Whole-Systems Research in Integrative Inpatient Treatment

Guest Editors: Thomas Ostermann, Andre-Michael Beer, Vassya Bankova, and Andreas Michalsen
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In the last years, medicine has seen a shift from a depersonalized towards a patient-centered individualized medicine. This, on the one hand, is based on the achievements in the field of genetics and molecular science fostering an individually designed drug therapy and treatment tailoring [1]. On the other hand, research on patient-practitioner interaction, psychosocial and behavioral conditions of chronic diseases, and a patient-centered treatment approach has revealed that nonpharmacological factors such as empathy might be essential parameters for the outcome of the patient [2]. Moreover, complementary therapies as traditional whole-medical systems (Ayurveda, traditional Chinese medicine a.o.) or homeopathy, which according to their definition are individualized, have attained increasing interest for improving the patient care, for example, in the treatment of chronic diseases and pains syndromes. More recently, the combination of conventional medicine, complementary medicine, and patient-centered approaches has been put into the conceptional frame of “integrative medicine” which covers these topics adequately [3].

The most common and comprehensive definition up to now has been given by the Consortium of Integrative Medicine in 2005. It describes integrative medicine as “the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals, and disciplines to achieve optimal health and healing” [4]. It therefore joins the latest scientific advances with the profound insights of traditional healing systems and individualized patient care in complementary medicine to regain and preserve health and to enhance self-efficacy and patient’s own capacities to recover from illness and to maintain health.

In the last decades, several hospitals have adopted this concept of integrative medicine for the treatment of chronic and acute states of illnesses in an inpatient treatment. For instance, Sendelbach et al. (2003) describe the development of an inpatient integrative therapies program in a cardiovascular tertiary care center [5]. Ernst and Ferrer (2009) also reflect on the implementation of a 7-year integrative hospital program in a cardiac hospital center from the viewpoint of the nursing staff [6].

In almost all cases, these hospitals have integrated one or more complementary disciplines as naturopathy, anthroposophical medicine, homeopathy, or traditional Chinese medicine. While, in the USA integrative medicine has emerged towards a marker for innovative quality patient care within the last two decades, other countries have a longer tradition in this field [7]. In Germany, for instance, the amendment to the German Drug Law in 1976 has recognized anthroposophic medicine, homeopathy, and phytotherapy as “Specific Therapeutic Systems” [8]. As a consequence, inpatient treatment opportunities for integrative medicine
increased, and specialized hospitals and hospital departments started to evaluate their programs also with respect to comparative cost scenarios [9] which are nowadays still seen as a major goal [10]. Thus, several approaches have already entered the platform of in-patient care in integrative medicine. A current study of Kligler et al. (2011) found a decrease in the use of medications resulting in substantial cost savings in the care of oncology patients treated with an integrative in-patient approach including yoga therapy, holistic nursing, and healing environment [11]. Unfortunately, due to heterogeneity of the approaches and evaluations, the meta-analyses and systematic reviews of such evaluations in most cases suffer from a lack of comparability of outcome parameters within these evaluations so far.

Of note, whole-systems evaluation of integrative in-patient treatment might also benefit from a systematic analysis of the patient characteristics of clinical pathways and flow processes between in- and outpatient treatments, which has been described [12].

Finally, concepts of combining education, teaching, and in-patient integrative treatment can be seen as an important milestone for the development of integrative medicine. If only students are able to discover and get some first insight into the potential different perspectives of medicine and healing, they might be able to argue open-mindedly about the best fitting therapeutic strategy for the individual patient to regain his optimal health [13].

Despite these current achievements, evaluations of the approach of integrative medicine as a whole system and its interactions with other services of patient care have only been seen marginally. Thus, the cutting edge for the future development of integrative medicine now is to close the “evidence gap” [4] and to summarize and communicate these findings of research to the public, the stakeholders, and policy makers of healthcare authorities [14].

This special issue tries to step into this direction by bringing together evidence from different perspectives. Apart from whole-systems evaluations of hospital programs, cost studies, and findings on educational aspects of integrative medicine, this issue also covers historical aspects of the development of integrative medicine and presents the meta-analyses of integrative approaches. Hopefully, science-driven implementation of integrative medicine into hospitals and patient care can improve the 21st century medicine.

Thomas Ostermann
Andre-Michael Beer
Vassya Bankova
Andreas Michalsen

References


Research Article

Inpatient Treatment of Community-Acquired Pneumonias with Integrative Medicine

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Introduction. The aim of the presented observational case series was to evaluate the experience in treating patients with community-acquired pneumonia (CAP) within integrative medicine, particularly anthroposophic medicine in a well-experienced and specialized unit. Patients and Methods. Patients with proven CAP were evaluated (CAP-study group) based on a retrospective chart review. To estimate the severity of pneumonia, the pneumonia severity index (PSI) was applied. Treatment efficacy was evaluated regarding body temperature, CRP level, leukocytes blood count, the need to be treated on ICU, and mortality. Results were compared with the inpatient data of the Pneumonia PORT Validation Cohort. Results. 15/18 patients of the CAP-study group belonged to risk class groups I–III (low and moderate risk), 2 patients to risk class IV, and one patient to risk class V (severe pneumonia). 16/18 patients were treated with anthroposophic medicine only and 2/18 got additionally antibiotic therapy (both of risk class IV). A significant reduction of body temperature, CRP level, and leukocytes blood count has been obtained by applying anthroposophic medicine, while neither complications nor pneumonia-related death occurred. Compared with the control group there was no significant difference in mortality rate, whereby no patient had to be treated on the ICU, but the duration of hospital stay was significantly longer in the presented series. Conclusion. Inpatient treatment of CAP with anthroposophic medicine without the use of antibiotics may achieve reasonable results in selected cases. Additional larger sized prospective controlled trials should further clarify the role of AM in the treatment of CAP.

1. Introduction

Optimal treatment of pneumonia plays a critical role in temporary medicine regarding morbidity and mortality [1–4]. In Germany, annual occurrence of pneumonias accounts for 400000 to 600000 patients, with an inpatient treatment rate of 30–50% [5]. Lethality amounts to 0.6% among outpatients and from 13 to 14% among inpatients whereby a significant age dependency is typical [4, 6].

According to treatment guidelines, applications of antibiotics or other specific agents are strongly recommended. The aim of these standard treatments is to eliminate the causative agent (bacteria, viruses or mycoids, etc.) [4]. With increasing resistance to antibiotics [7–11], alternative treatment options are under debate. Moreover, the increasing request of patients on alternative treatment options [12–22] as well as cumulating data which might indicate a potential anticancerous role of acute inflammatory diseases and/or an adverse effect in antibiotic treatment [23–31] is triggering the discussion regarding treatment efficacy. In contrast, some approaches of integrative medicine primarily intend to support the human resources of recovery for curation (“aspect of salutogenesis”), while reducing or eliminating the causative agents (bacteria, viruses, or mycoids) becomes a secondary result only.

However, data on treatment efficacy in pneumonias including complementary and alternative medicine (CAM)—in particular anthroposophic medicine (AM)—are limited.
The aim of the presented study is to evaluate the treatment experience in applying anthroposophic medicine on a specialized and experienced unit with focus on the treatment of pneumonia.

2. Patients and Methods

Patients with proven diagnosis of community-acquired pneumonia (CAP), according to current guidelines [4], who were treated within the Department of Homeotherapy in Heidenheim between March 1999 and September 2001 were registered and consecutively divided into five subgroups. There were no further selection criteria, despite the willingness and consent of the patients, who were requesting integrative treatment. The Department of Homeotherapy in the Hospital of Heidenheim (Teaching Hospital of the University of Ulm, Germany) looks back on a 65-year experience in practising anthroposophic medicine (AM) including a broad spectrum of different applications within the scope of integrative medicine (IM). The concept of integrative medicine seeks not to weigh up conventional and alternative medicine against each other but to optimize both forms of treatment while intending an individualized approach [14–16,21].

Chart review was carried out focusing on the following parameters: initial clinical symptoms, radiologic features, blood sample tests, and clinical followup. Clinical data were retrospectively reviewed based on the hospital records including medical history and on results from the contributing radiologists and laboratory.

According to current guidelines [4] the diagnostic criteria for CAP were the clinical picture of an acute pneumonia, such as possible fever, shivering, cough, phlegm, sputum, chest pain, dyspnea in association with increased leucocyte and/or CRP levels, and newly manifest infiltration in a chest X-ray [4]. Patients with atypical manifestations, particularly elderly people, were also included if a clinical change occurred, like confusion or mobility impairment which could not be explained by any other reason, but at the same time a newly manifest infiltrate had to be spotted on the chest X-ray [4]. All patients who did not fulfill these criteria, who had hospital-acquired pneumonia (HAP), or who had immune deficiency were excluded. Also, lost of followup was a reason for noninclusion.

Results of chest X-rays were reviewed by two—and for this case series reevaluated by additional one—indeed consultant radiologist(s) who were blinded concerning prior diagnosis but confirming radiological signs of pneumonia.

In order to reduce potential coaffecting circumstances five different groups were differentiated (Figure 1).

Group 1 includes patients pretreated with antibiotics before admission to the Department of Homeotherapy; group 2 includes patients with an acute cardiac decompensation and a congestive pneumonia (treatment of heart failure improves usually pneumonia too in these cases); group 3 includes patients in palliative care. All other patients were defined as the CAP-study group: treated either with AM only (group 4) or additionally with antibiotics (group 5).

Pneumonia severity index (PSI) was applied in order to indicate the severity level of pneumonia, divided into five risk classes [32–35] (Table 1).

As shown in Table 1, patients were scored between −10 and +30 points for the different parameters. Patients were assigned to a risk class (risk class II, III, IV, or V) according to the number of points they scored. Identifying patients in risk class I is extensively described by Fine et al. [32]. Fine et al. had derived a prediction rule for the prognosis by analysing data of 14,199 adult inpatients with CAP. This risk score was validated on 38,039 adults hospitalized and data of 2287 inpatients and outpatients with community-acquired pneumonia.

In case of missing classification data, only the available information were incorporated into risk assessments. Consecutively, in these cases the patient was classified at a lower risk category and therefore rather understaged. The amount of missing data was documented.

Patients were informed about different treatment options available and about the estimation of the treating physician, whether antibiotics were needed or not. Treatments were carried out only in agreement with the patients (informed consent). The individualized treatments were evaluated gathering
Extending thirty months, 48 patients with “pneumonia” were admitted to the department of Homeotherapy in Heidenheim and treated based on anthroposophic medicine. 26 patients (19 f:7 m) with a mean age of 65.5 years (19–90 a; SD 19.84) fulfilled the inclusion criteria “community-acquired pneumonia” (see Figure 1). The comorbidities are outlined in Table 2.

**Figure 1:** Flow chart of the inclusion and exclusion processes. *Other reasons for exclusion: patients with an immunodeficiency (n = 1), patients lost of followup (n = 1, this patient wanted to be moved to a hospital closer to home).
Table 2: Comorbidities of all included patients in the case series (𝑛= 26).

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Patients (𝑛)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>8</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1</td>
</tr>
<tr>
<td>Exsiccosis</td>
<td>1</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary emphysema</td>
<td>4</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>2</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol dependency</td>
<td>1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6</td>
</tr>
<tr>
<td>Cachexia</td>
<td>3</td>
</tr>
<tr>
<td>Thyroid diseases</td>
<td>4</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>1</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>12</td>
</tr>
</tbody>
</table>

18 of these patients showed no major comorbidities, which otherwise might mainly influence the course of the pneumonia (such as congestive heart failures, immunodeficiency), and therefore these 18 patients became the main focus for the evaluation of anthroposophic medicine (CAP-study group, see also Figure 1). The distribution of risk classification according to the pneumonia severity index (PSI) is outlined in Table 3.

On the whole 494 items could have been evaluated for calculating the PSI while 65 were missing. That counts for a missing data rate of 13.1%, from 0 to 4 data tops per patient (median 2.0). The pO₂ and pH value were the most common missing data, followed by respiratory rate and in few cases glucose and blood urea nitrogen.

16/18 patients were treated applying anthroposophic medicine and without the use of antibiotics; in 2/18 patients, antibiotics were applied in addition. The individualized application plan for each patient in regard to anthroposophic medication and treatment is outlined in Table 4.

With regard to parameters which indicate efficacy of treatment (in these series AM treatment) the body temperature, the leukocyte blood count, and CRP levels were documented. 70% of patients were free of fever after 72 hours (3d) consecutive to the onset of AM treatment. The maximal duration of febrile body temperature amounted to 10 days (Figure 2). In one patient (who has got additionally antibiotic therapy), allopathic antipyretic therapy (Novaminsulfon acid) was applied per os over a period of 5 days. Despite two patients (out of palliative care group 3) in all patients a highly significant decrease of initially elevated CRP levels was observed (Figure 3 and Table 5) beside normalization of leukocyte blood count in cases of initial leukocytosis (Tables 8 and 9).

The mean duration in hospital within the CAP-study group (𝑛= 26) was 20.2 days (Table 7). None of these patients needed to be treated on the ICU, compared to 9.2% within the control group, ranging from 4.3% to 5.9% in lower risk classes I–III, 11.4% in risk class IV, and 17.3% in risk class V whereby the duration in hospital is ranging from 5 to 11 days [32].

On the whole, one patient died for not pneumonia-related reasons (out of palliative care group 3), within the patients who fulfilled the inclusion criteria (groups 1–5, 𝑛= 26; 3.8%). In comparison to the control group (mortality rate of 8%), no significant difference (𝑃= 0.44) within statistical analysis, using the chi-square test, was observed (Table 6). Two of the primarily excluded patients with HAP (𝑛= 22, see Figure 1), who belonged to palliative care patients, died (age 90 and 91). In order to estimate whether a selection bias might influence not seeing a significant difference in comparison to the control group chi-square-test was applied also on
the whole collective included (excluded patients plus groups 1–5, n = 48) obtaining a mortality rate of 6.3% compared to 8.0% in the PORT control group (P = 0.69), indicating also no significant difference.

The CRP level was reduced significantly (P = 0.000) in all patients with CAP (n = 26, Table 5). Within the subgroup “treated with AM only” (group 4, CAP-study group) also a significant reduction of CRP levels was observed within 4–9 days and until discharge (P = 0.001 and P = 0.003, resp.). Within the subgroups pretreated or additionally treated with antibiotics (group 1 plus group 5) a significant reduction of the CRP level was only observed after 4–9 days until discharge (P = 0.04, Table 5).

Table 3: Patients of groups 1–5 according to risk class of PSI.

<table>
<thead>
<tr>
<th>Risk class</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
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<tr>
<td>Total</td>
<td>26</td>
<td>4</td>
<td>2</td>
<td>16</td>
<td>2</td>
<td>60</td>
</tr>
</tbody>
</table>

There were no additional complications observed within the presented study.

In order to present the data most transparent, each individual course is outlined within Tables 8, 9, 10, 11, and 12 according to the groups.

4. Discussion

From the background of achieving high cure rates, antibiotic therapy for community-acquired bacterial pneumonia is the treatment of choice today. However with increasing resistance to antibiotics, unpleasant adverse effects and not least with rising request of patients to be treated within the scope of an integrative approach, alternative treatment options are under debate. Moreover, available data in this context is limited within the established medical literature. Therefore, the aim of the presented observational case series is to evaluate the experience in treating community-acquired pneumonia (CAP) with anthroposophic medicine (AM) within a highly specialized and well-experienced medical unit. The data of the presented observational case series are documenting the availability of an integrative treatment option for the treatment of CAP in hospital with good and comparable results in certain cases, in the context of such a specialized medical unit. Herewith, the presented study reports on unique data on a very relevant topic. However, due to the retrospective study design, the small number of patients, and a mutually not to be underestimated selection bias, the weight of conclusions for future treatment strategies in bacterial pneumonias is limited. Therefore, controlled prospective trials remain to further clarify the role of integrative medicine in the treatment of pneumonias.

Out of 48 patients with pneumonia, 26 had CAP, and 18 patients out of these were primarily treated with AM (CAP-study group, see Figure 1 and Table 3), while two of the latter got additional antibiotic treatment during their course. The individual anthroposophic treatment (as outlined in Table 4) did significantly reduce body temperature, CRP level (P = 0.03), and white blood cell count, while no statistical difference with regard to morbidity or mortality was observed (P = 0.44; P = 0.69), but a 2-3-fold longer hospital stay was necessary in comparison to the conventional standard antibiotic treatment of bacterial CAP in the control group [36] (Table 7). This is in line with published data concerning the antibiotic treatment of CAP [37], while there are no comparable studies on CAM or AM regarding inpatient treatment of CAP. Within the CAP study group, there was no pneumonia-related death observed, and none of the patients needed to be treated on the ICU. Anyhow, it is questionable, whether the investment of a multifold longer hospital stay—at least with regard to the costs—might be at any time convincing in order to support the integrative approach in the management of pneumonia. However, despite the economical aspect at first step, which favours the antibiotic treatment, there are also critical data on long term adverse effects in context with antibiotic and antiinflammatory treatments published [27–31, 38], such as pro-cancerous effects and/or relations to the genesis of immunological disorders, for example, in melanoma of the skin [27], in breast cancer [31], and also in hemato-oncological diseases like acute lymphatic leukaemia [30] or non-Hodgkin lymphoma [31]. The use of antibiotics and antipyretic drugs seems to play a major role in the development of allergies and/or autoimmune diseases, too [38]. But these long term sequelae of antibiotic and antipyretic/anti-inflammatory drugs as well as a potential benefit by using alternative approaches are very difficult to evaluate and therefore remain to be further investigated in future studies. From the view point of integrative medicine, the intention to mobilize human natural resources of recovery (salutogenic approach) should reduce adverse events or any other harms to the patients but still remain to be proven yet. Moreover, the rate of recurrence might be a supplemental challenging issue with regard to treatment efficacy and sustainability. Whether the character of approach (integrative and salutogenic or allopathic) may substantially influence the recurrence rate of pneumonia or other sequelae diseases should be consecutively of interest, also regarding the economic debate.
Table 4: Individualized application plan for each patient.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Antipyretic</th>
<th>Application</th>
<th>Patient Nr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg.</td>
<td>m. p.</td>
<td>s. c.</td>
<td>1 ++ + + + +</td>
</tr>
<tr>
<td>Echinacea</td>
<td>D6</td>
<td>s. c/p. o.</td>
<td>2 + + + + + +</td>
</tr>
<tr>
<td>Ferr. sid.</td>
<td>D20</td>
<td>s. c.</td>
<td>3 Pretreated + + + + +</td>
</tr>
<tr>
<td>Milkefolium</td>
<td>D4</td>
<td>s. c.</td>
<td>4 + + D10 D6 + + + + +</td>
</tr>
<tr>
<td>Ferr. phos.</td>
<td>D6</td>
<td>p. o.</td>
<td>5 + + D10 D10 + D6 + + + + +</td>
</tr>
<tr>
<td>Equisetum</td>
<td>D20</td>
<td>p. o.</td>
<td>6 + + + D3 Dil. D6 + + + + +</td>
</tr>
<tr>
<td>Petasites</td>
<td>D3</td>
<td>s. c.</td>
<td>7 + + + + Dil. + + + + +</td>
</tr>
<tr>
<td>Prunus spi.</td>
<td>D3</td>
<td>p. o.</td>
<td>8 D10 D2 + + + + +</td>
</tr>
<tr>
<td>Sticta</td>
<td>pulm</td>
<td>D3</td>
<td>9 Pretreated + + + + + +</td>
</tr>
<tr>
<td>Tartaros</td>
<td>stibiatus</td>
<td>D3</td>
<td>10 Pretreated + + + D6 + + + + +</td>
</tr>
<tr>
<td>Bryonia</td>
<td>D4</td>
<td>Ext.</td>
<td>11 Pretreated + + D6 + + + + +</td>
</tr>
<tr>
<td>Gelomyrtol</td>
<td></td>
<td>Ext.</td>
<td>12 + + + + + + + + + + +</td>
</tr>
<tr>
<td>Carb. bet.</td>
<td></td>
<td>Ext.</td>
<td>13 Pretreated + + + + + + +</td>
</tr>
<tr>
<td>Ginger</td>
<td>Millefol.</td>
<td>Mustard</td>
<td>14 Pretreated + + + D2 and D6 Dil. + + + + +</td>
</tr>
<tr>
<td>Cochlearia</td>
<td></td>
<td>Potatoes</td>
<td>15 Pretreated + + + D6 + + + + +</td>
</tr>
<tr>
<td>Tartaros</td>
<td>stibiatus</td>
<td></td>
<td>16 Pretreated + + + + Dil. + + + + +</td>
</tr>
<tr>
<td>Bryonia</td>
<td>D4</td>
<td></td>
<td>17 + + + D2 Dil. + + + + +</td>
</tr>
<tr>
<td>Gelomyrtol</td>
<td></td>
<td></td>
<td>18 + + + D8 Dil. + + + + +</td>
</tr>
<tr>
<td>Carb. bet.</td>
<td></td>
<td></td>
<td>19 + + D10 + + + + + +</td>
</tr>
<tr>
<td>Ginger</td>
<td>Millefol.</td>
<td>Mustard</td>
<td>20 Pretreated + + + D10 + + + + +</td>
</tr>
<tr>
<td>Cochlearia</td>
<td></td>
<td>Potatoes</td>
<td>21 + + + + + + + + + + +</td>
</tr>
<tr>
<td>Petasites</td>
<td></td>
<td></td>
<td>22 + + + + + + + + + + +</td>
</tr>
<tr>
<td>Prunus spi.</td>
<td></td>
<td></td>
<td>23 + + + + + + + + + + +</td>
</tr>
<tr>
<td>Sticta</td>
<td></td>
<td></td>
<td>24 + + + + + + + + + + +</td>
</tr>
<tr>
<td>Tartaros</td>
<td></td>
<td></td>
<td>25 + + + + + + + + + + +</td>
</tr>
<tr>
<td>Bryonia</td>
<td></td>
<td></td>
<td>26 + + + + + + + + + + +</td>
</tr>
</tbody>
</table>

