines the need for improved awareness of adverse effects and red flag situations in clinical practice. It is, therefore, important that the homeopaths inform their patients to stay in contact if the worsening of symptoms last for more than three days.

It is also imperative that during the education in homeopathy, more emphasis is placed on the subject and that the students are trained to identify serious and red flag situations, as well as possible adverse effects of the treatment. The criteria developed to distinguish between homeopathic aggravations and adverse effects provide a tool which stands not in opposition to homeopathic theory and may help to increase patient safety.

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Disclosure Statement

The authors declare that they have no conflict of interest

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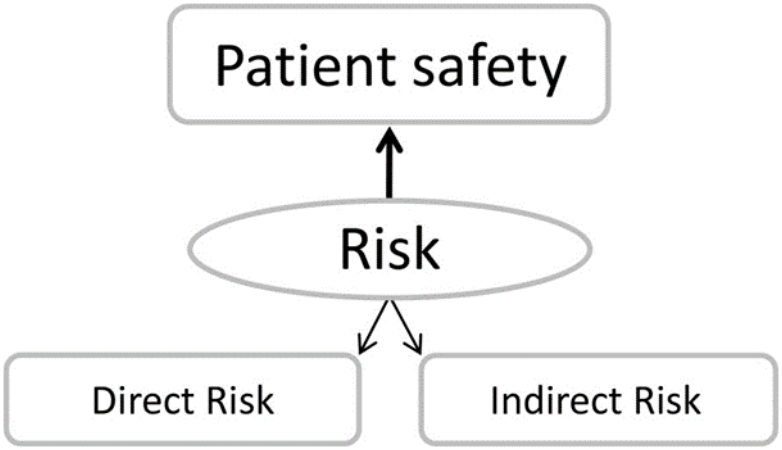

Figure 1a: Understanding of patient safety and risk in this paper. Direct risk is caused by the treatment itself and related directly to the intervention, while indirect risk is related to the setting effects, such as e.g. the practitioner, rather than the medicine.

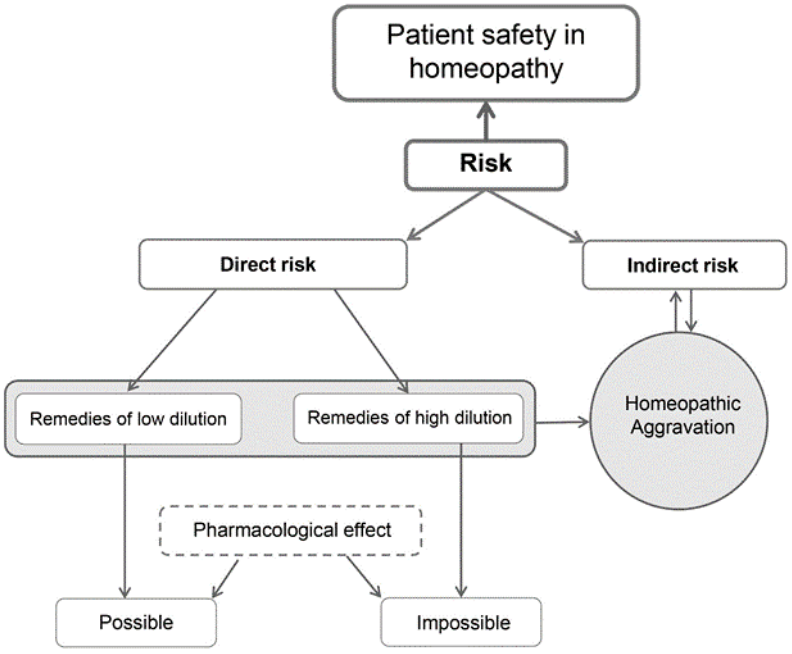

Figure 1b: Pharmacological model in association with direct and indirect risk in homeopathy. Indirect risk is related to clinical practice, the practitioner and applies likewise to remedies of low and high dilutions. In clinical practice the practitioner must decide whether the deteriorations of the patient's symptoms are homeopathic aggravations or not. The developed criteria to distinguish between homeopathic aggravations and adverse effects will provide a tool within homeopathic theory to facilitate this process.

Table1: Descriptors of risk grouped according to sources and concepts of risk.

Risk Concept	**Sources of risk**	**Descriptors/Origin**
Direct and indirect risk	Medical error	Human resources
Direct risk	Direct drug reaction	Adverse event Adverse drug reaction Adverse drug event Side effect
Direct and indirect risk	Comprehensive definitions	Adverse reactions Surveillance Adverse effect