IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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# Balneo-phototherapy[1]

# Executive Summary

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# Balneo-phototherapy

## Executive summary

### Background

The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) was commissioned by the Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA) to conduct an evaluation of the benefits and harms of different types of balneo-phototherapy. These therapies are used to treat chronic inflammatory skin diseases, and combine baths containing psoralens or salt with UVA or UVB radiation, respectively. The bath- and UV light-therapy can take place successively (asynchronous therapy) or simultaneously (synchronous therapy).

### Research question

The aims of this report were:

1) In patients with psoriasis vulgaris: The evaluation of **asynchronous balneo-phototherapy** using either a psoralen solution (bath-PUVA) or a salt water solution (photo-brine therapy), comparing these two options with each other or with tap water balneo-phototherapy or another therapy approved and available in Germany, or no therapy.

2) In patients with psoriasis vulgaris, acute exacerbation of atopic dermatitis, prurigo nodularis, prurigo caused by kidney disease, parapsoriasis en plaques, ichthiosis vulgaris, or vitiligo: The evaluation of **synchronous balneo-phototherapy** compared with tap water balneo-phototherapy or another therapy approved and available in Germany, or no therapy. (In Germany, the only type of relevant synchronous balneo-phototherapy is the so-called ToMeSa therapy [Totes Meer Salz = Dead Sea salt]).

The focus of both evaluations was on patient-relevant therapy goals.

### Methods

The evaluation was conducted on the basis of data from randomised controlled trials and non-randomised prospective controlled trials on the comparisons and indications mentioned above. In addition, retrospective comparative trials were included to compare the potential cancerogenicity of bath-PUVA and oral-PUVA.

In this investigation, outcomes were used that enabled an evaluation of patient-relevant therapy goals such as reduction or clearance of skin symptoms over a preferably long period, reduction of adverse effects as well as possible long-term complications of the (concomitant) therapy, improvement in disease-related quality of life and in treatment convenience.

The systematic literature search was conducted separately for asynchronous and synchronous balneo-phototherapy in the databases MEDLINE, EMBASE and Cochrane CENTRAL (in each case: coverage until March 2006). Moreover, the reference lists of primary and relevant secondary publications (systematic reviews, HTA reports, and evidence-based guidelines) were searched. Also considered were studies included in comments to the Federal Joint Committee within the framework of the underlying consultation on the project as well as documents requested from the industry. In addition, 3 clinical study reports on completed randomised trials were provided to the Institute.

The literature screening was performed by 2 reviewers independently of each other.

After an evaluation of the quality of the relevant trials to be included in the report (also performed by 2 reviewers independently of each other), the results of the single trials were organised according to treatment comparisons and therapy goals.

The preliminary evaluation conducted by IQWiG (preliminary report) was published on the Internet and comments were invited. Substantial comments were discussed within the framework of an oral scientific debate. Subsequently the final version of the report was produced.

**Results**

In total, 16 trials that initially fulfilled the inclusion and exclusion criteria of the underlying report plan were identified in the various steps of the literature search. Of these trials, 13 (including a total of 2326 patients) were included in the evaluation. Nine of the 13 trials (including 2032 patients) were randomised. Eleven trials investigated asynchronous balneo-phototherapy in patients with psoriasis. Two trials (one in patients with psoriasis and one in patients with atopic dermatitis) investigated synchronous balneo-phototherapy. Trials on synchronous balneo-phototherapy in patients with prurigo nodularis, prurigo caused by kidney disease, parapsoriasis en plaques, ichthiosis vulgaris, or vitiligo were not identified.

Of the trials included, 7 showed minor and 6 showed major deficiencies with regard to study and publication quality.

In addition, in order to compare potential cancerogenicity between bath- and oral-PUVA, a retrospective study was identified and included in the evaluation (this procedure deviated from the report plan).

*Asynchronous balneo-phototherapy (bath-PUVA and photo-brine therapy)*

The 11 trials investigated various types of balneo-phototherapy and also various control interventions. In total, 11 different treatment comparisons were performed in the 11 trials.