This table shows the individual therapy plan of each patient. Peroral (p.o.) and subcutaneous medication (s.c.) is outlined as well as external applications (Ext.). We omitted the illustration of conventional co-medication. If the applied homeopathic potencies differed from the described in the headline, it was particularly outlined in the table. CAP-study group are bold.
In addition, also multiresistance of pneumonia inducing bacteria has become a rising and challenging issue at present [7–11], which might be solved at least in selected patients who could be treated with anthroposophic medicine instead of antibiotics. Consecutively, selection criteria which may indicate secure application of integrative treatment options remain also to be further evaluated. In the presented course of patients with CAP the indication to additionally apply antibiotics appeared whenever a patient did not show any sign of recovering within three days after onset of treatment (like in two patients of the CAP study group) or if a progressive deterioration was obvious regarding parameters, such as dyspnea, body temperature, CRP level, or white blood cell count.

With regard to the well-validated classification of CAP into different levels of severity (PSI: pneumonia severity index), 15/18 patients of the CAP-study-group belonged to lower risk classes I–III, and all of these were treated with AM only (Table 3). Two patients of risk class IV were treated with antibiotics in addition to AM. Finally one patient classified into risk class V could also be treated with AM only. These data may show the practicability of AM in the treatment of pneumonia in principle, but neither do the low number of patients and the retrospective design allow to conclude reliable expectations on treatment results nor do they indicate certain limitations of the anthroposophic therapeutic concept. Therefore controlled prospective studies remain to be performed in order to clarify strengths and limitations of the integrative approach in the treatment of pneumonia.

Anyhow it is worth to notice that even severe pneumonias might be approachable by applying AM only, as indicated by the patient classified in risk class V. This is in accordance with recently published data reporting a successful treatment course in a case of a 96-year-old female with severe pneumonia, lung abscess, and associated septicemia, treated with AM only (without antibiotic) [39]. Therefore, it needs years of experience as well as a time-intensive dedication.
<table>
<thead>
<tr>
<th>Nr.</th>
<th>Sex</th>
<th>Age</th>
<th>Risk class</th>
<th>Temperature</th>
<th>First day subfebrile temp.</th>
<th>Leukocyte begin</th>
<th>Lc. end</th>
<th>CRP (1–3 days)</th>
<th>CRP (4–9 days)</th>
<th>CRP end</th>
<th>Comorbidities</th>
<th>Medical history and findings on admission</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>44</td>
<td>I</td>
<td>38.2</td>
<td>2</td>
<td>12.48</td>
<td>4.4</td>
<td>411</td>
<td>66.8</td>
<td>6.9</td>
<td>Pleurisy, hepatitis, burnout syndrome, sinusitis, and vertebral discprotrusion</td>
<td>For some days coughing with fever, temperature up to 40°C. Poor general condition, crackling sounds on the lungs.</td>
<td>Large infiltrate upper left lobe and lower right lobe.</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>40</td>
<td>I</td>
<td>39.9</td>
<td>7</td>
<td>Normal level</td>
<td>119</td>
<td>16</td>
<td>0.1</td>
<td></td>
<td>Hepatitis, sinusitis, recurring pyelonephritis, and hepatic steatosis</td>
<td>Sore throat and cough for 10 days, one week of fever. Poor general condition, obesity, dyspnea on exertion, chills, and crackling sounds on the lungs.</td>
<td>Infiltrate in the lingula of the left lung.</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>19</td>
<td>I</td>
<td>39.6</td>
<td>3</td>
<td>18.71</td>
<td>8.27</td>
<td>323</td>
<td>63.9</td>
<td></td>
<td>Pleurisy, accompanying hepatitis</td>
<td>Fever up to 41°C. Spastic and crackling sounds on the right side of the lung. Poor general condition.</td>
<td>Large infiltrate upper right lobe.</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>75</td>
<td>II</td>
<td>39.2</td>
<td>10</td>
<td>3.80</td>
<td>6.4</td>
<td>44.2</td>
<td>31.3</td>
<td>8.0</td>
<td>Arterial hypertension, adenoma of the thyroid</td>
<td>Cough and fever 3 days prior to admission. Good general condition. Cracking sounds on the lung.</td>
<td>Small infiltrate basolateral right.</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>58</td>
<td>II</td>
<td>39.2</td>
<td>7</td>
<td>Normal level</td>
<td>113</td>
<td>37</td>
<td></td>
<td></td>
<td>Schizophrenia, recurrent pneumonia</td>
<td>Cough with sputum and dyspnea 5 days prior to admission. Tachydyspnea, cyanosis of the lips, and crackling sounds on the lung.</td>
<td>Infiltrate lower left part of the lung.</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>51</td>
<td>II</td>
<td>39.7</td>
<td>3</td>
<td>2.90</td>
<td>4.6</td>
<td>96.2</td>
<td>17.2</td>
<td>3.6</td>
<td>Sinusitis, stomatitis, and dizziness</td>
<td>One week of fever up to 40°C, 2 days of strong cough with sputum. Sinusitis. Poor general condition, cracking sounds on the lungs.</td>
<td>Large infiltrate lower and middle lobes.</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>48</td>
<td>II</td>
<td>38.6</td>
<td>2</td>
<td>13.41</td>
<td>110</td>
<td>11.0</td>
<td>0.1</td>
<td></td>
<td>Pleurisy</td>
<td>Fever for one week, up to 39°C. Dry cough. Poor general condition, pleural sounds. Wheezing.</td>
<td>Initial: large infiltrate right middle and lower lobes.</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>40</td>
<td>II</td>
<td>37.0</td>
<td>1</td>
<td>Normal level</td>
<td>48</td>
<td>25.8</td>
<td>3.7</td>
<td></td>
<td>Depression</td>
<td>Cough, exhaustion, and pain in the limbs. Before admission fever, sputum, and dyspnea.</td>
<td>Infiltrate in the middle lobe of the lungs, bilaterally.</td>
</tr>
<tr>
<td>Nr.</td>
<td>Sex</td>
<td>Age</td>
<td>Risk class</td>
<td>Temperature</td>
<td>First day subfebrile temp.</td>
<td>Leukocyte begin</td>
<td>Lc. end</td>
<td>CRP (1–3 days)</td>
<td>CRP (4–9 days)</td>
<td>CRP end</td>
<td>† Comorbidities</td>
<td>Medical history and findings on admission</td>
<td>Chest X-ray</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>-----</td>
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<td>-------------</td>
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<td>----------------</td>
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<td>----------------</td>
<td>-------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>34</td>
<td>II</td>
<td>40.0</td>
<td>9</td>
<td>17.53</td>
<td>6.64</td>
<td>318</td>
<td>254</td>
<td>0.1</td>
<td>Pleurisy, burnout syndrome, and mild hyperthyreosis</td>
<td>One day before admission dry cough, fever up to 39°C. Poor general condition. Reduced breathing sounds.</td>
<td>Infiltrate lower right part of lungs.</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>32</td>
<td>II</td>
<td>39.9</td>
<td>3</td>
<td>17.43</td>
<td>4.72</td>
<td>320</td>
<td>42.8</td>
<td>2.1</td>
<td>Pleurisy, grand mal epilepsy. Recurrent pneumonia</td>
<td>Cough, chest pain on the right side, which got worse in the last few days, plus night sweats and a temperature up to 40.4°C. Poor general condition. Normal breathing.</td>
<td>Infiltrate middle lobes.</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>82</td>
<td>IIII</td>
<td>39.0</td>
<td>6</td>
<td>14.13</td>
<td>6.24</td>
<td>286</td>
<td>60.7</td>
<td>7.1</td>
<td>Chronic progressive respiratory insufficiency due to emphysema, post-tuberculosis condition with sintering of the left-sided lobe of the lungs, and arrhythmia</td>
<td>Poor general condition, bad nutritional state. Dyspnea.</td>
<td>Infiltrate left middle lobes.</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>67</td>
<td>III</td>
<td>38.6</td>
<td>2</td>
<td>18.47</td>
<td>6.64</td>
<td>55.6</td>
<td>11.4</td>
<td></td>
<td>Emphysema, chronic fibrosis of the lungs, and neurofibromatosis with cerebral microangiopathy, chronic alcoholism, and cachexia</td>
<td>Cough and sputum, temperature up to 39°C. At admission in a bad nutritional state, poor general condition, cyanosis, shortness of breath, neglected appearance, and crackling sounds on the lungs.</td>
<td>Infiltrate lower right lobe, pronounced emphysema, fibrosis, and cor pulmonale.</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>65</td>
<td>III</td>
<td>39.2</td>
<td>2</td>
<td>Normal level</td>
<td>6</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
<td>Breast cancer, arterial hypertension, and arrhythmia</td>
<td>Fever 1d prior to admission, at admission 39.2°C, dry cough, rare sputum, weakened general condition. Crackling sounds on the lungs.</td>
<td>Infiltrate lower right part of lungs.</td>
</tr>
</tbody>
</table>
### Table 8: Continued.

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Sex</th>
<th>Age</th>
<th>Risk class</th>
<th>Temperature</th>
<th>First day subfebrile temp.</th>
<th>Leukocyte begin</th>
<th>Lc. end</th>
<th>CRP (1–3 days)</th>
<th>CRP (4–9 days)</th>
<th>CRP end</th>
<th>† Comorbidities</th>
<th>Medical history and findings on admission</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>F</td>
<td>64</td>
<td>III</td>
<td>38.9</td>
<td>3</td>
<td>13.95</td>
<td>7.14</td>
<td>216</td>
<td>30.4</td>
<td></td>
<td>Chronic heart failure, burn-out syndrome, candidiasis, and pleurisy</td>
<td>One week of coughing without sputum, fever: 39-40°C, initial vomiting. Poor general condition, crackling sounds on the lungs.</td>
<td>Infiltrate lower right lobe.</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>31</td>
<td>III</td>
<td>39.4</td>
<td>5</td>
<td>Normal level</td>
<td></td>
<td>22.9</td>
<td>15.9</td>
<td>5.9</td>
<td>Emphysema, mental retardation, cardiac arrhythmia, mild hyperthyroidism, and mycoplasma pneumonia</td>
<td>One week of cough and fever, drinks little, received intravenous fluids 2 days prior to admission, poor general condition, cachetic, crackling sounds on the lungs.</td>
<td>Initial: large infiltrate middle and lower lobes right and left lower lobes.</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>71</td>
<td>V</td>
<td>38.8</td>
<td>6</td>
<td>Normal level</td>
<td></td>
<td>90.2</td>
<td>9.9</td>
<td>4.2</td>
<td>Breast cancer, uterus carcinoma, primary biliary cirrhosis, and current radiotherapy</td>
<td>Cough, sputum. Sinusitis. Poor general condition, breathing sounds on the right side. Crackling sounds on the lungs.</td>
<td>Large infiltrate lower right side of the lung, pleural effusion.</td>
</tr>
</tbody>
</table>

Sex: F: female; M: male; risk class after Fine et al [32]. "temperature" is the highest measured temperature within the first three days outlined. First day subfebrile temperature: the first day the patient shows temperatures below 38.0°C. Leucocytes: highest number of leucocytes within the first three days. Lc. end: the count of leucocytes at discharge of the hospital. In case of normal leucocytes, no further recording performed. CRP 1st and 3rd days: highest value within the first three days as inpatients. CRP days 4 till 9: the lowest value within this time span. CRP end: CRP at end of treatment. †: Death.
Table 9: CAP-study group: patients with AM and additionally treated with antibiotics (group 5).

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Sex</th>
<th>Age</th>
<th>Risk class</th>
<th>Temperature</th>
<th>First day subfebrile temp.</th>
<th>Leukocyte begin</th>
<th>Lc. end</th>
<th>CRP (1–3 days)</th>
<th>CRP (4–9 days)</th>
<th>CRP end</th>
<th>† Comorbidities</th>
<th>Medical history and findings on admission</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>79</td>
<td>IV</td>
<td>39.8</td>
<td>Normal level</td>
<td>94</td>
<td>39.0</td>
<td></td>
<td></td>
<td></td>
<td>Chronic heart failure, arterial hypertension, acute severe diarrhoea, acute hemorrhagic cystitis, decubitus ulcer (heel and coccygeal), and dehydration</td>
<td>Diarrhoea and fever: 39-40°C, dyspnea, Crackling sounds on the lungs, cyanotic lips. Poor general condition.</td>
<td>Infiltrate retrocardiac left, central pulmonary congestion.</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>75</td>
<td>IV</td>
<td>38.9</td>
<td>Normal level</td>
<td>44</td>
<td>34.0</td>
<td>4.0</td>
<td></td>
<td></td>
<td>Acute heartattack with aneurysm of the heart during inpatient treatment pancreatic insufficiency, condition after Billroth II resection of the stomach</td>
<td>38.9°C 3 days prior admission, shivering and sweating, and cough with sputum. Poor general condition.</td>
<td>Initial: no infiltrates. Control: infiltrates on the right and left sides.</td>
</tr>
</tbody>
</table>

Sex: F: female; M: male; risk class after Fine et al [32]. "temperature" is the highest measured temperature within the first three days outlined. First day subfebrile temperature: the first day the patient shows temperatures below 38.0°C. Leucocytes: highest number of leucocytes within the first three days. Lc. end: The count of leucocytes at discharge of the hospital. In case of normal leucocytes, no further recording was performed. CRP 1st and 3rd day: highest value within the first three days as inpatients. CRP day 4 till 9: the lowest value within this time span. CRP end: CRP at end of treatment. †: Death.
Table 10: Patients pretreated with antibiotics before admission (group 1).

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Sex</th>
<th>Age</th>
<th>Risk class</th>
<th>Temperature</th>
<th>First day subfebrile temp.</th>
<th>Leukocyte begin</th>
<th>Lc. end</th>
<th>CRP (1–3 days)</th>
<th>CRP (4–9 days)</th>
<th>CRP end</th>
<th>† Comorbidities</th>
<th>Medical history and findings on admission</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>86</td>
<td>V</td>
<td>38.6</td>
<td>4</td>
<td>Normal level</td>
<td>99</td>
<td>48</td>
<td>29.7</td>
<td></td>
<td>Dementia, cachexia, exsiccosis, breast cancer, mild hyperthyroidism, and large pleural effusion</td>
<td>Recurrent fever up to 39°C while on antibiotics; multiple pretreated with antibiotics (cephalosporins, quinolone). Very poor general status, malnutrition, and attenuation of the breathing sounds.</td>
<td>Large pleural effusion, large infiltrate on the right lung.</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>57</td>
<td>II</td>
<td>37</td>
<td>1</td>
<td>Normal level</td>
<td>56.0</td>
<td>11.4</td>
<td>0.0</td>
<td></td>
<td>Hypothyroidism, hepatitis</td>
<td>Fever, cough with sputum and fatigue 3 d prior to admission. Antibiotic pretreatment of 2 d. Poor general status, cyanosis of the lips, cold sweat, and abnormal breath sounds of right lung.</td>
<td>Infiltrate right upper part of lungs.</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>68</td>
<td>IV</td>
<td>40.8</td>
<td>5</td>
<td>Normal level</td>
<td>25</td>
<td>5.0</td>
<td>5.2</td>
<td></td>
<td>Gastric carcinoma, hypothyroidism</td>
<td>One week of fever, up to 39°C 3 d prior to admission. Antibiotic pretreatment of 3 d (quinolone), no crackling sound on the lungs.</td>
<td>Infiltrate of the lower right segment.</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>66</td>
<td>II</td>
<td>38.5</td>
<td>8</td>
<td>Normal level</td>
<td>70</td>
<td>53.7</td>
<td>7.4</td>
<td></td>
<td>Chronic obstructive pulmonary disease (COPD), coronary heart disease, arterial hypertension, spinal syndromes with paralysis of the legs, and chronic heart failure (NYHA II-III)</td>
<td>2a of COPD with dry cough and dyspnea, temperature up to 38.5°C, and cough for one week prior to admission. Antibiotic pre-treatment of 2 d (cefadroxil). Poor general status, obesity, and crackling sound on both lower parts of the lungs.</td>
<td>Infiltration right lower lung.</td>
</tr>
</tbody>
</table>

Sex: F: female; M: male; risk class after Fine et al. [32]. “temperature” is the highest measured temperature within the first three days outlined. First day sub-febrile temperature: the first day the patient shows temperatures below 38.0°C. Leucocytes: highest number of leucocytes within the first three days. Lc. end: the count of leucocytes at discharge of the hospital. In case of normal leucocytes, no further recording was performed. CRP 1st and 3rd days: highest value within the first three days as in-patients. CRP days 4 till 9: the lowest value within this time span. CRP end: CRP at end of treatment. †: Death.
<table>
<thead>
<tr>
<th>Nr.</th>
<th>Sex</th>
<th>Age</th>
<th>Risk class</th>
<th>Temperature</th>
<th>First day subfebrile temp.</th>
<th>Leukocyte begin</th>
<th>Lc end</th>
<th>CRP (1-3 days)</th>
<th>CRP (4-9 days)</th>
<th>CRP end</th>
<th>† Comorbidities</th>
<th>Medical history and findings on admission</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>85</td>
<td>III</td>
<td>39.0</td>
<td>13</td>
<td>13.28</td>
<td>71</td>
<td>44.5</td>
<td>6.1</td>
<td></td>
<td>Chronic heart failure, deep vein thrombosis, and arterial hypertension</td>
<td>Was admitted with a deep vein thrombosis. Enlarged swollen leg. Crackling sound of the lungs. Temperature 39°C.</td>
<td>Infiltrate on the left side. Enlarged heart, pulmonary vascular congestion.</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>87</td>
<td>V</td>
<td>39.0</td>
<td>Normal level</td>
<td>53</td>
<td>16.0</td>
<td>&lt;0.1</td>
<td></td>
<td></td>
<td>Chronic heart failure, rectal carcinoma, Pleuritis calcarea, and deep vein thrombosis</td>
<td>Dyspnea, fever, also thoracic pressure 3 d prior to admission. Poor general condition. Crackling sounds on the right side of the lungs.</td>
<td>Initial: no infiltrate, pleuritis calcarea, increased heart size, and central congestion. Control after four days: infiltrate right side infradacivial, decrease of heart size.</td>
</tr>
</tbody>
</table>

