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PROTOCOL

# Acupuncture for Symptom Relief in Palliative Care—Study Protocol and Semistandardized Treatment Schemes

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**Abstract**
The use of complementary and alternative medicine methods such as acupuncture in palliative care has increased over the past years. Well-planned trials are warranted to show its effectiveness in relieving distressing symptoms. The development of treatment schemes to be used in the trial for both acupuncture and medical symptom control is challenging, as both acupuncture and palliative care are highly individualized. Thus, standardized care plans of a randomized controlled trial will have difficulties in producing treatment results that compare to the clinical practice. As an alternative, treatment protocols for both acupuncture and medical symptom control of dyspnea, pruritus, hypersalivation, depression, anxiety, and xerostomia were designed with the input of experts. They are designed to provide sufficient symptom control and comparability for a three-arm, randomized controlled trial. Medical symptom control will be provided to all groups. The two control groups will be medical treatment and sham-laser acupuncture.

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## 1. Introduction

Palliative care aims at the improvement of the quality of life for patients with progressive incurable diseases [1]. According to the World Health Organization, the control of distressing symptoms within these patients is a high priority [2]. Usually, this goal is achieved by a highly individualized care plan combining medical, social, and spiritual care. Complementary and alternative medicine (CAM) plays an increasing role in the treatment of these patients [3,4]. Acupuncture is one of the most popular CAM methods [5]. It is a relatively safe procedure, assuming that rules are followed [6]. During recent years, an extensive amount of research regarding the effectiveness of acupuncture in treatment of cancer symptoms has been performed [7]. To date, there is some evidence for the treatment of chemotherapy-induced nausea and vomiting [8,9], pain [10], hot flashes [11,12], insomnia [13], myelosuppression [14,15], and fatigue [16] by acupuncture. For other important symptoms like e.g. dyspnea, depression and anxiety, there is still a lack of enough high-quality research to gather scientific evidence. To keep track of the principles of evidence-based medicine, more well-planned trials are necessary.

The design of clinical trials has been an important topic in acupuncture research for some years now [17—19]. Quality criteria have been published [20,21], and there is an ongoing discussion regarding the choice of the control (sham) treatment [22,23]. Therefore, any acupuncture trial has to consider the design of treatment schemes as well as the control device.

The choice of the control treatment in palliative care is equally challenging: In the daily palliative practice, an effective treatment often consists of a combination of the various different available medications. In the context of a randomized controlled trial, an individualized pharmacological combination is difficult to combine with the required comparability. Considering the variety and different intensity of the symptoms, a practitioner experienced in palliative care is usually required for optimum symptom control [24]. Therefore, we decided to involve several experts in the field of palliative care into the configuration of the pharmacological control for this trial.

Taking all these objectives into consideration, for the design of this trial evaluating the effectiveness of acupuncture for symptom control of highly relevant and distressing symptoms such as dyspnea, itching, hypersalivation, depression, anxiety, and xerostomia in palliative care (the AcuPall Study), it was required to develop:

1. Acupuncture treatment schemes with semistandardized choice of acupuncture points.
2. Pharmacological treatment schemes for an optimum of symptom control in every group.

## 2. Materials and methods

### 2.1. Design

The AcuPall study is a three-arm, partially blinded, randomized controlled trial. It investigates the efficacy of (a) pharmacological symptom control without additional treatment versus (b) add-on acupuncture versus (c) add-on sham laser acupuncture in a palliative care setting. The six different investigated symptoms are dyspnea, pruritus, hypersalivation, xerostomia, depression, and anxiety. Pharmacological treatment follows specially designed protocols. Treatment will be provided to all patients, ensuring that a sufficient symptom control is guaranteed. First, there will be the pilot study as an exploratory part of the trial. It aims to recruit 60 patients per symptom. A sample size calculation will be performed for the confirmatory part of the trial, according to the size of observed effects. Apart from the sample size calculation, the design will be similar in both parts: After randomization, patients in both acupuncture groups receive three treatment sessions per week over a minimum period of 2 weeks (maximum 4 weeks). Psychological, social, and spiritual care will be provided to all patients. The total follow-up study period per patient is 6 weeks. The study protocol is in accordance to the declaration of Helsinki and the "ICH E6 Guideline for Good Clinical Practice." Written informed consent is obtained from all patients. Ethical approval has been given by the Ethics Committee of the University of Munich, Munich, Germany (number 146-09).