The trial by the German Federal Professional Association of Dermatologists (BP-BVDD trial) including 1241 patients was by far the largest trial conducted and included 4 therapy arms (bath-PUVA; photo-brine therapy; tap water bath plus UVB radiation; and UVB monotherapy). It was therefore of special relevance to the evaluation. A fundamental problem

in the interpretation of this trial was that its results refer to a "mix" of different UVB spectra applied in Germany (narrow band [NB]; broad band [BB]; and selective UVB), i.e. to a "mix" of different therapeutic measures. For photo-brine therapy, additional analyses of the BP-BVDD trial suggest that the therapeutic effect was not dependent on the type of radiation used in the control intervention. However, for bath-PUVA such analyses were not available.

For the comparison **bath- vs. oral-PUVA**, the trials provided indications of a potential advantage of bath-PUVA with regard to the occurrence of nausea, and (with limitations) of vomiting, as well as weak evidence (based on data from a retrospective trial) in respect of the occurrence of squamous cell carcinoma. Data on other therapy goals were either not available or did not show noteworthy differences. However, as the trials were not clearly designed as equivalence or non-inferiority trials, this cannot be interpreted as a demonstration of equivalence.

For the comparison **bath-PUVA vs. NB-UVB monotherapy**, the trials showed weak indications of a potential advantage of NB-UVB monotherapy with regard to the reduction and clearance of skin symptoms. No clear differences between both therapies were shown in respect of adverse effects; data on long-term complications of the (concomitant) therapies were not available. Data on quality of life and treatment convenience were also not available.

For the comparisons **bath-PUVA vs. UVB monotherapy** and **bath-PUVA vs. tap water bath + UVB** (in each case with a mix of different UVB spectra in the control interventions), an advantage of bath-PUVA was shown with regard to the reduction and clearance of skin symptoms. The results on adverse effects were inconsistent: concerning the physician's and patient's assessment of tolerability and the occurrence of phototoxic reactions, advantages were shown for bath-PUVA; however, compared with UVB monotherapy, serious adverse events occurred more frequently (this difference was not statistically significant). Data on long-term complications of the (concomitant) therapies were not available. Data on quality of life did not show differences between therapies. Data on treatment convenience were not available.

For the comparison **brine bath + NB-UVB vs. NB-UVB monotherapy**, the trials showed indications of a possible advantage for brine bath + NB-UVB with regard to the reduction of skin symptoms. However, there were also indications of a potential disadvantage of brine bath + NB-UVB concerning the occurrence of adverse events (no detailed information was provided). Data on other therapy goals were either not available or not interpretable.

For the comparisons **brine bath + UVB vs. UVB monotherapy** and **brine bath + UVB vs. tap water bath + UVB** (in each case with a mix of different UVB spectra), an advantage for brine bath + UVB was shown with regard to the reduction and clearance of skin symptoms. The results on adverse effects were inconsistent: concerning the physician's and patient's assessment of tolerability, advantages for brine bath + UVB compared with UVB monotherapy were shown. However, in respect of the occurrence of phototoxic reactions, there were indications of a disadvantage of brine bath + UVB compared with tap water bath + UVB. Data on long-term complications of the (concomitant) therapies were not available. Data on quality of life did not show a difference between therapies. Data on treatment convenience were not available.

No differences between therapies were shown for the comparisons **brine bath + BB-UVB vs. BB-UVB monotherapy** and **tap water bath + BB-UVB vs. BB-UVB monotherapy** as well as **brine bath + NB-UVB vs. brine bath monotherapy**. However, the data from the underlying trial were only of limited interpretability.

For the comparison **bath-PUVA vs. brine bath + UVB**, there were indications of a potential advantage of bath-PUVA with regard to the reduction and clearance of skin symptoms. Results on adverse effects showed indications for sporadic advantages of bath-PUVA. Data on long-term complications of the (concomitant) therapies were not available. Data on quality of life showed no difference between therapies. Data on treatment convenience were not available.