Sex: F: female; M: male; risk class after Fine et al. [32]. "temperature" is the highest measured temperature within the first three days outlined. First day subfebrile temperature: the first day the patient shows temperatures below 38.0°C. Leucocytes: highest number of leucocytes within the first three days. Lc. end: the count of leucocytes at discharge of the hospital. In case of normal leucocytes, no further recording was performed. CRP 1st and 3rd days: highest value within the first three days as inpatients. CRP days 4 till 9: the lowest value within this time span. CRP end: CRP at end of treatment. †: Death.
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<th>Nr.</th>
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<th>Temperature</th>
<th>First day sub-febrile temp.</th>
<th>Leukocyte begin</th>
<th>Leukocyte end</th>
<th>CRP (1–3 days)</th>
<th>CRP (4–9 days)</th>
<th>CRP end</th>
<th>Comorbidities</th>
<th>Medical history and findings on admission</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>91</td>
<td>V</td>
<td>36</td>
<td>1</td>
<td>Normal level</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td>Renal insufficiency, chronic heart failure with acute decompenesation, tachyarrhythmia absoluta, and emphysema of the lungs</td>
<td>No fever, no cough, tachyarrhythmia absolutas (120 heart beats/minute), dyspnea, crackling sound of the lungs, and very poor general state of health (moribund).</td>
<td>Infiltrate lower right lobe.</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>90</td>
<td>IV</td>
<td>37.4</td>
<td>1</td>
<td>15.87</td>
<td>19.53</td>
<td>232.9</td>
<td>189</td>
<td>192</td>
<td>Chronic heart failure, acute decompenesation, arrhythmia, and cachexia</td>
<td>Patient was already diuretically treated as outpatient for heart failure and acute decompenesation. Consecutively developed an electrolyte imbalance (hypokalemia), deterioration of general status since 5 days prior to admission. 90-year-old patient with very weakened general condition and malnutrition, tachycardia (heart rate 120/min), and no increased body temperature. Ever recurring episodes of apnoea. Crackling sound on the lower right side and reduced breath sound on the right.</td>
<td>Large pleural infusion right lower lobe, infiltrate right lower lobe.</td>
</tr>
</tbody>
</table>

Sex: F: female; M: male; risk class after Fine et al. N. [32]. “temperature” is the highest measured temperature within the first three days outlined. First day sub-febrile temperature: the first day the patient shows temperatures below 38.0°C. Leucocytes: highest number of leucocytes within the first three days. Leucocyte end: the count of leucocytes at discharge of the hospital. In case of normal leucocytes, no further recording was performed. CRP 1st and 3rd days: highest value within the first three days as in-patients. CRP days 4 till 9: the lowest value within this time span. CRP end: CRP at end of treatment. †: Death.
of the attending physicians and care team whereby external administration is mandatory in anthroposophic treatment of CAP and moreover the competence in executing the task. Anthroposophic medicine is based on modern temporary natural science and medicine by aiming to extend these achievements with an additional holistic view on man, earth, and cosmos including the four aspects of elements and therefore intends to search for a specific individual treatment for each patient [22, 40]. AM is not intending to get in competition with modern temporary medicine but rather extending and eventually enriching it. Within a time of rising professionalised medicine with standardized clinical pathways there is almost no space for an individual treatment finding. The sketched background of AM is ordinarily excluded in conventional medicine, but within the presented case series it was intended to include all these mentioned dimensions of AM. It would be worth to further outline this characteristic process of therapy finding in an extra presentation. Further declaration of AM in detail would burst the scope of this paper and therefore remains to be outlined at other spaces.

Finally, within the context of the presented data it needs to be pointed out that integrative medicine—and as in the presented case series AM in hospital—needs a great personal effort, due to its time-intense care procedures that call for a high competence, and this might at least partly justify a prolonged hospital stay. At present, the reported data do not allow to indicate the use of anthroposophic medicine in the treatment of CAP in general. But the presented data are encouraging to further evaluate the role of integrative medicine within the treatment of CAP regarding efficacy, security, economy, and sustainability.

This case series contributed towards showing the usefulness of AM in the context with inpatient treatment of CAP. The data shows that it is possible to put selected patients with CAP on a comfortable path of recovery by treating them with AM only. Because health conscious patients in particular opt for AM, and, in our case AM, we cannot exclude the aspects of a selection bias towards healthier patients in the presented series. Therefore, it would be particularly useful to have a larger sized controlled prospective study on the treatment of pneumonia patients with AM.

Conflict of Interest
All authors declare no conflict of interests.

Acknowledgments
The authors thank Thomas Ostermann, Ph.D. and M.S., Professor for Research Methodology and Information System in Complementary Medicine, Center of Integrative Medicine, Faculty of Health, Witten/Herdecke University, Germany, for conducting the statistical work and analysis. They also thank Jan-Peter Schenkengel, M.D., Head of the Department of Radiology, Hospital Heidenheim, Teaching Hospital of the University Ulm, for his reevaluation of the X-rays. We do thank Angela Lorenz (Heidenheim) and Stephan Hampe (Berlin) for editorial assistance. And last but by no means not least do we thank all the nurses for their ongoing support and commitment to carry AM forward.

References
Review Article

The History of Inpatient Care in German Departments Focussing on Natural Healing

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We describe historic developments of inhouse facilities for natural healing in this paper, which were mainly located in German speaking regions. The naturopathic movement is a relabeling of the hydropathic movement in Germany, which was supported by a considerable proportion of the population in Germany during the mid 19th century. Due to the fact that hydropathic treatments were provided by nonmedical healers, discriminated as “quacks”, there was continuous hostility between hydropathy/naturopathy and medicine. However, among the many establishments providing inhouse treatment for acute and chronic diseases over weeks there were some which were controlled by medical doctors in the 20th century and some which were implemented by government. In many of the establishments there were approaches for measuring usefulness of the treatments, some of which have been initiated explicitly for that purpose.

1. Introduction

Natural healing uses the philosophy of naturopathy with a focus on a nature-orientated healthy life style. Naturally healing methods are also applied in the therapy of disorders and in rehabilitation. They are used in self-care often recommended by nonmedical and medical practitioners in ambulant settings. There are also special clinics, hospitals for inhouse treatments. We present the historical development of naturopathy with focus on inpatient natural healing with regard to present and future statuses. The asclepion of the ancient Greek temple facilities might be referred to as an early precursor of inpatient treatment with a programme similar in many aspects to that of contemporary natural healing. Apart from the medicinal water applications a dormitorium was also in use for inducing a healing sleep—some similarity might be seen with modern meditation [1].

A dogmatically independent and new development contrary to the medicine of the time [2] was constituted as late as the beginning of the 19th century; but the name for this programme was initially hydropathy or in German “Wasserheilkunde.” However, in the 18th century there was already an increased interest in medicine with a view towards mild hippocratic approaches of healing, inclusive internal and external water applications, healthy food and physical exercises, and avoidance of dangerous and rigorous interventions; all this was related sporadically to the term “medicina naturae” [3].

The hydropathic movement developed and was driven mainly by medical laymen [4]. About the mid 18th century, this romantic hydropathical movement changed its name to a more positive term, that is, “Naturheilkunde” (naturopathy, art of natural healing). Exercise, nutrition, and later other natural healing methods like herbal therapy were added to cold water. Natural treatments were provided by medical and nonmedical healers as well as in self-help groups in both in- and outpatient settings. This was in contrast to the established medical services—the conventional balneology is included, with its focus on special and locally available spa treatments. During the second half of the 19th century spas or hospitals specializing in natural healing developed worldwide.
The books and quarterly water journal of Eucharius Ferdinand Christian Oertel (1765–1851) and also his first association with hydropathic health were important for the dogmatic and medicine hostile development. Similar to other systems and disciplines of complementary medicine a very broad support of the population was the reason for its growth despite stakeholders in medicine and governments.

The aim of the paper is to describe the subsequent development of the relationship between naturopathy and conventional medicine with special regard to inpatient treatment of seriously ill patients.

2. Methods

The content of this paper relies on the literature review in AR96 (Deutsches Ärzteblatt), AZ72 (GLOBAL Health), BA70 (BIOSIS Previews), CB85 (AMED), CC00 (CCMED), CCTR93 (Cochrane Central Register of Controlled Trials), CDAR94 (Database of Abstracts of Reviews of Effects), CDSR93 (Cochrane Database of Systematic Reviews), CV72 (CAB Abstracts), DAHTA (DAHTA-Datenbank), DD90 (Derwent Drug File), EA08 (EMBASE Alert), ED93 (ETHMED), EM47 (EMBASE), GA03 (gms), GM03 (gms Meetings), IA70 (IPA), I178 (ISTP8 + ISTP/ISSHP), INAHTA (Health Technology Assessment Database), IS74 (SciSearch), ME60 (MEDLINE), MK77 (MEDIKAT), NHSEED (NHS Economic Evaluation Database), SM78 (SOMED), and ZT00 AnimAlt-ZEBET) using "NATUROPATH%## AND INPATIENT#" and "STATION? AND NATURHEIL?" for the search (with case insensitivity). The searches produced 48, respectively, 89, together 137 hits. After elimination of double or multiple hits of the same source 85 hits remained. 39 papers were excluded from further evaluation because they did not examine the naturopathic inpatient treatment according to their titles and abstracts. Another 25 sources were excluded by full-text analysis for the same reason or because they were only concerned with the naturopathic inpatient treatment of a special condition or disease. The remaining 11 papers, supplemented by own additional literature, which included already 9 of the 11 papers found by the systematic search, were used to elaborate the content of this paper. A previous published historical review of the development of naturopathic inpatient treatment was not found.

3. First Naturopathic Inpatient Facilities

The first and famous cold-water establishment was developed by the farmer Vinzenz Prießnitz (1799–1851) in Gräfenberg/Freiwaldau in Silesia [5]. Prießnitz opened his cold-water spa in 1822. He treated 45 patients in 1829, 500 patients in 1837, and two years later there were already 1700 patients, among them 120 physicians. The diagnoses of his patients during the years 1829 to 1839 are analysed and descriptively reported by Sajner and Křížek [6].

Some time later, hydrotherapy was extended by certain forms of nutrition therapy. Johann Schroth (1798–1856), a schoolfellow of Prießnitz, was striving for the concept of the naturopathy (Weißer Hirsch) near Dresden. However, two years later Bergmann opened his own facility in Saxony, where the physician Heinrich Lahmann (1860–1905) resumed the leadership of Zimmermann’s notable establishment in Chemnitz in 1886. However, two years later Bergmann opened his own facility for naturopathy (Weißer Hirsch) near Dresden.

4. The Kneipp Movement

A true renaissance of naturopathy all-over Germany and beyond started with the Catholic priest Sebastian Kneipp (1821–1897). His bestseller “My Water Cure” (1886) was intended to reduce personal provision of the treatment. However, the opposite happened (in 1889 over 2,600, 1892 over 12,000 patients in Wörishofen). Using donations by his patients, Kneipp established several hospitals “Sebastianium,” “Kneipps healing facility for children”, and the “Kneippianum.” The last was managed like a hospital by the Kneipp physician Alfred Baumgarten (1862–1924) who started in 1894.

The first Kneipp association was established in Wörishofen in 1891 and later named “Stamm-Kneipp-Verein” (Original Kneipp Society). The development of other local societies followed rapidly. The “Verein der Ärzte Kneippscher Richtung” (the Society of Kneipp Physicians) (later “Kneipp Ärztebund”, Union of Kneipp Physicians) was established in 1894.

Kneipp is regarded as the “reformer of hydropathy” due to his recommendation of a much shorter cold water stimulus, which led to a better initial reaction and better long-term results. Kneipp introduced affusions (from a watering can without sprinkling head or from a wide mouthed rubber
tube). Kneipp did not only—as could be assumed from the title of his book “My Water Cure”—focus on hydrotherapy (Part I of his book), but also combined his water therapy with herbal medicine. This was heavily criticised by other hydrotherapists and naturopaths, while they assumed a “bad compromise” that would detract patients from their strict self-healing process and soften the cure too much. Additionally, Kneipp combined water and herbs with exercise, diet, and guidelines to healthy and happy life, specially in his further books “Thou Shalt Thou Live” (1889) and “My Will for Healthy and Sick” (1894).

Diseases were described very simply and clearly: they originate either because of dysfunction of blood composites or circulatory disturbance. Accordingly, a therapy succeeded due to liquidation of obstruction or here of aroused harmful substances and their discharge and secretion. The cause of sensibility and susceptibility for getting sick is the absent self-purification.

Regarding the diet, Kneipp appeared not to be radical and puritan but rather praised the inartificial plain fare; clothing should not be restrictive; omitting footwear prevents driving blood up in a harmful way. The skilled weaver was against woolen clothes touching skin directly and preferred linen because of its rub effect. A fresh and unspoiled air was important as well.

The “five columns,” which nowadays are accredited to Kneipp, do not originate directly from him. They are formulated after 1950 by the Kneipp physician Josef H. Kaiser, and they include water, nutrition, physical exercise, herbal treatments, and “Ordnung” (balance of life or today: mind and body).

Kneipp was at the time reluctantly noticed by the conventional academically minded medical establishment and, for example, ignored by Wilhelm Winternitz (1834–1917), who considered himself a successor of the long, since deceased, Prießnitz. He was also looked down upon by Ferdinand v. Ziemssen of Munich hospital. In fact the academic writings of Professor Winternitz from 1877 never garnered such public attention as the books of the “simple” priest.

In 1889, the Jordan bath—the first Kneipp bath outside Wörishofen—was opened under leadership of Dr. Johann Nepomuk Stützle (1858–1938). Though numerous Kneipp establishments were founded, only some of them are still in operation like the one at Brixen (now Italy), founded in 1890 by Otto V. Guggenberg (1848–1914).

Another core area of naturopathy was Dresden and Saxony. The physician Paul Kadner (1818–1868) had opened the first diet cure establishment which had 20 beds as early as 1861. Later his brother-in-law Felix Klees (1832–1899) continued with focus on the Schroth cure. The physician Heinrich Lahmann (1860–1905), who served as head of a big naturopathic facility in Chemnitz before, established the leading sanatorium in the spa town Weiβer Hirsch at Dresden. Over 2000 patients were treated there in 1900. Several other health hospitals were situated in the neighbourhood and in the area around Dresden, part of which operating under control of physicians [13].

At the turn of century, greater political pressure was exerted upon medicine to use naturopathy to a greater extent. This appeared under the newly established branch of medical science “physical-dietary medicine” which ranged from hydrotherapy, massage, and remedial gymnastics to diet. Neither the medicinal herbs introduced by Kneipp nor some further specific ideas and treatments of naturopathy were recognized by the medical approach.

5. First Academic Naturopathy

Ernst Schweninger (1850–1924) [14, 15] was appointed professor for dermatology after his successful treatment of Bismarck in 1884–1900, and during 1900–1906, he was head of the first German hospital of naturopathy in Berlin-Groß-Lichterfelde associated with the Charité [16].

Schweninger treated 8, 359 patients in Groß-Lichterfelde, administering 262, 118 treatment days. Among those there were 479 consumptive patients (i.e. mainly tuberculosis), 264 acute joint-rheumatic patients, 219 gastro patients, 210 diphtheria cases, 165 scarlatina cases, 155 heart cases, 141 syphilis, 129 gonorrhea cases, 113 eczema cases, 104 pneumonia cases, 72 red murrain cases, 45 rubeola cases, 34 psoriasis cases, 27 typhus cases, and 16 pertussis cases [17].

The physician Georg Hauffe (1872–1936), a former assistant of Schweninger, devoted himself subsequently to Groß-Lichterfelde—a municipal hospital for physical-dietary therapy and in particular hydrotherapy.

Additionally, since 1901, there existed a hydrotherapeutic facility at the Charité under Professor Ludwig Brieger (1849–1919), who later also held the chair for general therapy [18]. Franz Schönener (1865–1933) [19] was proposed by the Prießnitz society as successor to Brieger, and though opposed by the faculty he was nominated professor and head of the hydrotherapeutic facility of the university. At the time, this consisted of a polyclinic with surgeries and a small hospital department with just 20 beds. 25,000 patients were medicated within nine years. Most were from a poverty stricken background from the north of Berlin. About 100 women and 50 men were treated in the bath facilities daily. 250,000 water applications were applied according to the prescriptions of physicians during that time. 56,000 patients were visiting the so-called “electrical department.” The department for Swedish remedial gymnastics and massage was reestablished in 1921, and 4,500 applications were provided within eight years.


In 1924, a second university department for naturopathy was opened at the Friedrich-Schiller University in Jena. Ernst Klein [21] was the first professor for naturopathy.

The first teaching hospital of naturopathy with 75 beds, the Prießnitz hospital in Berlin Mahlow, was established in 1927 and affiliated with the natural healing department of Professor Schönenger. The public acceptance was so great that the patients waited several months for admission.
The therapeutic measures described by Brauchle [18] included uncooked vegetarian food according to Bircher-Benner (1867–1939) [22], cold water hydrotherapy according to Prießnitz and Kneipp, warm applications according to Schweninger, and air and sun baths according to Rikli [10, 11] and Lahmann [23], as well as the Schroth cure in a moderate variant. Additionally, the fasting cure, massage, and gymnastics played a significant role. The successor was Alfred Brauchle (1898–1964) who stayed there until he left for Dresden.

6. “New German Medicine”

Naturopathy was abused under the state dictatorship of national socialism during the third Reich and was part of the intended “New German Medicine.” Different medical areas such as naturopathy, homeopathy, and biochemistry by Schüßler, the last mostly due to the impressive number of members in the nonmedical societies, were put together under “biological methods.” The anthroposophy was, however, labelled as “degenerated” and forbidden.

Ernst Klein in Jena was dismissed in 1933. The successor of Klein was the party politically active Karl Kötschau (1892–1945). The department of true naturopathy at the University of Jena was transformed under his leadership from a polyclinic for naturally healing systems into the “Clinic and Polyclinic for Biological Medicine” [24].

Among a number of initiatives at the Reich’s level that had to facilitate the prevalence of naturopathy the Reich’s working group of nature physicians (1935) voted for the establishment of a hospital for naturopathy as part of the medical university hospital in Erlangen.

This project was implemented not in Erlangen but at the Rudolf Heß hospital (former Johannstädter hospital) in Dresden. Restructuring the former huge hospital with about 1000 beds was completed in 1935, and the experiment of Dresden could start. Louis Redcliff Grote (1886–1960) was nominated as the head of the hospital for internal medicine with about 300 beds. In parallel, the hospital for naturopathy was subordinated to Brauchle and comprised after its extension about 250 beds [25, 26].