### 2.2. Randomization and blinding

For each symptom separately, patients will be randomized, using a series of sealed, sequentially numbered envelopes containing the treatment assignments. The envelopes will be prepared by an external person. When a patient fulfils the inclusion criteria, the acupuncturist will open the lowest numbered envelope to reveal the patient's group allocation. Neither the physician prescribing pharmacological treatment according to the treatment protocols nor the patient will know if they receive sham or verum treatment. Patients will be told that they will receive acupuncture, laser acupuncture, or standard medical treatment. They are further told that one treatment of the two types of acupuncture will be a placebo treatment. It will be left open if needle or laser acupuncture will be the sham treatment.

### 2.3. Patients

Patients will be recruited from the ward of the Interdisciplinary Palliative Care Centre, University of Munich and three other palliative care wards at community hospitals in Munich connected to the university and at the university hospital of the Paracelsus Medical University in Salzburg. Exclusion criteria are as follows: patients younger than 18 years, severe impairment of blood coagulation, noncompliance, pregnancy or lactation, acupuncture or transdermal electric neurostimulation treatment within the past 4 weeks, contraindications against one of the substances included in the treatment protocol (as listed in the summary of product characteristics), and the inability to sign written informed consent.

### 2.4. Participating physicians/acupuncturists

Participating trial physicians are from the above-mentioned institutions. All are experienced in palliative symptom

control. Pharmacological symptom control will be administered by a different physician than the physician who performs the acupuncture. Acupuncturists will be medical doctors who additionally fulfil the requirements for certification of the German medical Association.

## 2.5. Randomization and blinding

For each symptom separately, patients will be randomized, using a series of sealed, sequentially numbered envelopes containing the treatment assignments. The envelopes will be prepared by an external person. When a patient fulfills the inclusion criteria, the acupuncturist will open the lowest numbered envelope to reveal the patient's group allocation. Neither the physician prescribing pharmacological treatment according to the treatment protocols nor the patient will know if they receive sham or verum treatment. Patients will be told that they will receive acupuncture, laser acupuncture, or standard medical treatment. They will be further told that one treatment one of the two types of acupuncture will be a placebo treatment. It will be left open as to whether needle or laser acupuncture will be the sham treatment.

## 2.6. Outcome measures

The main outcome parameter is the alteration of symptom intensity prior to and at the end of the treatment sessions after 2 weeks [visual analogue scale (VAS), 0—100-10/10]. Secondary outcome parameters are the administered amounts of pharmacological symptom control (step on the medical treatment protocol).

## 2.7. Statistical analysis

The aim of the statistical analysis is the comparison of the main outcome measure [symptom intensity (VAS) after 2 weeks of treatment] between the three study groups (intervention groups: verum needle acupuncture, control groups: sham laser acupuncture control group and pharmacological symptom control group). For this variable, a non-normal distribution is assumed. Hence, a nonparametric method, the Kruskal—Wallis test, will be applied. *Post hoc* tests will be performed by pairwise comparisons of the three study groups using Mann—Whitney *U* test. Primary outcome is defined as symptom VAS in the needle acupuncture group in comparison to the pharmacological symptom control group.

## 2.8. Consensus process on treatment protocols

### 2.8.1. Pharmacological treatment protocols

To date, there are no standard recommendations regarding the most effective pharmacological combinations for symptom control in palliative care. Therefore, we chose the following procedure for the design of the pharmacological treatment protocols for this trial. In a first step, these protocols were designed according to standard recommendations [25]. In a second step, the protocols were reviewed by four experienced practitioners of palliative care and by a pharmacologist experienced in supervising medical combinations in palliative care. In a third step, the protocols were then sent out to German experts with more than 10 years of experience in palliative care. Medical treatment protocols are designed as a multiple-step ladder.

### 2.8.2. Acupuncture treatment protocols

The treatment strategies for acupuncture were developed based on a consensus process with experienced acupuncture experts from the faculty of one of the major German societies for medical acupuncture [German Medical Acupuncture Association, or Deutsche Ärztegesellschaft für Akupunktur (DÄGfA)]. A request was sent out to the members of the faculty of the DÄGfA asking them to list essential and optional acupuncture points in order of importance for the treatment of each symptom. Eight of them sent back their proposals, which were converted into the protocols according to the frequency in which the points were named (Table 7).