*Synchronous balneo-phototherapy with Dead Sea salt*

The results of both trials on psoriasis vulgaris and atopic dermatitis (taking the design flaws of the underlying trials and effects observed into account) can be summarised as follows:

In patients with psoriasis, an advantage of this procedure compared with NB-UVB monotherapy was shown; in patients with atopic dermatitis, only indications of an advantage existed. All the advantages stated relate to the therapy goal “reduction of skin symptoms”; from this, an advantage regarding the therapy goal “clearance of skin symptoms” can also be indirectly inferred. With regard to the therapy goal “reduction of adverse effects/long-term complications”, the results were consistent, i.e. no differences between treatment groups were shown. Data on possible long-term complications were not available. For the therapy goal “maintenance or improvement of disease-related quality of life”, indications existed that in patients with psoriasis, the improvement of symptoms through treatment with synchronous balneo-phototherapy was also associated with a positive effect on quality of life, in particular with regard to physical symptoms and the patient’s assessment of his or her state of health. In patients with atopic dermatitis, no favourable effects on quality of life were shown. Data on the therapy goal “improvement in treatment convenience” were not available.

Both studies have limitations that impair their evidential value: UVB monotherapy as the sole control intervention seems to be inadequate. A comparator intervention “tap water balneo-phototherapy” could have provided essential information about an unspecific effect caused by the bath. The non-blinded recording of results may have led to bias. Furthermore, the number of patient-related discontinuations of therapy was substantially higher in the control group than in the test group. With the unblinded design, it is therefore difficult to differentiate between discontinuation due to therapy failure or discontinuation due to the disappointment of “only” being allocated to the control intervention. In respect of the data on health-related quality of life, the rate of missing values lay between 20% and 30%. Data on follow-up after the end of therapy could not be utilised, as evidently (in both groups), an intensive disease-related therapy after the end of the intervention took place, and a high proportion of missing values (largely >30%) was noted.

**Conclusion**

In this report, 3 types of balneo-phototherapy were evaluated: bath-PUVA, asynchronous photo-brine therapy, and synchronous balneo-phototherapy. The indications investigated were "psoriasis vulgaris" (for all 3 therapies stated above) and "atopic dermatitis" (for synchronous balneo-phototherapy only).

- **Asynchronous bath-PUVA** has an additional benefit compared with UVB monotherapy or tap water bath + UVB concerning an improvement of skin symptoms and a reduction of adverse effects/long-term complications. This statement only applies to the use of a mix of different UVB spectra in the comparator intervention.
- Asynchronous **photo-brine therapy** (brine bath + UVB) has an additional benefit vs. UVB monotherapy (and also vs. tap water bath + UVB) with regard to the improvement of skin symptoms.
- For **bath-PUVA,** there are indications of an additional benefit compared with **asynchronous photo-brine therapy** (brine bath + UVB) concerning the improvement of skin symptoms and a reduction of adverse effects/long-term complications. This statement only applies to the use of a mix of different UVB spectra in the comparator intervention.
- Compared with **oral-PUVA**, **bath-PUVA** has a lower damage potential with regard to acute adverse effects (nausea and vomiting). Weak indications are available in respect of a reduced damage potential for long-term complications (squamous cell carcinoma of the skin). Treatment is more convenient for patients, due to the type of procedure applied. An equivalent benefit of asynchronous bath-PUVA with regard to the improvement of skin symptoms is, however, neither proven, nor can it be excluded.
- For the therapy goal "improvement of disease-related quality of life", no evidence of additional benefits or harms is available for **all types of asynchronous balneo-phototherapy**.
- For **synchronous balneo-phototherapy** (treatment with Dead Sea salt), an additional benefit was shown in patients with psoriasis compared with UVB monotherapy concerning the reduction of skin symptoms. A limited benefit was shown for the therapy goal "disease-related quality of life". In patients with atopic dermatitis, there are indications of an additional benefit with regard to the improvement of skin symptoms.

**Key words:**

Balneo-phototherapy, bath-PUVA, photo-brine therapy, balneo-phototherapy with Dead Sea salt, psoriasis vulgaris, atopic dermatitis, systematic review.