Hydrotherapy, massage and gymnastics, and air and sun baths, as well as the upcoming psychotherapy (according to Coué und Wetterstrand) were applied in Brauchle’s Department. Clinical visits were arranged during daily air baths. Regular meetings of medical staff were held. They were therapeutically supervised by a physician of the ward of the true naturopathic department and assisted by an internist assigned for diagnostic advisory [18, 27]. Both departments had daily rotating admission shifts. The people treated ranged from patients with internal diseases as well as patients of conservative gynecology, orthopedics, neurology, and dermatology. Brauchle and Grote performed associated visits at the common ward which was the core place for critical dialogs regarding specific cases.

The treatment was purposely aligned with simplicity and strict manageability in order to evaluate the effects of naturally healing systems under the preconditions of a large-scale hospital. After the initial examination, a treatment program was developed by the team of true naturopathic physicians. Medication was given only with the objective to improve the prospective effect of physical–dietary therapy.

Relaxation techniques were administrated to all patients. Regular lectures of the physicians to public health, detailed final meetings with proposals for individual arrangements, and daily hydrotherapy were also available for the inpatients.

According to Krauß [27] the duration of stay in the hospital for true naturopathy lasted 22 days, in the department of Grote 21 days. The average costs of medication were 35 Pfennig per day at Grote and between 4–6 Pfennig per day at Brauchle (skin oils and herbal teas included).

The difference of total costs was due to different usage of medication, number of nurses, and therapeutic staff. It was also dependent on complexity of laboratory-technical work. No documentation of daily personnel costs during the “experiment of Dresden”, which reassesses the methods of naturopathy [28], is available.

In accordance with the political development Brauchle elaborated at the beginning of the forties his psychological collective treatment into a form of mass suggestion (“Massensuggestion”) [29].

Death was declared by Brauchle as “best cure” for patients when naturopathic methods could not help them [28]—a cynical point of view.

After 1942, the deteriorating general situation during the second world war stopped the harmonic cooperation of Brauchle and Grote [30].

The occupation of naturopathy by national socialism recharged the beginning of academic recognition which naturopathy gained at 1920 (chair for naturopathy at the charité) and 1924 (chair for naturopathy at the Friedrich-Schiller University Jena) [31].

A number of naturopathic departments and Kneipp’s departments at municipal hospitals were, however, operating further up to 50 s or 60 s when new techniques and new specific medication replaced them.

7. Modern Progression of Naturopathy

After the second world war, the naturopathic movement redeveloped in the West and the Kneipp movement with its new concept of five columns was the most successful. In GDR, a part of true naturopathy was integrated into physiotherapy. The Prießnitz hospital, Mahlow, continued its service also.

Presently, there are fewer establishments in the acute inpatient care sector (Table 1)—in contrast to the outpatient care provided by nonmedical healers and specialized physicians. Complementary and specially naturopathic orientated therapies are practiced within conventional medical hospitals and in rehabilitation hospitals in an increasing scope [32].

Naturopathy is mostly applied by practitioners in the ambulant sector, with about 20.000 physicians specialized in natural healing and about 15.000 nonmedical practitioners in Germany.

In 1968 the “Krankenhaus für Naturheilweisen” at Munich emerged from the former hospital for homoeopathy,
Table 1: Overview of the departments providing naturopathic inpatient care today.

<table>
<thead>
<tr>
<th>Institution</th>
<th>Time period</th>
<th>Treatment approach</th>
<th>Number of beds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waldhausklinik Deuringen, Stadtbergen</td>
<td>Since 1966</td>
<td>Naturopathy and homoeopathy</td>
<td>40</td>
</tr>
<tr>
<td>Hufeland-Klinik, Bad Ems</td>
<td>Since 2000</td>
<td>Naturopathy, homoeopathy, and hyperthermia</td>
<td>40</td>
</tr>
<tr>
<td>Klinik für Naturheilverfahren, Akupunktur und Allgemeine Innere Medizin,</td>
<td>Since 2007</td>
<td>Naturopathy, homoeopathy, and traditional Chinese medicine</td>
<td>10</td>
</tr>
<tr>
<td>Krankenhaus St. Josef-Stift, Bremen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krankenhaus für Naturheilverfahren, München</td>
<td>Since 1883 homoeopathy, since 1966</td>
<td>Naturopathy and homoeopathy</td>
<td>110</td>
</tr>
<tr>
<td>Zentrum für Naturheilkunde, Immanuel</td>
<td>Since 1901 in Berlin, Lichtenfelde,</td>
<td>Naturopathy</td>
<td>40</td>
</tr>
<tr>
<td>Krankenhaus, Berlin</td>
<td>since 2001 in Berlin/Wannsee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klinik für Naturheilkunde u. Integrative Medizin, Essen</td>
<td>Since 1999</td>
<td>Naturopathy, homoeopathy, and traditional Chinese medicine</td>
<td>63</td>
</tr>
<tr>
<td>Abteilung für Naturheilkunde, Klinik Blankenstein, Hattingen</td>
<td>Since 1997</td>
<td>Naturopathy</td>
<td>60</td>
</tr>
</tbody>
</table>

which was already founded in 1883, and extended its treatment options to naturopathy [42].

In 1989, Berlin's professorship for true naturopathy was established and located in the Moabit Hospital. Since 1991, the hospital wards are located in the Immanuel hospital at Wannsee [33].

In succession, consistently donation professorships are instituted. There is no government funded professorship yet.

The union of associated hospitals of the "Munich model," established in 1993, was supported by the Bavarian Ministry of Labour, Family, Social Affairs and Public Health and operated in the first instance until 1999 [43]. The union of hospitals was enlarged by the Dr. Köhler-Parkkliniken, Bad Elster (Saxony) hospital in 1997 (since 2004: German Hospital for Integrative Medicine and Natural Healing). Since 2000, the union of hospitals is named "The Network of Hospitals for Naturally Healing Systems/Complementary Medicine" and is extended by some further hospitals.

In 1995, the Blankenstein hospital in Hattingen applied for the possibility of introducing naturally healing systems in an acute hospital in North Rhine-Westphalia (NRW). With support of health insurance companies the Blankenstein hospital was developed as the first model department. Since 1997, the Blankenstein hospital consists of the Departments of Internal Medicine, Surgery, Anesthesia and Otorhinolaryngology, as well as Model Department of Naturopathy. During 1999–2003, the department was scientifically monitored at the first time [36–38]. In 2005, a further scientific monitoring in association with university hospitals of the Ruhr University of Bochum was implemented to perform an interhospital comparison of naturopathic and conventional inpatient treatment [40]. The running third scientific monitoring concerns the sustainability of the achieved progress of the inpatient stay. The "Ordnungs therapy" is a subject of the evaluation. In an interhospital comparison in the Ruhr area the naturopathic department got better scores for patient satisfaction than the mean of conventional orthopedic departments [39].

In 1999, the second naturopathic model department of the Federal Land NRW was established in the Hospital of Essen, Mitte—the Department "Hospital for True Naturopathy and Integrative Medicine" with 54 beds [41].

Some other naturopathic departments, for example, Hufeland hospital in Bad Ems and Kneipp'sche Kliniken in Bad Wörishofen [44], are developing all over Germany and neighbouring countries, for example, Slotervaart hospital, department of pediatrics, in Amsterdam [45].

8. Evaluation of Naturopathy in History

Different ways to describe and evaluate naturopathic treatment in history up to now are delineated in Table 2.

Though naturopathy and conventional medicine were directly compared "side by side" already in the thirties of the last century at Dresden, the published results are academic conversations but no comparable physical or psychological measurements [25, 26]. Comparison of naturopathy and conventional medicine remains difficult. Only one study exists which compares treatment results between naturopathic and conventional orthopaedic, respectively, rheumatologic treatment [46]. Because this study could not randomly assign the patients to the treatment groups, interpretation of the results is difficult. Nevertheless naturopathy seems to be at least as effective as conventional orthopaedic, respectively, rheumatologic treatment. All other modern studies evaluating naturopathic treatment on the whole are one-armed cohort studies without control group.

9. Discussion and Conclusions

Naturopathic hospitals have always tried to evaluate their results. Outcome research was a central issue of inpatient naturopathic treatment. Kusche [16] already compared costs of prescribed drugs in 1955, Krauß [27] compared duration of
### Table 2: Evaluation of inpatient naturopathy in history.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Institution analysed</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grote and Brauchle [25, 26]</td>
<td>1935–1938</td>
<td>Rudolf Heß hospital in Dresden</td>
<td>Descriptive dialogues, outlining of methods, and clinical case results</td>
</tr>
<tr>
<td>Kusche [16]</td>
<td>1955</td>
<td>Naturopathic hospital at Berlin, Lichterfelde (1900)</td>
<td>Historical descriptive, outlining of methods, and analysis of admitting physicians</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Naturopathic hospital at the Charité, Berlin (1920)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Naturopathic hospital at Jena university (1924)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mahlow hospital at Berlin (1927)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rudolf Heß hospital in Dresden (1934)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital at Murnau (1932)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Department of naturopathy at the Ochsenzoll hospital, Hamburg (1953)</td>
<td></td>
</tr>
<tr>
<td>Dieckhoefer [31]</td>
<td>1987</td>
<td>Naturopathic hospital at Berlin, Lichterfelde</td>
<td>Historical narrative/descriptive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Naturopathic hospital at the Charité, Berlin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Naturopathic hospital at Jena university</td>
<td></td>
</tr>
<tr>
<td>Kühner et al. [33]</td>
<td>1995</td>
<td>Naturopathic department at Moabit hospital/Berlin 1987</td>
<td>Historical description, outlining of therapeutic concepts, and academic teaching</td>
</tr>
<tr>
<td>Krauß [27]</td>
<td>1987</td>
<td>Rudolf Heß hospital in Dresden (1934)</td>
<td>Retrospective two-armed cohort study, analysis of duration of stay and average costs of medication</td>
</tr>
<tr>
<td>Melchart et al. [34]</td>
<td>1999</td>
<td>Dermatologic Hospital at Höhenkirchen 1994-1995</td>
<td>Prospective, one-armed cohort study, subjective estimation of symptom severity by patients</td>
</tr>
<tr>
<td>Melchart and Saller [35]</td>
<td>2002</td>
<td>None</td>
<td>Theoretical concepts</td>
</tr>
<tr>
<td>Beer et al. [36–38]</td>
<td>2001-2002</td>
<td>Naturopathic department at Blankenstein hospital, Hattingen</td>
<td>Prospective, one-armed cohort study, standardized questionnaires, statistical evaluation</td>
</tr>
<tr>
<td>Beer et al. [39]</td>
<td>2005</td>
<td>Comparison of regional hospitals including Blankenstein hospital, Hattingen, treating orthopedic diseases</td>
<td>Prospective, multicenter, standardised questionnaires and statistical evaluation</td>
</tr>
<tr>
<td>Wiebelitz et al. [40]</td>
<td>2011</td>
<td>Naturopathic department at Blankenstein hospital, Hattingen</td>
<td>Prospective, multicenter, 3-armed cohort study, standardised questionnaires, statistical evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orthopedic department, St. Josef hospital, university of Bochum</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatologic department, St. Elisabeth hospital, university of Bochum</td>
<td></td>
</tr>
<tr>
<td>Lauche et al. [41]</td>
<td>2012</td>
<td>Hospital for True Naturopathy and Integrative Medicine, Essen university</td>
<td>Prospective, one-armed cohort study, standardized questionnaires, statistical evaluation</td>
</tr>
</tbody>
</table>

The future development of the inpatient treatment with naturopathy in Germany is uncertain at this time, especially due to discussions on the Law on Modernization of Public Health and decreasing financial resources in public health sector. Also the adopted system of case allowances (DRG-System) complicates the accounting of natural healing treatments in the hospital. The classical naturally healing systems propose ideal prerequisites for prevention and complementary treatment of numerous diseases. Because of the recent political statements considering the development of prevention as one of the central tasks of the future German
public health system and implementation of, for example, "the German Forum of Prevention and Facilitation of Public Health" the political intention for maintenance and development of inpatient treatment with naturopathy in Germany may play an important role.

References

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Active Student Participation May Enhance Patient Centeredness: Patients’ Assessments of the Clinical Education Ward for Integrative Medicine

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Objectives. To examine the impact of active student participation on quality of care in an integrative inpatient setting. Methods. Over a two-year period, we surveyed all patients treated on the Clinical Education Ward for Integrative Medicine (CEWIM), where final-year medical students are integrated into an internal medicine ward complementing conventional medicine with anthroposophic medicine. Patients treated on the regular wards of the same internal medicine department served as the control group (CG). General quality of care was studied with the Picker Inpatient Questionnaire, physician empathy with the Consultation and Relational Empathy measure, and patient enablement with the Patient Enablement Index. ANCOVA was used to control for covariates while examining significant differences between both patient groups. Results. Comparison of the CG wards and the CEWIM revealed no significant differences in medical treatment success. The CEWIM, however, achieved better results for physician-patient interaction, physician empathy, and patient enablement. Eighty Percent of the CEWIM patients rated student participation as positively impacting quality of care. Conclusion. Our results indicate that incorporating students in an integrative healthcare setting may result in greater patient centeredness. Further studies are needed to determine whether this is due to organizational advantages, students’ empathic activity, the impact of teaching, or learner-teacher interaction.

1. Introduction

Over the last two decades, increased attention has been given to the concept of active learner participation in the so-called “community of practice” [1, 2]. Studies have suggested that apart from the explicit knowledge typically taught in the classroom, learners must also acquire certain implicit skills and knowledge within their future workplace. In addition, active participation in patient care in particular seems to play a crucial role in the acquisition of professional and interpersonal competencies and the development of a sense of role identity [3].

In the field of medicine, active student participation (ASP) typically takes place during clinical clerkships and final-year rotations. However, from different studies, we know that participation in clinical rotations alone does not necessarily automatically result in the professional development of learners. Instead, it is the degree of active participation (as opposed to being involved in primarily passive learning experiences) together with certain qualities of the
learning environment that determine the success of clinical education [3, 4]. In Germany, for example, medical students are usually required to do three 16-week final-year rotations in internal medicine, surgery, and one field of their choice. However, as in other countries [4, 5], the educational quality of these rotations has been criticized as being suboptimal. Students tend to be provided with mere passive experiences rather than actively participating in patient care. They are all too often assigned routine tasks, and do not receive sufficient clinical supervision. These shortcomings have been shown to lead to insufficient training of independent patient management and to feelings of uncertainty among medical students [6].

In response to these deficits and in order to offer students a structured clinical learning environment tailored to their learning needs, the Clinical Education Ward for Integrative Medicine (CEWIM) was established in 2007 and implemented into one of the wards of the Department of Internal Medicine at the Gemeinschaftskrankenhaus Herdecke (GKH), an academic teaching hospital of Witten/Herdecke University in Germany. The two main aims of the CEWIM are [7] (1) to promote ASP in clinical patient care while providing students with close supervision and (2) to help students learn and practice integrative medicine (in this case, to complement conventional medicine with anthroposophic medicine [8]).

While most studies investigating ASP focus on its educational value for learners, few have explored its potential influence on the community of practice and on the learners' work, including quality of care. The findings of such studies have indicated that ASP may also be of benefit to patients, since they gain a better understanding of their disease [9] and are more satisfied that their needs have been met [10]. This raises the question whether ASP has an effect on patient centeredness, which the Institute of Medicine defines as "providing care that is respectful of and responsive to individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions" ([11], page 40). The aim of the present study was, therefore, to determine whether ASP has a certain impact on quality of care in an integrative inpatient setting. More specifically, we wished to compare the experiences of patients on the CEWIM to those of patients on the regular internal medicine wards at the GKH with respect to the following aspects of patient centeredness:

(a) physician-patient interaction,
(b) physician empathy, defined as a specific ability to communicate and help patients based on a deeper understanding of their situation, their perspectives, and their feelings [12],
(c) patient enablement, defined as the extent to which a patient feels empowered after a medical consultation, in terms of being able to cope with, understand, and manage their illness [13]).

2. Methods

2.1. Clinical Setting. The Department of Internal Medicine at the GKH, which offers the same diagnostic and interventional services as a regional hospital (including an intensive care unit), is divided into three different wards: one short-term ward with 20 beds, which is mainly for patients with fewer symptoms and less severe diseases (average stay: 4.5 days), and two long-term wards for patients with more complex and severe diseases. Particularly on these long-term wards, there are patients with specific interest in complementary medicine. One of the two long-term wards is more specialized in oncological and palliative care (26 beds; average stay: 9.9 days); the other is focused on gastroenterological and cardiological care (36 beds; average stay: 11.2 days). The CEWIM was incorporated into the latter medical ward, using 10 to 12 of the ward's 36 beds. On the CEWIM, four to five students take over the work of one house officer on the ward, meaning that together they are responsible for the care of a total of 10 to 12 patients. The students are supported and supervised by the house officer and a consultant. Important decisions, such as making changes to a patient's medication or arranging diagnostic interventions, may only be made after consultation and in agreement with the two supervising physicians. Students' care of the patients on the ward involves the usual diagnostic and therapeutic procedures performed on a conventional medical ward as well as complementary medicine being offered to interested patients. Based on a holistic view of the patient, students provide conventional and specific complementary treatments, such as natural remedies, rhythmic massage, external applications, art therapy, therapeutic eurythmy (a form of meditative movement), and biographic counseling [8]. Student rotations on the CEWIM are 16 weeks in duration and have taken place twice a year each year since 2009.

2.2. Educational Setting. Originally launched as a pilot project in 2007, the CEWIM became a permanent program in 2009. The CEWIM is part of the Integrated Curriculum of Anthroposophic Medicine (ICURAM), an optional program in anthroposophic medicine that is integrated into the full six-year program of the regular undergraduate medical curriculum at Witten/Herdecke University [14]. The main goal of the ICURAM program is to emphasize a broader, multifaceted, and holistic view of human beings and to prepare students for patient-centered integrative and anthroposophic care. In order to achieve this goal, learner-centered educational strategies and learning objectives were developed in close contact and together with students. These strategies have been summarized into what is called the ESPRiT approach, which combines exploratory learning, supported participation, patient-oriented learning, reflective practice, integrated learning, an integrative approach, and team-oriented learning [14]. The CEWIM was developed based on this approach. Apart from providing students with clinical training through ASP, it also offers students specific learning opportunities.

(i) Students learn how to integrate the different perspectives and treatment options of conventional medicine and complementary anthroposophic medicine and to appreciate the specific values and limitations of each approach.
(ii) Students are involved in interprofessional learning by being fully integrated into the healthcare team and by working together with nurses and healthcare practitioners practicing art therapy, music therapy, therapeutic eurythmy, massage, physiotherapy, and psychotherapy. Interprofessional learning is enhanced by an interprofessional module (held during Week 1), weekly team meetings with therapists, and monthly meetings with the nursing team.

(iii) Reflective practice is promoted through a clinical reflection training seminar [15] held every two weeks with a professional supervisor. During the seminar, students reflect on challenging situations faced during their rotation, such as interactions with patients, difficulties working with team members, and professional self-manage issues. This seminar was developed because participating students had expressed the desire for the opportunity to process and discuss their sometimes difficult experiences and their professional development.

2.3. Research Instruments. The following instruments were used to evaluate and compare the perceived quality of care received by patients of the CEWIM and by patients of the regular “nonstudent” wards of the Department of Internal Medicine at the GKH.

(i) The Picker Inpatient Questionnaire (PIQ). Originally developed in the USA by Cleary et al., the PIQ was accredited in 1997 by the Joint Commission for Accreditation of Health Care Organizations [16, 17]. Patients surveyed using the PIQ are asked to report their experience with specific events and processes in the hospital. The questionnaire includes eight questions on patient-physician interaction as well as two general quality items, for example, asking patients whether they have recommended their ward to friends and relatives. For the purpose of our study, the German version of the PIQ was used. We also supplemented the PIQ with additional items in order to assess specific qualities of integrative care and anthroposophic medicine.