## 2.9. Acupuncture treatment

Patients in the acupuncture group and the sham laser group will receive Chinese-style acupuncture treatment at the same acupuncture points. Detailed diagnosis according to Traditional Chinese Medicine (TCM) diagnostic considerations (including pulse and tongue diagnosis) is assessed in every patient. Additional acupuncture points chosen according to TCM diagnosis are recorded in both groups.

Needle acupuncture will be performed using expendable needles (Seirin 0.15 × 20 mm or 0.3 × 30 mm) at defined acupuncture points. In patients with an extremely weak constitution, thin needles were chosen. Needling may be superficial, and deqi response (a deep aching or full feeling at the needle) is not obligatory. Needle techniques can include very point technique and dry needling.

Sham laser acupuncture was chosen as the placebo treatment. The device is a nonfunctioning laser pen that has been deactivated by the manufacturer (Handy CW 100, Schwa-Medico, Ehringshausen, Germany). Only red light is emitted. To strengthen the credibility of the imaginary power of this sham procedure, visual and acoustic signals accompany the red light emission. Patients will be treated for 15 seconds per point without skin contact.

# 3. Results

For the planned study on symptom relief in palliative care, seven different treatment protocols were designed in a consensus process for both the acupuncture treatment group and the control groups, as described below (Tables 1—6).

## 3.1. Acupuncture

Acupuncture treatment protocols were designed as semi-standardized protocols with obligatory points that must be treated. Additionally, the acupuncturist can choose from the pool of optional points chosen according to the diagnostic pattern and its corresponding meridian systems. Both

**Table 1** Medication protocol for dyspnea

| Possible routes of administration | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 | Step 7 |
|---|---|---|---|---|---|---|---|
| po (not extended-release preparations)/iv/sc | Opioid naive: Morphine $\leq$1 mg/d (1 mg po, o.d.) | Opioid naive: Morphine $\leq$3 mg/d (1 mg, po o.d.) | Opioid naive: Morphine daily dose $<$ 15 mg/d (1−3 mg morphine o.d.) | Permanent daily dose depending on prior titration with on-demand dose (1−3 mg morphine o.d.) | See below | See below | See below |
| | or | or | or | | | | |
| po (not extended-release preparations)/iv/sc | Nonopioid naive: $\leq$1 $\times$ 1/6 of morphine equivalent daily dose | Nonopioid naive: $\leq$3 $\times$ 1/6 of morphine equivalent daily dose | Nonopioid naive: $>$3 $\times$ 1/6 of morphine equivalent daily dose | Increase of daily dose depending on prior titration with on-demand dose (1 dose = 1/6−1/10 of Tagesdosis) | See below | See below | See below |
| | | | or | or | | | |
| iv/sc | | | Increase of permanent daily dose by $>$80% and $<$200% of initial morphine equivalent dose | Increase of daily dose by $>$200% of initial morphine equivalent dose | Increase of opioids does not provide sufficient control of dyspnea + Midazolam (Ramsay score 2) Anfangsdosis: 5−10 mg/24 h | Increase of opioids does not provide sufficient control of dyspnea + Midazolam (Ramsay score 2) | Increase of opioids does not provide sufficient control of dyspnea + Midazolam s.u. |
| po/iv/sc | | | | | | + Levomepromazine $\leq$40 mg/d | + Levomepromazine $\leq$40 mg/d |
| iv/sc | | | | | | | + Midazolam (Ramsay score $>$3) |
| Additional options | Corticosteroids (dexamethasone) | Inhalative oxygen | = + 1 step each | | | | |

Semistandardized protocol; pharmacological symptom control according to the different steps on the ladder: if no sufficient symptom control can be achieved on one step, then treatment will move in to the next step.
Corticosteroids (dexamethasone) or oxygen can be administered additionally (each +1 step). The dose per step is for evaluation only; the individual dosing will follow the particular needs of each patient.
iv = intravenous; o.d. = on-demand; po = *per os* (oral); sc = subcutaneous.