(ii) The Consultation and Relational Empathy (CARE) Questionnaire. Developed by Mercer et al. [18] as a patient-reported outcome measure for physician empathy, the CARE contains 10 items, all beginning with the words “how was the doctor at...” (“really listening,” “making you feel at ease,” etc.). For the purpose of our study, the German version of the CARE measure was used. The original English version showed good internal validity (Cronbach’s alpha: 0.92) and face validity [18]. Evaluation of the German version confirmed that the one-dimensional structure of the original English version had been replicated [19].

(iii) The Patient Enablement Instrument (PEI). Developed by Howie et al. [13], this six-item questionnaire asks patients whether as a result of their visit to their doctor they feel they are able to understand their illness, help themselves, and so forth. Since we used the questionnaire for the evaluation of a clinical stay, we worded the first part of each of these items to say “As a result of the treatment received at the hospital, do you feel you are...” The German version of the PEI was used in the study [20].

(iv) Patients of the CEWIM were also asked to rate whether student participation on the ward had a positive, neutral, or negative impact on their care.

To ensure that medical students were included in the patients’ assessments of the quality of care they received, the word “physician” was replaced with the phrase “the team of physicians” in all relevant questions. A note was also made that students should be considered a part of this team.

2.4. Sampling. To evaluate the perceived quality of care received on the CEWIM, a survey was conducted of all patients that had been treated by four cohorts of medical students between the fall of 2010 and the summer of 2012. All patients meeting the inclusion criteria (n = 215, see Table 1) were surveyed by anonymous written questionnaire within eight weeks after their discharge. Completed questionnaires were then sent back to the Picker Institute, Germany, where the data were sampled and a preliminary analysis was performed.

The perceived quality of care received by patients of the regular internal medicine wards (control group, n = 250) was assessed using results taken from the most recently conducted routine evaluation of the GKH. Every two years, the GKH undergoes an evaluation, the last of which was conducted in the fall of 2011 over a period of two months. The data collection procedure and the questionnaires used for the routine GKH evaluation are the same as those used for the CEWIM patient survey.

2.5. Statistical Analysis. The patient characteristics of each patient group were calculated and compared using the Mann-Whitney U test. Only those characteristics for which a significant difference was found between both groups (age, education, interest in anthroposophic medicine, and number of nonphysician therapies obtained) were included as covariates in a univariate ANCOVA where the outcomes of the PIQ, the CARE, and the PEI were compared. IBM SPSS 20.0 was used for these analyses. A P value <0.05 was considered to indicate a significant statistical difference.

3. Results

Of the 215 CEWIM patients, 103 returned the questionnaire (response rate 47.9%), whereas in the control group, this was 94 out of 250 (37.6%). Patients of the CEWIM were, on average, six years younger (60.7 versus 66.6 years), had a better education (e.g., 20.6% versus 11.6% finalized tertiary education), were more often very interested in anthroposophic medicine (55% versus 29.6%), and obtained more often nonphysician therapies (59.8% versus 40.5%) than
patients in the control group. No significant differences were found between the two patient groups for the other characteristics assessed, including sex, possession of private health insurance, duration of disease, and health status (see Table 1).

While the results of the PIQ (see Figure 1) revealed no significant differences between the two types of patient wards in terms of the success of medical treatment, the CEWIM demonstrated significantly better results than the other wards with regard to the success of overall care and received higher ratings on six out of the eight physician-patient interaction items (see Figure 2) and also better CARE and PEI scores (see Table 2). These analyses were performed after controlling for all covariates showing a significant difference

Table 1: Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>CEWIM</th>
<th>Control group (CG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>234</td>
<td>494</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>&lt; 18 years</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 2-night stay</td>
<td>9</td>
<td>80</td>
</tr>
<tr>
<td>Readmission</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Sum of patients excluded</td>
<td>19</td>
<td>169</td>
</tr>
<tr>
<td>Patients contacted</td>
<td>215</td>
<td>250</td>
</tr>
<tr>
<td>Questionnaires returned</td>
<td>103 (47.9%)</td>
<td>94 (37.6%)</td>
</tr>
<tr>
<td><strong>Sex (female)</strong></td>
<td>65 (63.1%)</td>
<td>56 (60.9%)</td>
</tr>
<tr>
<td><strong>Age (mean, SD)</strong></td>
<td>60.7 ± 17.3 years</td>
<td>66.6 ± 16.3 years</td>
</tr>
<tr>
<td>Private health insurance</td>
<td>22 (21.8%)</td>
<td>19 (20.4%)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary education</td>
<td>3 (2.9%)</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Lower secondary education</td>
<td>12 (11.8%)</td>
<td>14 (16.3%)</td>
</tr>
<tr>
<td>Lower sec. ed. + apprenticeship</td>
<td>30 (29.4%)</td>
<td>33 (38.4%)</td>
</tr>
<tr>
<td>Lower sec. ed. + postsecondary education</td>
<td>19 (18.6%)</td>
<td>23 (26.7%)</td>
</tr>
<tr>
<td>Upper secondary education</td>
<td>17 (16.7%)</td>
<td>4 (4.7%)</td>
</tr>
<tr>
<td>Tertiary education (university)</td>
<td>21 (20.6%)</td>
<td>10 (11.6%)</td>
</tr>
<tr>
<td><strong>Duration of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–12 months</td>
<td>21 (32.3%)</td>
<td>16 (29.1%)</td>
</tr>
<tr>
<td>1–3 years</td>
<td>7 (10.8%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>9 (13.8%)</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>28 (43.1%)</td>
<td>21 (38.2%)</td>
</tr>
<tr>
<td><strong>AM important for choice of hospital</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, very much</td>
<td>55 (55.0%)</td>
<td>24 (29.6%)</td>
</tr>
<tr>
<td>Yes, somewhat</td>
<td>20 (20.0%)</td>
<td>16 (44.4%)</td>
</tr>
<tr>
<td>No</td>
<td>25 (25.0%)</td>
<td>41 (50.6%)</td>
</tr>
<tr>
<td><strong>Health status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>20 (19.8%)</td>
<td>15 (16.5%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>50 (49.5%)</td>
<td>44 (48.4%)</td>
</tr>
<tr>
<td>Good</td>
<td>21 (20.8%)</td>
<td>29 (31.9%)</td>
</tr>
<tr>
<td>Very good</td>
<td>10 (9.9%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Excellent</td>
<td>0 (0%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td><strong>Number of nonphysician therapies obtained</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41 (40.2%)</td>
<td>50 (59.5%)</td>
</tr>
<tr>
<td>1–3</td>
<td>45 (44.1%)</td>
<td>21 (25.0%)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>16 (15.7%)</td>
<td>13 (15.5%)</td>
</tr>
</tbody>
</table>

1 Randomly drawn from the sample of 325 patients remaining after exclusion.
2 These therapies include art therapy, music therapy, clay modeling, speech therapy, therapeutic eurythmy, rhythmic embrocations, massage, physiotherapy, and psychological counseling.
* indicates a significant difference between CEWIM patients and controls; Mann-Whitney U test, P < 0.05.
Table 2: Differences of patient groups in physician patient interaction, empathy (CARE), and patient enablement (PEI).

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Mean</th>
<th>SD</th>
<th>Analysis of variance (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empathy (CARE)</td>
<td>CEWIM</td>
<td>1.46</td>
<td>±0.55</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>1.83</td>
<td>±0.90</td>
</tr>
<tr>
<td>Patient enablement</td>
<td>CEWIM</td>
<td>0.95</td>
<td>±0.64</td>
</tr>
<tr>
<td>(PEI)</td>
<td>Controls</td>
<td>0.68</td>
<td>±0.63</td>
</tr>
</tbody>
</table>

*a* Low values indicate high empathy.

*b* High values indicate high enablement.

between the two patient groups (age, education, interest in anthroposophic medicine, and number of nonphysician therapies obtained).

Eighty Percent of the CEWIM patients reported that student participation on the ward had a somewhat positive or very positive impact on the quality of care they received. Only one percent felt it had a somewhat negative impact on the quality of care received. None considered it to have had a very negative impact (see Figure 3).

4. Discussion

The aim of our study was to determine whether there is a difference in the quality of care experienced by patients on the CEWIM, where students actively participate in patient care, and wards of the same department where students are not involved in care. In particular, we were interested in whether ASP has an impact on certain qualities of patient centeredness, namely, patient-physician interaction in general, perceived physician empathy, and patient enablement.

The results of our study indicate that while ASP—as implemented on the CEWIM—has no significant impact on the success of medical treatment in terms of the improvement of complaints or the rate of reported complications after discharge, it does improve patient-physician interaction, physician empathy, and patient enablement. The CEWIM also fared better than the control group wards in other areas which are specific to integrative medicine; namely, the practice of holistic and humanistic medicine, a noticeable anthroposophic orientation, and collaboration between healthcare professionals.

A preliminary study of the initial two-rotation pilot phase of the CEWIM [21] had found the patient-physician relationship to be rated better by patients on the CEWIM than by patients on the same medical ward at the GKH without ASP (control group 1) and by patients from conventional internal medicine wards in Germany (control group 2). However, only the difference between the CEWIM and control group 2 was found to be statistically significant. It was, therefore, impossible to determine whether the positive assessments of physician-patient interaction on the CEWIM were the result of ASP on the ward or whether they are merely attributable to the medical setting at the GKH. Exploration of additionally collected qualitative data did, however, indicate that care on the CEWIM was perceived as more holistic and individualized.

By including a greater number of patients and students in the present study, it was possible to detect a significant difference between the CEWIM and the GKH medical wards without ASP, in particular with regard to certain qualities of patient centeredness. The results of our study seem surprising given that patients tend to prefer to be treated by experienced professionals rather than by students still in medical school. This preference is, of course, understandable, since students tend to be more uncertain of themselves, slower, overstrained at an earlier stage, and need more time and attempts to perform most procedures and practical tasks (e.g., inserting an IV catheter or performing a physical examination). It is also assumed that resident physicians and fully licensed physicians have greater practical knowledge and are better in other areas, such as time management, clinical thinking, and clinical decision making.

Several hypotheses can be offered to explain why patients' ratings of patient centeredness were higher on the CEWIM.

1. **Organizational Advantages.** Since students are responsible for the care of fewer patients than regular physicians, they can dedicate more time to their patients. In addition, unlike physicians on the regular wards, students on the CEWIM do not have night shifts and are continuously on the ward. These two organizational advantages may be reflected in the better PIQ scores for “physician availability” and “having a clearly assigned physician.” Similarly, another study found that time and physician availability to have a comparable positive effect on patients’ assessments of physician empathy among patients with private health insurance [21].

2. **Specific Qualities of Student Communication with Patients.** The results of the CARE questionnaire suggest that patients on the CEWIM found students to be better at letting them tell their story, at really listening, and at being interested in them as a whole person. These aspects require not only dedicating more time to patients but also motivation, an open interest in another person, and a high level of commitment. These outcomes on empathy are supported by the better PIQ scores for “enough friendliness,” “relationship of trust,” and “possibility to talk about fears” in the CEWIM group. Moreover, patients on the CEWIM more frequently reported receiving “understandable answers to important questions,” which could be explained by the fact that students still tend to use more everyday language instead of medical terms.

3. **The Impact of Teaching and Supervision.** On the CEWIM, student learning is promoted through reflection and discussion on the daily problems and tasks associated with each of the students’ patients. In addition to the usual ward rounds and seminars, students participate in weekly teaching rounds and integrative case conferences. These activities give students opportunities to deduce greater focus to individual patient cases and find optimal solutions.
Figure 1: Frequency of problems with general aspects of integrative care as reported by CEWIM patients and the CG. Note that * indicates a significant difference between the CEWIM and the CG wards; analysis of covariance (ANCOVA), $P < 0.05$; ** $P \leq 0.01$.

Figure 2: Frequency of problems with physician-patient interaction as reported by CEWIM patients and the CG. Note that * indicates a significant difference between the CEWIM and the CG wards; analysis of covariance (ANCOVA), $P < 0.05$; ** $P \leq 0.01$; * $P < 0.1$

to their problems. In other words, they have more time to work through cases thoroughly and conscientiously than a regular physician would have. This may further be supported by the reflective practice module held every two weeks, which offers students opportunities to reflect on challenging interactions with their patients.

(4) Students’ Impact on the Healthcare Team. It is possible that, by asking relevant questions, students may
encourage healthcare professionals to reassess and improve the usual procedures on the ward and to work with greater mindfulness and reflection. Being asked to act as a role model may also promote better and more comprehensive performance.

The results of our study correspond with those of other studies, which have found ASP to have a positive impact on patient care. A study by Coleman and Murray, for example, found that patients enjoyed being involved in a community-based teaching program, had acquired greater knowledge about their disease, had enhanced self-esteem, and felt that the service they received was better [9]. Patients treated on an interprofessional clinical education ward in London [10] indicated being more satisfied than patients on a conventional ward with the care they received. They felt that students had communicated better in terms of active listening and answering their questions. Greater motivation and enthusiasm on the part of students were also seen as a relevant factor contributing to higher satisfaction with the education ward.

Although, as this study has shown, ASP plays a significant role in perceived quality of care, it is also vital to provide the proper learning environment that supports students during their participation on the ward. Various studies have shown that empathy and patient centeredness tend to decline during participation in clinical education and in residency [22]. While the reasons for this are still not fully clear, it seems that the process of adaptation to the contemporary culture of clinical practice may lead to a more effective and focused, yet less patient-oriented, attitude. Qualities of empathy and patient centeredness may therefore be stronger at the beginning of clinical education. Carmel and Glick, for example, analyzed the characteristics of compassionate and empathic physicians and found a significant correlation with younger age and fewer years of medical experience [23]. Studies on residents, on the other hand, have reported higher levels of stress, depression, and burnout in residents [24, 25], all of which lead to less patient-centered and empathic interaction with patients. A qualitative study from Belgium describes patient centeredness as being negatively affected by tiredness and perceived time pressure, by nonpatient-centered role models, and by feeling overwhelmed by powerful experiences [26]. Thanks to the learning environment provided on the CEWIM, medical students still experience a sense of security and assurance while working under close supervision; the additional attendance and perceived learned-centered approach may make it easier for them to practice patient-centered care.

4.1. Strength and Limitations. Both the CEWIM patient group and the control group were comparable in size (103 versus 94 patients), sex, insurance status, health status, and duration of disease. A possible explanation for the lower response rate of the control group compared to the CEWIM patient groups (38% versus 48%) may be that this group had more older age patients and more patients with dementia, making it more difficult for them to complete a written survey. The fact that more of the CEWIM patients were satisfied with their care may have also contributed to a higher response rate. The lower percentage of patients in the control group with an interest in anthroposophic medicine reflects the fact that two of the three internal medicine wards at the GKH offer a greater range of complementary therapies. The “short-term ward” does not offer so many art therapies and other nonphysician therapies. The number of patients with an interest in anthroposophic medicine was therefore higher on the CEWIM than on the control group wards, one of the reasons why it was important to control for different patient characteristics as part of our study.

Since the long-term wards have more patients with a specific interest in anthroposophic medicine, it may be that the resulting higher amount of patients obtaining more complementary nonphysician therapies led to greater satisfaction with the CEWIM. However, inclusion of the patient characteristic “number of nonphysician therapies obtained” as a covariate did not change the significance of the differences in quality of care found between the two patient groups. Furthermore, 80% of the CEWIM patients rated the impact of student participation on their care as positive while only one out of the 103 CEWIM patients reported it to have a somewhat negative influence.

5. Implications for Future Research

The results of this study suggest that ASP has a positive effect on perceived patient centeredness. Further studies are needed to determine whether similar results can be observed in other contexts, such as in other clinical specialties or in conventional hospitals. A comprehensive economic analysis is also desired to assess cost intensiveness of the CEWIM compared to a regular ward. Also, more research is necessary to analyze the specific conditions of the learning environment enabling a positive influence of ASP on the quality of care.

6. Conclusion

Our study shows that ASP may enhance patient-physician interaction, physician empathy, and patient enablement. In addition, our findings suggest that the relationship between
students and the community of practice is not just a one-way street. Active student participation in the community is of benefit both to students and to the healthcare team and patients. Student participation and the establishment of a favorable and supportive learning environment may therefore be considered factors which can be used to improve the care provided by future healthcare teams practicing integrative medicine.

References

Cost Analysis of Integrative Inpatient Treatment Based on DRG Data: The Example of Anthroposophic Medicine

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Background. Much work has been done to evaluate the outcome of integrative inpatient treatment but scarcely the costs. This paper evaluates the costs for inpatient treatment in three anthroposophic hospitals (AHs).

Material and Methods. Cost and performance data from a total of 23,180 cases were analyzed and compared to national reference data. Subgroup analysis was performed between the cases with and without anthroposophic medical complex (AMC) treatment.

Results. Costs and length of stay in the cases without AMC displayed no relevant differences compared to the national reference data. In contrast, the inlier cases with AMC caused an average of €1,394 more costs. However, costs per diem were not higher than those in the national reference data. Hence, the delivery of AMC was associated with a prolonged length of stay. 46.6% of the cases with AMC were high outliers. Only 10.6% of the inlier cases with AMC were discharged before reaching the mean length of stay of each DRG.

Discussion. Treatment in an AH is not generally associated with an increased use of resources. However, the provision of AMC leads to a prolonged length of stay and cannot be adequately reimbursed by the current G-DRG system. Due to the heterogeneity of the patient population, an additional payment should be negotiated individually.

1. Introduction

Integrative medicine according to the US National Center for Complementary and Alternative Medicine "combines treatments from conventional medicine and complementary medicine (CAM) for which there is some high-quality evidence of safety and effectiveness" [1]. One of the approaches which fits this definition is anthroposophic medicine (AM) established in the 1920s by Rudolf Steiner and Ita Wegman along with some other doctors [2]. In the last decades, AM has developed to become one of the main representatives of integrative medicine in Germany and is currently practised in over 60 countries [3].

Furthermore, it is explicitly designated and mentioned in the German Drug Law as a "Special Therapeutic System" alongside herbal medicine and homeopathy [4]. AM explicitly sees itself as an extension and supplement to the "conventional medicine" and not as an alternative medicine [5]. A special feature of AM compared to other integrative medical disciplines is that AM is established both in the outpatient sector and in many acute hospitals [6].

Since 2002 German hospital payment is based on the German refined diagnosis-related groups (G-DRGs) [7]. DRGs are defined by the patients’ diagnoses, gender and age, treatment procedures, complications or comorbidities, and further attributes. Based on this data, a predetermined rate per case is calculated.

The German official classification of operational procedures (Operationen und Prozeduren Schlüssel: OPS) is used to code operations and other medical procedures. Within the OPS, anthroposophic medical complex treatment was established in 2005 as a special code (OPS 8-975.3; Table 1) [8, 9]. This is owed to the fact that AM requires an intense use of resources (counseling, diagnosis, and treatment planning), therapeutic intervention (physical therapy, such as...
Table 1: OPS complex code 8-975.3 from OPS catalog 2011.

<table>
<thead>
<tr>
<th>8-975.3 anthroposophic medical complex treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>The treatment is carried out using several specific therapies with a total of at least 30 therapy sessions (each of at least 30 minutes) from the following areas:</td>
</tr>
<tr>
<td>(i) Applications and baths</td>
</tr>
<tr>
<td>(ii) Massages, rubs, and wraps</td>
</tr>
<tr>
<td>(iii) Movement therapies</td>
</tr>
<tr>
<td>(iv) Arts therapies</td>
</tr>
<tr>
<td>(v) Supportive therapy and patient education</td>
</tr>
</tbody>
</table>

The treatment is carried out using several specific therapies with a total of at least 30 therapy sessions (each of at least 30 minutes) from the following areas:

(i) Applications and baths
(ii) Massages, rubs, and wraps
(iii) Movement therapies
(iv) Arts therapies
(v) Supportive therapy and patient education

eurhythmy, art therapy, music therapy, and rhythmical massage), and nursing interventions (external applications such as wound and liniments). Once a patient receives at least 30 therapeutic units within his inpatient treatment coded with this digit, an additional unweighted payment "ZE-26" (anthroposophic complex medical treatment additional payment) is generated [9, 10]. This additional payment has to be negotiated and agreed on by each hospital individually with insurance companies as a part of the remuneration negotiations according to the hospital remuneration act [11].

The present study examined whether the provision of AMC is associated with an increased use of resources.

2. Material and Methods

2.1. Data Selection. The current analysis is based on German cost and performance data from 2009 which had already been approved and sent to the Institute for the Hospital Remuneration System (InEK). From the seven AM hospitals or departments which calculate the ZE-26 in Germany, three hospitals, namely, the Community hospital Havelhöhe (Berlin), the Community hospital Herdecke, and the hospital Öschelbronn, take part in the annual cost calculation of InEK.

Thus, valid cost data are only available from these three institutions (Figure 1). These data were grouped into the 2011 version of the G-DRG system and valued at the federal base rate 2011.

Weighted additional payment was considered in compliance with the price of the Case Fees Agreement (German: Fallpauschalenvereinbarung FPV) of 2011. Unweighted additional payments were, if possible, taken into account using the individual hospital prices from 2009. In the rare cases in which no individual hospital arrangement was made, treatments were considered with 600€. Cases which were grouped into unweighted G-DRGs were already subject to the individual hospital agreement anyway and were not included in the analysis. The length of stay was always calculated in days of occupancy, so the day of discharge was not considered unless it was also the day of admission.

Cases were separated into two groups: those with anthroposophic medical complex (AMC) treatment and those without. Collected data was compared between the included hospitals and the with national reference data published by the German Institute for the Hospital Remuneration System (InEK). Cases with the length of stay between individually for each DRG defined boundaries (lower and upper trim point) are named "inliers." Cases with a length of stay longer than the upper trim point of the DRG into grouped are referred to as high outliers, while cases that stay shorter than the lower trim point which they are referred to as low outliers, respectively (Figure 2). They are subject to special surcharges/deductions to their relative weight. Cases transferred to or transferred from other hospitals that stay shorter than the average length of stay of the respective DRG are also subject to deductions to their relative weight and not considered as inliers. As the reference group only includes inliers certain analyses could only be made with the respective cases of collected data.

With costs deriving from 2009 and revenues calculated with the base rate from 2011, costs and revenues cannot be matched directly as, for example, the development of the base rate should partly compensate for rising costs.

2.2. Statistical Analysis. The average DRG costs of inlier cases of the reference group are based on a cost matrix published by the Institute for the Hospital Remuneration System (InEK). These costs do not include costs reimbursed by additional payments (ZE). To be able to compare the collected cost data with the InEK reference group, the costs of each inlier case were adjusted for included costs for additional payments by the amount of reimbursement the additional payments would have realized. In the DRG costing, a distinction is made within the InEK cost matrix for the determination of deductions and surcharges for outliers. While the costs...
for the “key service” are regarded relatively independent of length of stay, the so-called “differential costs” are considered to be dependent on the length of stay and therefore used to calculate deductions and surcharges. The “key service” is defined as the sum of the cost values in the account groups 04 (operating room), 05 (anesthesia), 06 (delivery room), 07 (cardiac diagnosis/treatment), and 08 (endoscopic diagnostics/therapy) plus the cost values of the cost element group 05 (implants) which have not yet been included. The remaining costs of the InEK cost matrix are referred to as “differential costs.”

Statistical analysis was performed with SPSS 18.0 for Windows. Descriptive analysis was used to determine rates and proportions. Means and standard deviations (SDs) were calculated for continuous data. Two-tailed Chi-square test was used to analyze differences in frequencies; t-test was used to analyze differences in means. A P value of less than 0.05 was regarded as indicating a statistically significant difference.

2.3. Ethical Considerations. The present study is based on secondary data collected from the hospitals and for the reference group provided by the InEK. As such, the recommendations for good practice in secondary data analysis (e.g., anonymization of data on prescriptions and diagnoses) developed among others by the German Working Group on the Collection and Use of Secondary Data were applied in full [12].

3. Results

3.1. Sample Description. From the three hospitals included in our analysis, a total of 23,180 cases discharged in 2009 were available. Of them, only 1,331 cases (6.1%) received AMC. This value varies considerably from hospital to hospital and ranges between 2.6 and 19.8% (Table 2; P < 0.001).

The patient groups or types of diseases were also heterogeneous. The spread ranges over 308 different G-DRGs corresponding to 26% of all inpatient G-DRGs at a level of 1,189 in the 2011 version of the G-DRG system. An accumulation was found in the medical collectives of solid malignant neoplasm, chronic diseases such as heart failure, COPD/asthma, hypertension, diabetes mellitus, gastritis, inflammatory bowel disease, and psychosomatic or psychiatric principal diagnoses (Table 2).

The respective case collectives receiving AMC differ clearly among the three participating hospitals. The average DRG cost weight CMI (case mix index) was 2.16 among the cases with AMC; cases without this AMC achieved on average a CMI of only 0.83. Thus AMC cases achieve an average DRG income 2.6 times higher. The CMI indicates already higher resource consumption.

Cases classified as “inliers” without AMC (N = 21,849) caused an average of InEK-compliant costs of 2,451€ (SD: 3,037€), while “inlier” cases with AMC (N = 1,331) amounted to 6,724€ (SD: 9,323€) which is significantly different (t-test, P < 0.001).

3.2. Comparison with a Reference Group

3.2.1. Cases without AMC. The comparison of the average length of stay as well as the percentage of cases which stay shorter than the average residence times of the InEK reference collective (only inlier) shows no abnormalities for cases without AMC and also corresponds to the expected values (Table 3).

The adjusted costs of an inlier with an average of 2,394€ nearly correspond to the cost of 2,387€ stipulated by InEK (Table 3).

In the distribution of personnel, equipment, and infrastructure costs, as well as in the mean length of stay, no relevant differences to the InEK comparison group can be identified; thus treatment in anthroposophically oriented hospitals excluding AMC patients is not associated with an increased use of resources.

3.2.2. Cases with AMC. The average length of stay of cases with AMC was 19.5 days while the average in the inlier group was 14.7 days. In the InEK reference group (only inliers), the value for length of stay was given as 10.9 days which is 3.8 days shorter than the respective value of the AMC group.

This is due to the fact that nearly half of the cases (46.6%) with AMC were high outliers while inliers amounted to 53.1%. Therefore low outliers only occurred in 0.3%. Only 5.9% of the cases were discharged before reaching the mean length of stay of each DRG. Moreover only 10.6% of the inliers with an

Table 2: Patient allocation according to diagnoses and procedures.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Without AMC</th>
<th>With AMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant neoplasms and their treatment</td>
<td>1,719 (86.5%)</td>
<td>269 (13.5%)</td>
</tr>
<tr>
<td>Chronic diseases of the heart and the lungs</td>
<td>1,071 (87.7%)</td>
<td>150 (12.3%)</td>
</tr>
<tr>
<td>Psychosomatic principal diagnoses</td>
<td>164 (80.0%)</td>
<td>41 (20.0%)</td>
</tr>
<tr>
<td>Surgical procedures and interventions</td>
<td>91 (47.9%)</td>
<td>99 (52.1%)</td>
</tr>
</tbody>
</table>

Figure 2: Length of stay: definition of inlier and outlier cases (annually calculated for each DRG individually).
Table 3: Structural and cost data distribution in cases with/without anthroposophic medical complex (AMC) treatment.

<table>
<thead>
<tr>
<th></th>
<th>Without AMC</th>
<th>With AMC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital 1</td>
<td>10,617 (97.4%)</td>
<td>273 (2.6%)</td>
</tr>
<tr>
<td>Hospital 2</td>
<td>9,405 (92.6%)</td>
<td>697 (7.4%)</td>
</tr>
<tr>
<td>Hospital 3</td>
<td>1,827 (80.2%)</td>
<td>361 (19.8%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21,849 (93.9%)</td>
<td>1,331 (6.1%)</td>
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<thead>
<tr>
<th></th>
<th>Without AMC</th>
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<tbody>
<tr>
<td><strong>Average length of stay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (SD)</td>
<td>6.1 (5.2)</td>
<td>19.5 (14.9)</td>
</tr>
<tr>
<td>Inlier (SD)</td>
<td>6.2 (4.9)</td>
<td>14.7 (7.9)</td>
</tr>
<tr>
<td>German InEK catalog</td>
<td>6.2</td>
<td>10.9</td>
</tr>
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<table>
<thead>
<tr>
<th></th>
<th>Without AMC</th>
<th>With AMC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% under average length of stay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>55.7%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Inlier</td>
<td>50.7%</td>
<td>10.6%</td>
</tr>
<tr>
<td><strong>% cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low outlier</td>
<td>15.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Inlier</td>
<td>76.0%</td>
<td>53.1%</td>
</tr>
<tr>
<td>High outlier</td>
<td>6.8%</td>
<td>46.6%</td>
</tr>
<tr>
<td>Transferred&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2.0%</td>
<td>0.2%</td>
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<thead>
<tr>
<th></th>
<th>Without AMC</th>
<th>With AMC</th>
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</thead>
<tbody>
<tr>
<td><strong>Remuneration of all cases in €</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRG income&lt;sup&gt;1&lt;/sup&gt; (sd)</td>
<td>2,473 (2,864)</td>
<td>6,405 (12,619)</td>
</tr>
<tr>
<td>ZE income&lt;sup&gt;2&lt;/sup&gt; (sd)</td>
<td>66 (417)</td>
<td>111 (635)</td>
</tr>
<tr>
<td>Total income (sd)</td>
<td>2,540 (2,956)</td>
<td>6,516 (12,835)</td>
</tr>
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<thead>
<tr>
<th></th>
<th>Without AMC</th>
<th>With AMC</th>
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</thead>
<tbody>
<tr>
<td><strong>Remuneration inlier in €</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRG income&lt;sup&gt;1&lt;/sup&gt; (sd)</td>
<td>2,650 (2,779)</td>
<td>5,863 (11,109)</td>
</tr>
<tr>
<td>ZE income&lt;sup&gt;2&lt;/sup&gt; (sd)</td>
<td>57 (392)</td>
<td>86 (606)</td>
</tr>
<tr>
<td>Total income (sd)</td>
<td>2,707 (2,865)</td>
<td>5,949 (11,344)</td>
</tr>
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<tr>
<th></th>
<th>Without AMC</th>
<th>With AMC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost in €</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost (all) (sd)</td>
<td>2,417 (3,145)</td>
<td>7,992 (11,019)</td>
</tr>
<tr>
<td>Cost (inlier) (sd)</td>
<td>2,451 (3,037)</td>
<td>6,724 (9,323)</td>
</tr>
<tr>
<td>Cost (inlier)/ZE income</td>
<td>2,394</td>
<td>6,638</td>
</tr>
<tr>
<td>Cost (InEK)</td>
<td>2,387</td>
<td>5,244</td>
</tr>
</tbody>
</table>

<sup>1</sup>DRG income: revenues through lump compensation.
<sup>2</sup>ZE income: revenues through additional remuneration.
<sup>3</sup>Cases transferred to or transferred from other hospitals with length of stay shorter than the average of the respective DRG (and therefore subject to deductions).

AMC are discharged before reaching the mean length of stay of each DRG according to the DRG catalog.

In contrast to the cases without AMC, cost data of the cases with AMC was strikingly different. Cases with AMC produced average costs of 7,992€; inliers only produced adjusted costs of 6,638€ which was still 1,394€ higher than in the InEK reference group (5,244€). It is remarkable that in the cases with AMC (inliers and high outliers) the differential costs per day were not higher than those in the InEK reference group. This shows that the additional costs of cases with an AMC are caused by a longer length of stay and not by the use of more resources per day.

4. Discussion

Much work has been spent to evaluate the outcome of integrative in-patient treatment [13,14], but only some articles deal with the costs of such strategies [15, 16]. This article for the first time evaluates the costs for integrative in-patient treatment in three hospitals using cost and remuneration data, which in contrast to other approaches takes the perspective of the healthcare suppliers. This study in particular analyzes cases with anthroposophic medical complex treatment (AMC).
As a first result, we found a wide dispersion of the G-DRG spectrum for the provision of AMC. This may be explained by the fact that the use of AM is patient-specific and, in addition to the clinical picture, determined by the personality of the patient and the patient’s will [17]. Thus it is primarily not the type of illness or the DRG group which triggers the provision of the anthroposophic additional payment, but the individual therapeutic process negotiated between physician and patient.

Our evaluation also revealed significant cost differences among the hospitals in the provision of AMC. Apart from patient-physician interactions, this is owed to the hospital-specific processes and medical collectives treated. This in-house treatment structure was not a part of this evaluation but however should be analyzed in a subsequent study, in which, for example, by means of a clustering based on performance groups, the costs and treatments’ side of comparable entities of the anthroposophic hospitals to be calculated are compared [18]. At this present time, it thus can be inferred that AMC should not be subject to a nationally standardized additional payment and should be determined and negotiated from hospital to hospital.

This hospital-specific procedure for the additional payment of the ZE-26 is not unique in the G-DRG system. According to the catalog for additional payments, there is a total of 64 payments listed which are to be negotiated individually with each hospital [10]. The majority of these are attributable to drugs, operational and medical interventions (e.g., ZE2011-53 “additional charge stent graft prosthesis for aortic aneurysms with fenestration or branch”) which, due to their complexity or limited use, are not subject to the federal calculation. Still to be found in this catalog next to the anthroposophic complex medical treatment are three similar additional payments declared as “special treatments” by the InEK Institute, which, due to their characteristics, might be accompanied by a desired longer length of stay: the ZE2011-36 “care for the severely disabled;” the ZE2011-40 “additional payment alternative complex treatment,” and the nationally weighted ZE60 “palliative complex treatment”. Whilst the literature research did not show any further useful information for the first two payments, it turns out that the additional payment for palliative care is affected by similar remuneration problems which are currently discussed in the literature [19] and lead to a calculated additional payment compensating for the desired prolonged length of stay [20].

Another study of Romeyke and Stummer [21] analyzed complex rheumatic treatment and similar to our study found a prolonged stay of patients without higher costs per day associated with this form of treatment. However that study used data from the beginning of the DRG calculation and reliability data was weak. Because of the limited range of DRGs affected, a specific DRG (1972) for the complex rheumatic treatment could be established and calculated meanwhile. Our study showed that the provision of AMC is associated with a prolonged length of stay, and this is not just since there is a compensation by the additional fee “ZE-26.” Thus, it is not the doctor or therapist input per day which leads to the financial shortfall compared to the InEK patient population with regard to the G-DRG remuneration, but rather the extended hospital stay which is not compensated by a high outlier surcharge which only partially compensates for an increased use of resources after the upper trim point of the DRG has been exceeded [22]. For inlier collectives with systematically longer stays that do not reach the upper trim point, no compensation exists at all.

Consequently all inpatients with a longer stay than the DRG-average tend to be remunerated with a deficit and not only the affected cases in anthroposophic hospitals. What is relevant, however, is that it can be balanced out, from an economic aspect, by cases with a short stay. After 55.7% of all cases and 50.7% of all inliers without AMC could be discharged before reaching the mean residence time of each DRG, there is no underfunding due to the length of stay for this case collectives. If, however, a longer residence is not due to inefficiency but to a medical specialty or complex treatment, such as the anthroposophic complex medical treatment, then a sanctioning of the economic disadvantages by a “right shift” of the lengths of stay (for long inliers and high outliers) is not appropriate.

5. Limitations

Although this study has used validated data, it still has limitations. Firstly 2,100 hospitals do exist in Germany, but only 113 of them take part in the annual cost calculation of InEK of which three are anthroposophic hospitals. This of course denotes an overproportional participation of anthroposophic hospitals in the annual calculation of InEK. But although the participation rate of anthroposophic hospitals is significantly higher than those of conventional hospitals, the large data basis of 4.5 million patients in total suggests that the bias caused by anthroposophic hospitals is marginal.

Secondly no information about the most relevant diagnostic groups (represented by the MDC class in the DRG classification) is given. This is due to the fact that the cases with AMC distribute over a total of 308 G-DRGs and thus our data did not allow to do a valid clustering on diagnostic groups. As a consequence, we were not able to compare cases with or without AMC in more detail at the level of DRGs. This unfortunately leads to the problem of a certain amount of impreciseness while mapping difference costs and cases. However, this does not affect the general results of this work.

Finally from a methodological point of view, cost data are notoriously skewed, which in our data is suggested by the high standard deviations relative to the means. Thus, other statistical approaches like bootstrapping might be more appropriate for this situation [23]. However, the structure of the raw data given for this analysis did not allow for more complex statistical tests.

6. Implications for Health Policy

Anthroposophic medicine in Germany is legally recognized as a special type of integrative treatment which is highly demanded on the patients’ side. We were able to demonstrate that anthroposophic medicine at the moment can only establish itself in the acute in-patient sector when compensation of
the increased use of resources calculated individually by each hospital is effected over the ZE-26.

Currently the compensation rates, at least among the three participating hospitals, do not cover the costs and are thus associated with a negative contribution margin per supplied AMC. Therefore the hospitals do not have any economical incentive to provide this type of medicine for economic reasons [24].

Whether anthroposophic medicine with its special use in therapy can establish itself under these conditions in an in-patient setting either mid-term or long term, will mainly be a political or social decision which, in the end, should be supported by arguments as have been described and carried out in this paper.

Conflict of Interests

W. Fiori is a member of the DRG Research Group and carries out analyses, consultation and seminars for a multitude of different stakeholders in the healthcare system as well as gives expert opinions for social and civil courts. The DRG evaluation of the anthroposophic medicine was funded by the AnthroMed gGmbH. J. Heinz is the Managing Director of an anthroposophic hospital.

Acknowledgment

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References


Review Article

The Effects of Integrative In-Patient Treatment on Patients’ Quality of Life: A Meta-Analysis

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1. Introduction

Integrative medicine according to the definition of the consortium of the Academic Health Centers for integrative medicine is “the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals, and disciplines to achieve optimal health and healing” [1]. It therefore may combine the treatment of conventional medicine and complementary alternative medicine (CAM) and assists the patient’s own capacities to recover from illness.

In the last decades, several hospitals have adopted this concept of integrative medicine for the treatment of chronic and acute states of illnesses in in-patient treatment [2, 3]. This includes hospitals with a special focus on mind body therapies, naturopathy, anthroposophical medicine, homeopathy or traditional Chinese medicine. From those institutions, a variety of high-quality clinical studies in special therapies like acupuncture [4], leeches therapy [5], fasting [6], or cupping [7] have been performed and published which demonstrate the power of single components of integrative in-patient treatment. Moreover large studies have also investigated safety aspects of these approaches [8]. To provide additional evidence for the whole system in real world treatment, concept evaluations of the approach of integrative medicine for in- and out-patient treatment have been proposed [9].

Already in the very early years of these institutions such whole systems evaluations, that is, with the focus on comparative health economic analysis, demonstrated the therapeutic potential of these approaches [10]. Nowadays such
evaluations have regained the interest of stakeholders of the health care system such as health insurances or governmental authorities mainly to develop special diseases management pathways or to create specific diagnose related groups and additional payments [11, 12]. In particular scientific interest was focused on the sustainability of integrative treatment outcomes after in-patient treatment. Studies in this field so far have shown high patient satisfaction, and reduced out-patient expenses and doctor’s visits [13].