**Table 2** Medication protocol for depression

| Possible routes of administration | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 | Step 7 |
|---|---|---|---|---|---|---|---|
| po | Mirtazapine 15 mg/d or citalopram 20 mg/d | Mirtazapine 30 mg/d or citalopram 40 mg/d | Mirtazapine 45 mg/d or citalopram 60 mg/d | Mirtazapine 45 mg/d and citalopram 20 mg/d | Mirtazapine 45 mg/d and citalopram 40 mg/d | Mirtazapine 45 mg/d and citalopram 40 mg/d | Mirtazapine 45 mg/d and citalopram 40 mg/d |
| sl/po<br>iv/sc | | | | | | Lorazepam ≤6 mg/d | lorazepam ≤6 mg/d + Midazolam (Ramsay score 2) Anfangsdosis: 5–10 mg/24 h |

Pharmacological symptom control according to the different steps on the ladder: if no sufficient symptom control can be achieved on one step, treatment will move on to the next step. Caution is warranted in combining high doses of mirtazapine, citalopram and tramadol because of the risk of developing a serotonin syndrome.
The dose per step is for evaluation only; the individual dosing will follow the particular needs of each Patient.
iv = intravenous; po = *per os* (oral); sc = subcutaneous; sl = sublingual.

**Table 3** Medication protocol for anxiety

| Possible routes of administration | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 | Step 7 |
|---|---|---|---|---|---|---|---|
| sl/po | Lorazepam ≤1.5 mg/d | Lorazepam ≤6 mg/d | Lorazepam >6 mg/d | Lorazepam >6 mg/d | Lorazepam >6 mg/d | Lorazepam >6 mg/d | Lorazepam >6 mg/d |
| sc/iv | | | | + Midazolam (Ramsay score 2) Anfangsdosis: 5–10 mg/24 h | + Midazolam (Ramsay score 2) | + Midazolam (Ramsay score 2) | + Midazolam (higher dosing as described below) |
| po/sc/iv | | | | | + Haloperidol ≤1.5 mg/d (≤3 × 0.5 mg) | + Haloperidol ≤9 mg/d (≤3 × 3 mg) | + Haloperidol ≤9 mg/d (≤3 × 3 mg) |
| iv/sc | | | | | | | + Midazolam (Ramsay score >3) |

Pharmacological symptom control according to the different steps on the ladder: if no sufficient symptom control can be achieved on one step, treatment will move on to the next step.
The dose per step is for evaluation only; the individual dosing will follow the particular needs of each Patient.
iv = intravenous; po = *per os* (oral); sc = subcutaneous; sl = sublingual.

**Table 4** Medication protocol for pruritus

| Possible routes of administration | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 |
|---|---|---|---|---|---|---|
| po | Skin care | Desloratadine 5 mg/d | Dimetindene maleate ≤12 mg/d | Dimetindene maleate ≤4 mg/d, iv | Dimetindene maleate ≤4 mg/d, iv | Dimetindene maleate ≤4 mg/d, iv |
| iv/sc | | | | | Dexamethasone 8 mg/d | Dexamethasone 8 mg/d |
| iv/sc | | | | | | + Midazolam (Ramsay score 2) |

Semistandardized protocol; pharmacological symptom control according to the different steps on the ladder: if no sufficient symptom control can be achieved on one step, treatment will move on to the next step; gabapentin, mirtazapine, methylnaltrexone can be administered additionally (each +1 step). The dose per step is for evaluation only; the individual dosing will follow the particular needs of each Patient.
iv = intravenous; po = *per os* (oral); sc = subcutaneous.

**Table 5** Medication protocol for hypersalivation

| Possible routes of administration | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 | Step 7 |
|---|---|---|---|---|---|---|---|
| po | salvia | Amitriptyline 25 mg/d | Amitriptyline 50 mg/d | Amitriptyline 75 mg/d | Amitriptyline 100 mg/d | Butylscopolamine bromide 80 mg/d iv | Butylscopolamine bromide 120–150 mg/d iv |

Pharmacological symptom control according to the different steps on the ladder: if no sufficient symptom control can be achieved in one step, treatment will move on to the next step.
The dose per step is for evaluation only; the individual dosing will follow the particular needs of each Patient.

**Table 6** Medication protocol for xerostomia

| Possible routes of administration | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 |
|---|---|---|---|---|---|
| | Oral hygiene | Oral hygiene<br>Saliva substitutes | Oral hygiene<br>Saliva substitutes<br>Air moistening | Oral hygiene<br>Saliva substitutes<br>Air moistening<br>Pilocarpin ≤5 mg/d | Oral hygiene<br>Saliva substitutes<br>Air moistening<br>Pilocarpin ≤30 mg/d |

Pharmacological symptom control according to the different steps on the ladder: if no sufficient symptom control can be achieved in one step, treatment will move on to the next step.
The dose per step is for evaluation only; the individual dosing will follow the particular needs of each Patient.

the obligatory and the optional points were selected according to the input from the experts. Depending on each patient's individual TCM diagnosis, further points were possible as well as ear points or microsystem points. In very weak patients, single-point acupuncture might be indicated. For these cases, the most important acupuncture point for each symptom are described. In this case, the most important point is indicated by bold letters in Table 7 displaying the acupuncture scheme.