In the appraisal of patient’s benefits several measures like patient’ mood, depression, or pain perception were applied to demonstrate the effects of integrative in-patient treatment. However health related quality of life very early became the main and most important outcome parameter and denotes the least common denominator of such evaluations [14].

Up to now, published data is widespread and no systematic review so far has collected the results of the studies to get a broader picture of the effects of integrative in-patient treatment. The aim of this paper was to summarize the current evidence for a possible effectiveness of integrative in-patient treatment on patients’ quality of life by means of a meta-analysis.

2. Material and Methods

2.1. Search Strategy. The following databases were used to find articles: MEDLINE, EMBASE, AMED, PsycInfo, PsycLit CCMED, and CAMbase [15]. We also screened the journal databases of relevant publishers, that is, gms, Karger, Kluwer, Krause and Pachernegg, Springer, Thieme, and Wiley-Interscience, to find relevant information. Finally, we searched the archive of the specialist library for CAM of Witten/Herdecke University for gray literature not listed in the above mentioned databases. The search terms were (naturopathy OR “integrative medicine” OR anthroposophical OR homeopathic) AND (clinic OR hospital).

2.2. Inclusion and Exclusion Criteria. Articles were included if patients were treated in a hospital (no out-patient or day clinic treatment). To guarantee comparability SF-36 was the predefined outcome measure for patients’ quality of life. To get a picture the sustainability of the effects, we decided to concentrate on the differences between “baseline” and “followup” with a follow-up duration of three months. Finally the aspect of “real world data” was covered and thus controlled clinical trials of a single drug or treatment were excluded.

All articles were fully read and their reference lists were checked for further relevant publications. To guarantee validity of the selection process, all abstracts of excluded papers were double checked. The complete search was performed between March and May 2012. The reporting of the results adhered to the MOOSE and QUOROM guidelines [16].

2.3. Data Extraction. Details of eligible studies were extracted and summarized using a data extraction sheet including the study indicators year, origin, institution, therapeutic approach, diseases, treatment duration, number of patients, and mental and physical scores of the SF-36 (mean and standard deviations at baseline and followup). Extracted data was cross-checked again.

2.4. Statistical Analysis. When a trial was found to be eligible, data of pre/post effects on the mental and physical scores of the SF-36 were converted into effect sizes and their standard deviation using an MS Excel sheet. We used the formulas

$$d = \frac{m_1 - m_2}{\sqrt{(s_1^2 + s_2^2)/2}}$$

$$\text{STD}(d) = \sqrt{\frac{2(1 - r)}{n} + \frac{d^2}{2(n - 2)}}$$

(1)

to calculate the effect size $d$ between the two time points and its standard deviation $\text{STD}(d)$ according to the recommendations of Dunlap et al. [17], where $m_1$, $s_1$ and $m_2$, $s_2$ denote the means and standard deviations of the pre- and post-SF-36 scores and $r$ represents Pearsons correlation coefficient between them. In cases where the correlation between pre- and post-measures was not reported, we set $r = 0.7$, which according to [14] is a suitable upper bound.

To calculate overall estimates of the treatment effect we chose a random effects model according to the recommendations and algorithms given in Borenstein et al. [18] assuming that the studies were showing different treatment effects with some degree of unknown variability. Heterogeneity between trials was assessed by standard Chi-Square tests and the $I^2$ coefficient measuring the percentage of total variation across studies due to true heterogeneity rather than chance. Results were displayed using a forest plot.

3. Results

A total of 364 records were found, of which 36 could be identified as reviews. After screening the abstracts of the remaining 328 records, 268 records were excluded because they did not fit to the inclusion/exclusion criteria. The remaining 60 articles were assessed for eligibility and other 52 were excluded according to the inclusion/exclusion criteria after reading the full text as they provided data on out-patient treatment or did not report on SF-36 quality of life data. Thus eight articles published between 2003 and 2010 were included in the final meta-analysis. A flow chart of the inclusion process is provided in Figure 1.

Six of the eight articles described a traditional European medicine in-patient treatment strategy including the five therapeutic elements “hydrotherapy,” “phytotherapy,” “exercise therapy,” “nutrition/dietetics,” and “lifestyle modification” of classical naturopathy as originally described by Kneipp. One of the studies included “traditional Chinese medicine” as an additional therapeutic element; another one had a focus on spa therapies. The remaining two articles reported on an integrative mind body approach and on a biopsychosocial treatment strategy. Seven of the eight studies were conducted in German hospitals or hospital departments. Only one study provided data from integrative in-patient treatment from the USA.

The mean number of patients enrolled was 897 ranging from 22 to 4253. The treatment duration varied between
Evidence-Based Complementary and Alternative Medicine

Records identified through database searching (n = 364)

Reviews excluded (n = 36)

Records after reviews removed (n = 328)

Records excluded (n = 268)

Full-text articles assessed for eligibility (n = 60)

Articles excluded (n = 52)

Studies included in qualitative synthesis (n = 8)

FIGURE 1: Flow chart of the inclusion process.

two and three weeks. The majority of patients were treated because of diseases of the musculoskeletal system and connective tissue (ICD chapter M00–M99) including pain syndroms. The data on the 8 included articles is summarized in Table 1.

3.1. Meta-Analysis. Random effect meta-analysis of the eight studies revealed an overall effect size of 0.37 (95% CI: [0.28;0.45]) in the physical score and 0.38 (95% CI: [0.30;0.45]) in the mental scores of the SF-36. $I^2$ statistics indicate a high heterogeneity in the effects in both the physical and mental scores of the SF-36 ($I^2 = 91.8\%$, $P < 0.001$, resp.; $I^2 = 86.7\%$, $P < 0.001$).

In the physical dimension effect sizes were quite heterogenous ranging from small effects of $d = 0.16$ and $d = 0.18$ in the studies of Greeson et al. [24] and Wiebelitz et al. [25] to moderate effects of $d = 0.50$ and $d = 0.51$ in the studies of Weidenhammer et al. [22] and Buchner et al. [23] (Figure 2).

In the mental dimension the lower bound lower bound of effect sizes is identical to the physical dimension ($d = 0.16$ in the study of Stange et al. [26]). However the upper bound sees remarkably higher effects of $d = 0.56$ in the study of Buchner et al. and $d = 0.69$ in the study of Wiebelitz et al. [25] (Figure 3).

In both dimensions the overall effect is mainly influenced by the huge cohort study of Weidenhammer et al. from 2007 [22], which included about 59% of all patients of this meta-analysis and had the second highest effect sizes in the physical score of the SF-36 (0.50 [0.48, 0.52]) and the third highest in the mental score of the SF-36 (0.44 [0.42, 0.46]). Nevertheless the results stay stable with a slightly broader confidence interval when data from Weidenhammer et al. is excluded (0.35 [0.25, 0.45], $I^2 = 87.7\%$ in the PSF-36, and 0.37 [0.28, 0.45], $I^2 = 84.9\%$ in the MSF-36).

4. Discussion

This is the first systematic review and meta-analysis to cover whole systems evaluations of integrative in-patient treatment. Based on the data of 7180 patients treated with integrative concepts ranging from classical naturopathy to traditional Chinese medicine we were able to calculate moderate total effect size almost three months after discharge from hospital. Quite fortunately all scientific evaluations have used standardized outcome measures and most of them included the SF-36 as a standardized measure for health related quality of life (HRQoL). Although setting parameters and patient characteristics did differ to a certain extent between the included studies, the results of this meta-analysis both from the perspective of sample size and indications and outcome measures can be regarded as a valid indicator of effectiveness for integrative in-patient treatment.

The by far most treated conditions in the 8 included studies are musculoskeletal and pain disorders [27]. It is well known from the literature that existing chronic conditions have a negative impact on HRQoL. As Langley reported, in an internet survey in Germany an estimated 24% of the adult German population reported experiencing pain in the last 30 days. Of these 13% reported severe pain. The experience of frequent severe and moderate pain has a significant deficit impact on HRQoL, both on a physical as well as a mental level [28]. This is particularly true in musculoskeletal disorders as shown by Falsarella et al. [29] who analyzed the influence of rheumatic diseases and chronic joint symptoms on the quality of life of the 2209 patients aged 60 years or over. There was a significant impact of rheumatic diseases on physical health. Furthermore joint symptoms affected self-evaluations of physical and mental health. Rheumatic diseases affected functional capacity and pain and joint symptoms relevantly...
Table 1: Description of the included articles.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Origin</th>
<th>Year</th>
<th>Institution</th>
<th>Therapeutic approach</th>
<th>Diseases</th>
<th>Treatment duration (days)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melchart et al. [19]</td>
<td>Germany</td>
<td>2003</td>
<td>TCM-Klinik, Kötzing</td>
<td>Classical naturopathy, traditional chinese medicine</td>
<td>29.7% musculoskeletal disorders</td>
<td>N.A.</td>
<td>803</td>
</tr>
<tr>
<td>Hofmann et al. [20]</td>
<td>Germany</td>
<td>2004</td>
<td>Knappschafts-KH, Essen</td>
<td>Classical naturopathy, mind body therapies</td>
<td>42.1% musculoskeletal disorders, 17.1% pain and migraine</td>
<td>14.7 ± 4.2</td>
<td>212</td>
</tr>
<tr>
<td>Ostermann and Matthiessen</td>
<td>Germany</td>
<td>2005</td>
<td>Klinik Blankenstein, Hattingen</td>
<td>Classical naturopathy</td>
<td>62.7% musculoskeletal disorders, 17.1% diseases of the circulatory system</td>
<td>21.8 ± 4.8</td>
<td>894</td>
</tr>
<tr>
<td>Weidenhammer et al. [22]</td>
<td>Germany</td>
<td>2007</td>
<td>Klinikverbund, München</td>
<td>Classical naturopathy, spa therapies</td>
<td>36.8% psychovegetative exhaustion, 19.5% chronic back pain</td>
<td>N.A.</td>
<td>4253</td>
</tr>
<tr>
<td>Buchner et al. [23]</td>
<td>Germany</td>
<td>2007</td>
<td>Orthopädische Chirurgie, Heidelberg</td>
<td>Biopsychosocial therapies</td>
<td>100% chronic low-back pain</td>
<td>21</td>
<td>405</td>
</tr>
<tr>
<td>Greeson et al. [24]</td>
<td>USA</td>
<td>2008</td>
<td>Jefferson Center, Philadelphia</td>
<td>Integrative medicine, mind body therapies</td>
<td>11.8% fatigue, 9.7% myalgia</td>
<td>N.A.</td>
<td>370</td>
</tr>
<tr>
<td>Wiebelitz et al. [25]</td>
<td>Germany</td>
<td>2010</td>
<td>Klinik Blankenstein, Hattingen</td>
<td>Classical naturopathy</td>
<td>100% chronic-low back pain</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Stange et al. [26]</td>
<td>Germany</td>
<td>2012</td>
<td>Immanuel KH, Berlin</td>
<td>Classical naturopathy</td>
<td>41.6% low back pain, 30.8% cervicobrachial syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

affected all components of the SF-36 [29]. Thus choosing the SF-36 as outcome parameter for the present analysis is conclusive.

Without question, due to its high relevance and burden, effective multimodal interventions are needed and a moderate total effect size almost three months after discharge from hospital proves the value of this special approach especially but not exclusively in these fields of medicine. Further frequent diagnoses for integrative in-patient treatment are chronic cardiovascular, gastrointestinal or pulmonary diseases, or even oncological diseases, but currently, data to evaluate these fields of interest are lacking.

Therefore, this meta-analysis only digs a small corridor in the field of evidence. Some of the studies included in our analysis have tried to identify responders and non-responders to integrative medicine. Although they finally did not succeed in doing so, this might still be an option if data from these studies are aggregated and reanalyzed. Apart from conducting an individual patient data meta-analysis as proposed by Vickers et al. [30], this approach may also be used to model the patient response to integrative therapies more distinctly that it can be done by a conventional meta-analysis.

However this idea is somehow limited. The fact should not be hidden that there are still several studies on whole systems evaluation of integrative in-patient treatment which have not seen the light of publication. One of the most deplorable examples in this respect is the model project Charlottenstift which aimed at integrating traditional European and traditional Chinese medicine [31].

Thus, this meta-analysis might be seen as an episode one of in-patient evaluation and might help to rediscover
the importance of this field for patients, physicians, and stakeholders of the health care system.

Conflicts of Interest

The authors declare that they have no conflict of interests.

Acknowledgment

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of multidimensional therapy for inpatients with different conditions of chronic musculoskeletal pain,” *BMC Complementary and Alternative Medicine*, vol. 12, supplement 1, p. 228, 2012.


Fibromyalgia poses a challenge for therapy. Recent guidelines suggest that fibromyalgia should be treated within a multidisciplinary therapy approach. No data are available that evaluated multimodal treatment strategies of Integrative Medicine (IM). We conducted a controlled, nonrandomized pilot study that compared two inpatient treatment strategies, an IM approach that included fasting therapy and a conventional rheumatology (CM) approach. IM used fasting cure and Mind-Body-Medicine as specific methods. Of 48 included consecutive patients, 28 were treated with IM, 20 with CM. Primary outcome was change in the Fibromyalgia Impact Questionnaire (FIQ) score after the 2-week hospital stay. Secondary outcomes included scores of pain, depression, anxiety, and well-being. Assessments were repeated after 12 weeks. At 2 weeks, there were significant improvements in the FIQ ($P < 0.014$) and for most of secondary outcomes for the IM group compared to the CM group. The beneficial effects for the IM approach were reduced after 12 weeks and no longer statistically significant with the exception of anxiety. Findings indicate that a multimodal IM treatment with fasting therapy might be superior to CM in the short term and not inferior in the mid term. Longer-term studies are warranted to assess the clinical impact of integrative multimodal treatment in fibromyalgia.

1. Introduction

Fibromyalgia is a complex clinical pain syndrome. Patients typically suffer from widespread musculoskeletal pain, fatigue, insomnia, and impairment of physical and psychological quality of life [1, 2]. The international prevalence of fibromyalgia ranges from 0.7 to 3.3% in the general adult population with an increase in recent years and a continuous majority of female patients [2–4].

The etiology of fibromyalgia is still unclear, although research showed an abnormal pain processing and lowered mechanical and thermal pain threshold by fMRI [5] as well as dysfunction of descending pain modulatory systems, for example, in the rostral anterior cingulate cortex (rACC) [6] and distinct neurotransmitter activities in cerebrospinal fluid [7]. Further discovered dysfunctions of the neuroendocrine axis could explain concomitant complaints as fatigue, irritable bowel, and mood disorders that are predominant in most of the fibromyalgia patients [8]. An association with psychosocial stressors is most likely [1, 8, 9].

Recent guidelines recommend a multimodal, multidisciplinary therapeutic approach involving medication, exercise, patient education, and behavioral and psychosomatic therapy [4, 10]. Due to frequent unsatisfying results of conventional treatment a substantial proportion of patients use complementary and integrative approaches such as Mind-body medicine, supplements, acupuncture, massage, and various nutritional therapies [11]. Clinical experience and preliminary evidence from uncontrolled prospective studies suggest that an integrative approach including nutritional
and fasting therapies may help to decrease symptoms and increase the quality-of-life in inpatients with fibromyalgia [12, 13]. However, it would be useful to know how such an Integrative Medicine approach compares with conventional multimodal treatment which is established in specialized hospital units of rheumatology or pain medicine.

Prolonged modified fasting (Fasting cure, fasting therapy) with defined periods of voluntary abstention from solid food and a daily total energy intake <500 kcal has been found effective in several randomized trials on rheumatoid arthritis [14, 15]. The anti-inflammatory, pain relieving, antinoceptive, and mood-enhancing effects of fasting and caloric restriction have been well described in experimental and clinical studies [16–19]. Both, patients with rheumatoid arthritis and fibromyalgia frequently report that elimination diets and meal skipping alleviate their symptoms [13, 20, 21]. In a controlled nonrandomized study on the influence of a Mediterranean diet or a fasting cure on the intestinal microflora the subgroup of patients with fibromyalgia experienced a greater improvement than nonfasters [13]. In another trial with a heterogeneous sample of chronic pain patients fasting led to an amelioration of mood and well-being [22].

In Germany, several academic hospital departments for naturopathic and integrative medicine have accumulated clinical experience in inpatient treatments of fibromyalgia. Within the treatment concepts of the integrative approach, modified fasting therapy is a mainstay of therapy. Notably, fasting treatments have been found to enhance health-promoting lifestyle modification [12], thus supporting a further key element of integrative therapy in fibromyalgia, mind-body medicine.

We conducted this first controlled nonrandomized pilot-study to compare an integrative treatment strategy including fasting cure with a conventional rheumatologic treatment strategy.

We investigated quality of life, pain intensity, and psychological outcomes before and after the treatment of fibromyalgia in inpatients of two different departments of Internal Medicine, Integrative Medicine, and Rheumatology, of the same hospital, which is a tertiary center for Rheumatologic diseases. We hypothesized that fasting and integrative treatment would lead to a beneficial add-on effect with regards to quality-of-life, pain, and further psychological outcomes at time of hospital dismissal.

2. Material and Methods

2.1. Study Design and Participants. The study was conducted as a prospective, controlled nonrandomized study. The study protocol was reviewed and approved by the Ethics Committee of the Charité-University Medical Center, Berlin, and all patients gave their informed consent to study participation. Collection of data was performed by trained study personnel.

All study subjects were inpatients from two departments of the Immanuel Hospital Berlin which is specialized in the treatment of rheumatic and chronic pain diseases, (1) patients of the Department of Integrative and Complementary Medicine and, (2) patients of the Department of Internal Medicine and Rheumatology. The primary diagnosis and reason for hospital admission of all participants was primary fibromyalgia. The study sample consisted of consecutively admitted inpatients during a 9-month period, who regularly stayed 14 ± 2 days in hospital for multidisciplinary treatment.

Inclusion criteria were a manifest fibromyalgia, as diagnosed by a rheumatologist, pain specialist, or internist, an age between 18 and 70 years, and a BMI between 20 and 45 kg/m². Patients with a start or change in drug therapy of their FMS less than 6 weeks ago, clinical relevant progressive or malignant diseases, current addiction or pregnancy, and inadequate cognitive abilities of cooperation were not included in the study. Further exclusion criteria were eating disorders, manifest liver disease, renal failure, gastric ulcer, and severe comorbidity including cancer and AIDS, premedication with immunosuppressive drugs (except corticosteroids) or coumarins, alcoholism, malnutrition, serious chronic infections, psychosis, epilepsy, type-1 diabetes, pregnancy, lactation, and a weight loss during the previous 3 months of >3 kg.

2.2. Interventions

2.2.1. Conventional Treatment. The conventional rheumatologic treatment approach consisted of a complex multidisciplinary treatment schedule with the following elements: group physiotherapy, hydrotherapy, thermal therapy, psychosomatic therapy, aerobic exercise, pool exercise, cognitive behavioral therapy, and education. The integrative and Complementary Medicine approach used the same treatment elements. In addition, fasting therapy and nutritional therapy supported by a group-based Mind-Body-Medicine concept was applied. The patients of both departments received a similar global amount of treatments with a total of 1600 to 2200 treatment minutes within the 2-week hospital period, according to agreements with health insurance companies in Germany.

The method of fasting was adapted from the technique described by Buchinger [23–26]. A fasting period with 7 to 8 days of subtotal caloric restriction (daily nutritional energy intake <500 kcal) was predefined. Fasting was preceded by one or two prefasting days, using a 800 kcal/day monodiet of fruit, rice, or potatoes according to patients’ choice. Fasting then began the following day with ingestion of an oral laxative, Natrium sulfuricum ("Glauber’s salt", 20–40 g). During fasting an enema or, if not wished by the patient, a mild laxative was applied every other day. The patients were recommended to drink 2–3 L of fluids each day (mineral water, small quantities of juice, and herbal teas). Vegetable broth was taken at lunch. The daily energy intake during the fast amounted to 350 kcal/day. For breaking the fast an apple was slowly eaten. The breakfast was followed by stepwise reintroduction of food with achievement of normocaloric intake by vegetarian meals on the third postfasting day. In the postfasting days a focus is set on reintroducing mindfulness to eating.