### 3.2. Pharmacological treatment

All experts agreed upon the statement that symptom control in palliative care requires multidisciplinary treatment that focuses on psychological, social, and spiritual aspects. These points are crucial. Thus, they will be provided to all patients regardless of the treatment group in this study. We have therefore not further mentioned these aspects in our treatment protocols.

Treatment protocols were designed as treatment ladders with multiple steps for each symptom. Sometimes the different steps consist of different medications. Sometimes they indicate the difference between a low and a high dosage of the same substance. The pharmacological dosages on the different steps are meant for evaluation. Individual titration is allowed and required. For some symptoms, additional treatments can be added at the best time for the individual patient, resulting in an elevation on the treatment ladder (+1 step).

For some symptoms (dyspnea and anxiety), the last treatment option is palliative sedation. In clinical practice (including study participants), this step will only be taken in

**Table 7** Semistandardized acupuncture treatment protocol for symptom control in palliative care

| Symptom | Obligatory acupoints | Optional acupoints |
|---|---|---|
| Dyspnea | CV17/PC 6/LU 7 | LU1/LU5/LU9, Bl13, ST 40/LG26/Ex Ding-Chuan |
| Pruritus | HT7/LI11; GV20 | Le3/HT7; SP 10; LG14 |
| Hypersalivation | Lokal: **ST4**/GV 26/CV24/; ST 40; | SP6/LI4/KD3; Bl20; LI20; ST36; further local: TW17/ST6/ |
| Depression | **HT7**; LI3/SP6/HT5 | Bl 18/Bl/20/ST 36; Bl 15/Bl 44/Bl23/LG20/KD6/HT3/Bl52/CV6/ Gb25/CV17/Ying-tang/LU7 |
| Anxiety | **HT7**; KD 3; GV20 | Bl23; Bl15; LU7/KD6/Bl44/Dü3/Bl62/HT3 |
| Xerostomia | ST6; ST7; KD3 | SP6; ST36/LI4/LI20/CV23/ST4 |

Obligatory points have to be treated (apart from the case of extreme weakness in which a single-point acupuncture can be chosen. In this case, the most important point is indicated by bold letters). Depending on his/her opinion, the acupuncturist can choose from the pool of optional points.

very rare cases and only after a decision-forming process that includes psychological/spiritual care and intensive discussion by a multidisciplinary team. Patients who express the wish for palliative sedation will be excluded from this study.

### 3.3. Dyspnea

Reasons for dyspnea can vary widely. This makes it difficult to settle for one treatment protocol. Symptomatic relief will be mainly achieved owing to the depression of breathing and the anxiolytic effect of opioids and benzodiazepines. In this context, opioids will be administered on demand. The dosage will depend on the pre-existing medication of the patient. If a patient is naïve to opioids, morphine will be given in an initial dose of 1 mg. In patients on fast opioid medication, the demand dosage for dyspnea will be 1/6 of the daily opioid dose. Besides the treatment ladder, patients can receive additional corticosteroids and/or oxygen if reasonable. For evaluation, this will be counted as one step higher on the treatment ladder.

### 3.4. Anxiety/depression

For depression, mirtazapine or citalopram will be administered in increasing dosages depending on whether a sedative or activating effect is preferred. From step 5 onward, both substances will be combined. For anxiety, lorazepam will be given. If more than 6 mg/d is insufficient, a permanent midazolam infusion will be added starting with 5—10 mg/24 h. Apart from medication, psychological/spiritual care is also essential and will be provided to all patients in the study.

### 3.5. Pruritus

Skin care forms the basis for further treatment. An antihistamine is the first step of pharmacological treatment followed by corticosteroids. Depending on the reason for pruritus, patients can receive additional medications beside the treatment ladder (methylnaltrexone, gabapentin, mirtazapine). For evaluation, each additional medication will be counted as one step higher on the treatment ladder.

### 3.6. Xerostomia

The treatment of xerostomia after radiotherapy includes oral hygiene, saliva substitutes, and pilocarpine.

### 3.7. Hypersalivation

Medical treatment for hypersalivation is mainly restricted to substances with anticholinergic activity as the antidepressant amitriptyline or butylscopolamine bromide. No antihistamines, beta-blockers, or invasive strategies are included owing to the limited scientific evidence of therapeutic effectiveness.

## 4. Discussion

We presented treatment schemes for both acupuncture and pharmacological symptom relief of dyspnea, anxiety, depression, pruritus, xerostomia, and hypersalivation designed with the input of experienced practitioners in the field of acupuncture or palliative care. The concept of semistandardized treatment protocols was inspired by a recent development in acupuncture trials: It has been criticized that a fast acupuncture scheme in a study protocol can result in an inflexible and nonindividual treatment. Assumedly, the results of these trials do not reflect the effects of acupuncture in the general practice [26]. Thus, there is an ongoing discussion on how to develop more individual acupuncture protocols that still meet requirements for clinical trials. Some researchers choose a semistandardized treatment protocol [27]. Others have their treatment protocol developed in an expert consensus process [28]. In the AcuPall protocol, we chose to combine both ideas for optimum effects. Having treatment protocols designed in a consensus process has the advantage that the knowledge and experience of a number of experts are combined. It is the strength of our study design that all treatment protocols (medication and acupuncture) were designed under the influence of expert opinions. However, it is a shortcoming that none of the published methods [29,30] were used for this consensus process.

During the process of designing pharmacological treatment schemes, some experts expressed doubts that a standardized protocol will sufficiently cover the patients' needs. We still believe that it will be possible to provide a

sufficient symptom control with the designed treatment protocols. Meanwhile, in 2015 the German Palliative Care Association has published S3 guidelines for some symptoms in palliative care including dyspnea, cancer pain, obstipation, depression, communication, and the last phase of life [31]. Recommended medication in these guidelines is in accordance with our protocols. However, most recommendations are expert opinions, as for some symptoms the scientific evidence, even for frequently used drugs, is low, mainly because of a lack of high-quality studies [32—36]. Even less evidence exists regarding the combination of different substances. However, in a clinical scenario, combinations of medication are often required for symptom relief. Because of this lack of reference points, we believe that our concept of creating a ladder scheme and adapting it according to expert opinions was the best available procedure. The pilot phase of the planned study will provide insight on this.

One point of critics might be the fact that the design of this trial tries to meet too many requirements and is not standardized enough. However, highly standardized efficacy trials have been criticized for their limited impact on decision making in clinical practice [37]. Thus, there is a current trend in medicine for comparative effectiveness research; the advantage of this type of research is its capacity to evaluate complementary and alternative treatment methods such as acupuncture as an optional add-on to conventional treatment, or as an alternative to it [38]. It aims to investigate the overall treatment effects in more pragmatic clinical settings and to examine the effectiveness of a treatment in less standardized, but closer to real-world scenarios [39]. Even though in this trial acupuncture will be used as an add-on treatment, the option to compare the steps on the treatment ladder of the different groups will still provide insight on the direct therapeutic effectiveness in symptom control.

Another item that has been discussed at length in acupuncture research is the choice of the control procedure [17—19]. The choice of sham-laser acupuncture in this study has the disadvantage that technical devices are not directly comparable to the manual skills of acupuncture. However, it has the advantage over minimal acupuncture (needle insertions at locations distant from real acupuncture points) that activation of nonspecific physiological effects such as stimulation of Aβ fibers or C fibers can be easily avoided. Furthermore, blinding of patients is easily achieved. The treatment setting of laser acupuncture carries equal weight to needle acupuncture in many respects, for example, attention, relaxation, and concentration on body sites distant from the affected painful area. Sham-laser acupuncture has been shown to be a valid placebo control for acupuncture trials [23] and has been successfully used in clinical studies before [40,41].

The design of this study (AcuPall) was planned to master the challenge of combining two highly individualized disciplines of medicine (acupuncture and palliative care) with the standardized processes in a high-quality clinical trial. Semistandardized protocols for medical and acupuncture treatment were developed with the help of experts in both fields. Their clinical value will be demonstrated during the course of the trial.

## Disclosure statement

DI received honorarium and travel costs from nonprofit academic organizations, from physician chambers, and from universities for teaching and lecturing. The other authors declare that they have no competing interests.

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