Both departments are well experienced with the treatment of fibromyalgia syndrome and patients are received in a general appreciating manner. Inpatient treatments for
fibromyalgia syndrome are recommended by German S-3 guidelines [1] and by health insurance companies for patients which do not respond adequately to outpatient care, including multimodal outpatient treatment. Patients are referred to both departments by internists, family practitioners, and rheumatologists comparably with patients’ preference for Integrative Medicine and fasting treatment being the main criteria for choice of hospital department.

2.3. Measurements. All measures were assessed by trained study nurses at three study visits, at baseline, after 2 weeks (at dismissal from hospital) and at study week 12 (10 weeks after dismissal). The primary outcome measure was the change in the Fibromyalgia Impact Questionnaire (FIQ) score from baseline to the end of the in-hospital intervention. The FIQ is a validated, multidimensional measure to assess the severity of fibromyalgia as rated by patients. The total score ranges from 0 to 100, with higher scores indicating more severe symptoms [27]. The validated German version was used [28].

Global pain status was assessed additionally by asking the patients for the global severity of the disease-related pain by means of a self-rating 100 mm Visual Analogue Scale (VAS) with a value of 100 indicating maximum pain and 0 indicating no pain. Patients were carefully instructed before first self-ratings on the correct use of the VAS.

Prespecified other secondary outcomes included (1) a 100 mm visual analogue scale for self-rated global quality of sleep; (2) the German version of the Spielberger State-Trait Anxiety Inventory (STAI), which consists of 20 items relating to state anxiety and 20 items relating to trait anxiety [29]; (3) the Bf-S Zerssen well-being scale, which measures momentary emotional well-being and consist of three answer categories with higher scores indicating lower well-being [30]; (4) the German version of the Hospital Anxiety and Depression Scale (HADS) [31], a validated standard measure for anxiety and depression which uses a 14-item scale with seven of the items related to anxiety and seven related to depression [32]; (5) the German version of the Pain Perception Scale for Adolescents (SES), which assesses sensory pain perception in chronic pain patients [33].

Subjects height and body weight were measured following a standardized protocol while patients wore light clothing and no shoes after an overnight fast. BMI was calculated as weight (kg)/height\(^2\) (m). Anthropometrical and clinical data were collected by trained study personnel. Seated blood pressure was measured after 5 min rest with a calibrated sphygmomanometer at the nondominant arm by trained nurses.

2.4. Statistical Analysis. As the study was designed as a nonrandomized pilot study no sample size calculation was conducted. However, we intended to include 60 patients and assumed a drop-out rate of 15%, giving a study sample of about 50 patients with full data sets.

Baseline differences were calculated by Kruskal-Wallis test. All outcome criteria were analyzed by intention-to-treat; including all subjects, irrespective whether or not they adhered to the protocol or gave a full set of data. For each outcome we fitted a generalized estimation equation (GEE), analysis of covariance (ANCOVA) which included treatment group (binary covariate), and the respective baseline value (linear covariable) as independent variables. Treatment effects were estimated within these models, and reported as adjusted group differences including their respective 95% confidence intervals (CI) and P values. All reported P values were based on two-sided tests, and a P-value < 0.05 was considered significant. All statistical computations were performed with SAS/STAT statistical software version 9.1 (SAS institute, Cary, North Carolina, USA).

3. Results

3.1. Baseline. During the 9-month study recruitment period we screened 56 screened patients with manifest fibromyalgia which were admitted to one of the two hospital departments. Of these, 48 volunteered to participate in our study; 20 in the department of Rheumatology and 28 in the department of Integrative and Complementary Medicine. Data assessments were complete for study visits 1 (baseline) and 2 (week 2). After 12 weeks data from 25 patients of the department of Integrative and Complementary Medicine and 17 of the department of Rheumatology were available.

Baseline characteristics of the study population revealed a middle-aged and predominantly female study population. Patients of the Department of Rheumatology showed a significantly greater impaired quality of life, the primary outcome, and had slightly higher pain scores and were more emotionally distressed with slightly higher scores for depression and anxiety compared to patients of the Department for Integrative and Complementary Medicine (Table 1). Use of medication prior and during the hospital stay, for example, with amitriptyline and other antidepressants, was not different between groups.

3.2. Primary Outcome. The FIQ score decreased substantially in the Integrative Medicine Group and to a significantly greater extent compared to the Rheumatologic group after 2 weeks (Table 2). At 12 weeks, the FIQ score increased again in both groups resulting in improvements of only 12% for the integrative and fasting approach and 6% for the control group, resulting in a nonsignificant difference between the groups.

3.3. Secondary Outcomes. At 2 weeks, the Integrative Medicine group had greater mean improvements in all secondary outcomes and most pronounced in the scores of quality of sleep, pain, pain perception, and anxiety (HADS, STAI) (Table 2).

At 12 weeks, the pain score and pain perception score only showed a trend towards a beneficial outcome for the Integrative Medicine group compared to the Rheumatologic group. All psychological outcomes were better in the Integrative Medicine group compared to the Rheumatologic group, however group differences were reduced and no longer statistically significant with the exception of anxiety. All of the outcomes deteriorated again compared to the 2-weeks
data resulting in mild mid-term treatment effects compared to baseline levels.

3.4. Safety. There were no serious adverse events in both groups. About 35% in each group reported some minor side effect. Within the Integrative Medicine group the first fasting days were frequently accompanied by dizziness, minor headache, and tiredness. Patients in the Rheumatology group reported frequently about muscle pain and tiredness, most likely due to exercise and physical therapies. 24 out of 28 patients in the integrative Medicine group declared that they would participate in fasting as again. 17 out of 20 patients in the Rheumatology group declared that they would like to repeat the treatment.

4. Discussion

In this controlled nonrandomized trial we compared the effectiveness of two time- and attention-balanced inpatient multimodal treatment strategies: an Integrative Medicine approach that included fasting therapy versus the conventional Rheumatologic therapy. While patients in the Rheumatologic group were more diseased at baseline, adjusted data analysis showed a more beneficial effect of the Integrative Medicine approach after 2 weeks for all of the clinical outcomes. At week 12, effects in both groups were reduced but still favored the Integrative Medicine approach, for example, for the psychological outcomes. The minimally clinically important difference of the FIQ is estimated to amount to 14%. In the present study the reduction of the FIQ at 2 and 12 weeks was 30.2% and 12.2% with Integrative Medicine versus 13.1% and 6.0% with multimodal Rheumatologic care. Thus, our results point to a relevant immediate effect of the Integrative Medicine approach while the long-term effects appear to be only mild.

We were surprised to see an only mild effectiveness of the Rheumatologic multimodal treatment approach although it combined several evidence-based treatment methods such as aerobic exercise, pool exercise, thermal therapy, psychotherapy, and cognitive behavioral therapy. However, it has to be noted that patients that are admitted to an inpatient treatment in Germany are highly selected as they have to be documented nonresponders to outpatient treatments according to requirements of health insurance companies and thus may be especially difficult to treat.

A recent study has evaluated the effects of a conventional multimodal inpatient treatment of 3 weeks within the setting of a specialized Rheumatologic rehabilitation hospital [34]. For the outcomes that were used (Pain, HADS) the results of the Integrative Medicine approach used in this study were also favorable, thus confirming our results.

Principally, treatment of fibromyalgia is still unsatisfying and most patients continue to be in considerable pain years after the first diagnosis and experience reduced quality of life. New approaches are needed and the majority of patients with fibromyalgia frequently also use methods of complementary medicine. Various types of exercise and mind-body medicine have been advocated, yet long-term adherence is limited. In Germany, nutritional therapies and fasting are very popular. Fasting treatments have found to be effective in the treatment of rheumatoid arthritis and pain syndromes, furthermore they may support motivation and self-efficacy in health-promoting lifestyle modification [12, 15, 21, 35]. In a preliminary study we observed a moderate pain-relieving effect of fasting in fibromyalgia [13].

Of note, we found a partially persisting mood-enhancing effect in the integrative medicine group which may be related to fasting therapy. Previous research has documented mood-enhancing effects of caloric restriction and fasting. Several mechanisms including increased central serotonin availability have been described experimentally [17].

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**Table 1: Baseline characteristics.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Integrative medicine group</th>
<th>Rheumatology group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female, No.</td>
<td>0/28</td>
<td>2/18</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>53.6 ± 10.8</td>
<td>51.8 ± 10.1</td>
<td>0.516</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8 ± 4.5</td>
<td>30.3 ± 6.7</td>
<td>0.281</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122.3 ± 13.2</td>
<td>128.5 ± 13.7</td>
<td>0.072</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>76.8 ± 7.8</td>
<td>78.8 ± 10.1</td>
<td>0.656</td>
</tr>
<tr>
<td>Physical well-being</td>
<td>7.1 ± 1.9</td>
<td>8.0 ± 1.2</td>
<td>0.089</td>
</tr>
<tr>
<td>Practice of exercise, No. / (%)</td>
<td>21 (75.0%)</td>
<td>13 (65.0%)</td>
<td>0.452</td>
</tr>
<tr>
<td>Practice of Relaxation, No. / (%)</td>
<td>8 (28.5%)</td>
<td>5 (25.0%)</td>
<td>0.784</td>
</tr>
<tr>
<td>FIQ score</td>
<td>54.3 ± 15.0</td>
<td>68.0 ± 8.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Pain score</td>
<td>58.2 ± 19.6</td>
<td>66.5 ± 19.5</td>
<td>0.135</td>
</tr>
<tr>
<td>Quality of sleep</td>
<td>60.5 ± 26.7</td>
<td>68.3 ± 27.6</td>
<td>0.191</td>
</tr>
<tr>
<td>STAI state score</td>
<td>50.4 ± 11.2</td>
<td>58.4 ± 13.0</td>
<td>0.027</td>
</tr>
<tr>
<td>STAI trait score</td>
<td>51.1 ± 11.2</td>
<td>54.3 ± 12.0</td>
<td>0.341</td>
</tr>
<tr>
<td>HADS-Anxiety</td>
<td>10.4 ± 3.8</td>
<td>11.3 ± 5.1</td>
<td>0.607</td>
</tr>
<tr>
<td>HADS-Depression</td>
<td>8.3 ± 4.8</td>
<td>11.1 ± 5.2</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Values are mean ± SD if not indicated otherwise. SBP: systolic blood pressure; DBP: diastolic blood pressure. STAI: State and Trait Anxiety questionnaire, FIQ: Fibromyalgia impact questionnaire; HADS: Hospital Anxiety and Depression scale.
Table 2: Outcomes in both groups at baseline, week 2 and 12 with group differences as indicators of change.

<table>
<thead>
<tr>
<th></th>
<th>Integrative medicine group</th>
<th>Rheumatology group</th>
<th>Mean diff</th>
<th>Mean diff (95% CI)</th>
<th>P value</th>
<th>V 1-2 (95% CI)</th>
<th>V 1-3 (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIQ score</td>
<td>54.3 ± 15.0</td>
<td>38.0 ± 17.3</td>
<td>47.7 ± 19.3</td>
<td>68.0 ± 8.9</td>
<td>59.1 ± 15.3</td>
<td>63.9 ± 20.7</td>
<td>−11.2 (−20.1, −2.3)</td>
<td>0.014</td>
</tr>
<tr>
<td>Pain score</td>
<td>58.2 ± 19.6</td>
<td>37.4 ± 19.9</td>
<td>48.8 ± 26.1</td>
<td>66.5 ± 19.5</td>
<td>58.3 ± 22.8</td>
<td>64.4 ± 25.7</td>
<td>−17.5 (−28.8, −6.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Quality of sleep</td>
<td>60.5 ± 26.7</td>
<td>43.6 ± 27.8</td>
<td>48.3 ± 26.4</td>
<td>68.3 ± 27.6</td>
<td>61.1 ± 29.0</td>
<td>67.4 ± 20.4</td>
<td>−15.5 (−30.6, −0.4)</td>
<td>0.044</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>10.4 ± 3.8</td>
<td>6.9 ± 3.2</td>
<td>8.9 ± 3.9</td>
<td>11.3 ± 5.1</td>
<td>10.3 ± 5.0</td>
<td>11.6 ± 4.2</td>
<td>−2.9 (−4.6, −1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>8.3 ± 4.8</td>
<td>6.1 ± 4.2</td>
<td>7.8 ± 4.1</td>
<td>11.1 ± 5.2</td>
<td>9.3 ± 5.1</td>
<td>11.6 ± 4.2</td>
<td>−1.5 (−3.3, 0.3)</td>
<td>0.097</td>
</tr>
<tr>
<td>SES Pain Perception</td>
<td>30.7 ± 9.1</td>
<td>22.1 ± 6.6</td>
<td>29.8 ± 10.2</td>
<td>36.4 ± 8.6</td>
<td>34.2 ± 9.1</td>
<td>37.0 ± 10.5</td>
<td>−10.1 (−14.7, −5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STAI State Score</td>
<td>50.4 ± 11.2</td>
<td>39.7 ± 10.2</td>
<td>48.2 ± 11.5</td>
<td>58.4 ± 13.0</td>
<td>51.4 ± 12.6</td>
<td>57.6 ± 11.5</td>
<td>−8.2 (−13.9, −2.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>STAI Trait Score</td>
<td>51.1 ± 11.2</td>
<td>43.9 ± 9.7</td>
<td>48.6 ± 9.3</td>
<td>54.3 ± 12.0</td>
<td>53.5 ± 10.0</td>
<td>55.5 ± 9.6</td>
<td>−8.3 (−12.3, −4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BfS Well-being</td>
<td>21.3 ± 11.6</td>
<td>17.5 ± 14.1</td>
<td>23.4 ± 11.8</td>
<td>27.2 ± 9.0</td>
<td>27.8 ± 8.2</td>
<td>26.0 ± 10.4</td>
<td>−6.8 (−12.5, −1.2)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Values are mean ± SD if not indicated otherwise. SBP: systolic blood pressure; DBP: diastolic blood pressure.
STAI: State and Trait Anxiety questionnaire; FIQ: Fibromyalgia impact questionnaire; HADS: Hospital Anxiety and Depression scale.
∇ 1-2 = difference between groups from baseline to visit 2 at 2 weeks, ∇ 1-3 = difference between groups from baseline to visit 3 at 12 weeks.
P values for between group difference of change, adjusted.
Only a few studies have investigated multimodal treatment programs for fibromyalgia that focus on Integrative and Complementary Medicine. A small uncontrolled study in 28 patients found an Ayurvedic program, also focusing on nutrition and mind-body techniques, to be effective with a lasting effect up to 24 months [36]. However, the treatment was not compared to another intervention, thus selection bias and unspecific effects were most likely contributing factors to the effect.

In view of our documented effects and safety of the Integrative Medicine approach further research on the effectiveness of complex multimodal Integrative treatments and comparisons with standard care in fibromyalgia is warranted. Such a study should have a larger sample size, allocate patients randomly, and include an attention control for the fasting intervention. Here the conventional group could be deprived of some specific food ingredient without inducing fasting metabolism. As it is difficult to randomize patients into complete treatment settings due to patient preferences and obligations of cost coverage, also outcome research might be useful in benchmarking the best strategy in intensified treatment strategies of fibromyalgia.

Some limitations relate to our study. First, we used a nonrandomized study design as it is currently not possible to randomize patients to hospital departments when costs are covered by health insurance companies under usual care. Nonrandomized studies may introduce a bias by patient selection and different prognostic and response factors between the groups. In fact, baseline values found patients of the Rheumatologic department to be more diseased and more distressed. However, most of the baseline differences were statistically nonsignificant and all our data analysis included baseline values as covariates. Of note, Physicians can refer patients to both hospital departments only if they are documented nonresponders to intensive outpatient outpatient treatment. The selection of the department (Rheumatology or Integrative Medicine) is mainly influenced by patients’ preference. Here a specific selection bias may be introduced as patients interested in integrative medicine are possibly more likely to search for comprehensive treatments in less severe disease states. Second, our study population was of limited size. Smaller study populations hold the risk of overestimation of effects on the one side and nondetection of moderate treatment effects on the other side. However, if significant effects are found the magnitude of effects and the related possible clinical relevance of the intervention is emphasized, which our results reflect. A third limitation is the short observation period of 3 months. Further studies should include observation periods of 12 months and longer to assess long-term symptom control.

A strength of our study relates to the fact, that both departments are situated in the same hospital and that, beside fasting and mind-body medicine, all other treatments were comparable and applied by the same personnel. Thus setting effects, attention effects and other nonspecific factors that may otherwise introduce bias in comparative studies were minimized.

In conclusion, our preliminary findings indicate that a multimodal Integrative Medicine treatment approach that included fasting therapy might be superior to the multimodal conventional Rheumatologic approach in the short-term in patients with severe fibromyalgia. At 12 weeks neither of the studied interventions was significantly superior or achieved clinically relevant improvement. Longer-term studies are warranted to assess the clinical impact and potential of multimodal Integrative Medicine in fibromyalgia.

Conflict of Interests

The authors do not have any conflict of interests with the content of the paper.

Acknowledgments

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References

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Review Article

Add-On Effect of Chinese Herbal Medicine on Mortality in Myocardial Infarction: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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In China, Chinese herbal medicine (CHM) is widely used as an adjunct to biomedicine (BM) in treating myocardial infarction (MI). This meta-analysis of RCTs evaluated the efficacy of combined CHM-BM in the treatment of MI, compared to BM alone. Sixty-five RCTs (12,022 patients) of moderate quality were identified. 6,036 patients were given CHM plus BM, and 5,986 patients used BM only. Combined results showed clear additional effect of CHM-BM treatment in reducing all-cause mortality (relative risk reduction (RRR) = 37%, 95% CI = 28%–45%, $I^2 = 0.0\%$) and mortality of cardiac origin (RRR = 39%, 95% CI = 22%–52%, $I^2 = 22.8\%$). Benefits remained after random-effect trim and fill adjustment for publication bias (adjusted RRR for all-cause mortality = 29%, 95% CI = 16%–40%; adjusted RRR for cardiac death = 32%, 95% CI = 15%–46%). CHM is also found to be efficacious in lowering the risk of fatal and nonfatal cardiogenic shock, cardiac arrhythmia, myocardial reinfarction, heart failure, angina, and occurrence of total heart events. In conclusion, addition of CHM is very likely to be able to improve survival of MI patients who are already receiving BM. Further confirmatory evaluation via large blinded randomized trials is warranted.

1. Background

1.1. Myocardial Infarction: Disease Burden and Therapeutic Options. Incorony artery disease, a critical reduction of the blood supply to the heart may result in myocardial infarction (MI), a phenomenon owing to the formation of an area of necrosis in heart muscles caused by inadequate supply of blood to the muscles, usually as a result of occlusion of a coronary artery. About a quarter of MI patients will die from it due to complications including cardiogenic shock, cardiac perforation, embolism, heart failure, papillary muscle rupture, rhythm disturbances, or autoimmune pericarditis. Current evidence on biomedicine (BM) treatment suggests that aspirin, thrombolitics with or without adding low-molecular-weight heparin, beta-blockers, ACE inhibitors, and nitrates are beneficial for improving outcomes in people with MI. Invasive procedures including coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA, balloon angioplasty) were also found to be useful. However, their efficacy in preventing death is not without limitations. For instance, beta-blockers have no short-term effect on mortality, and they may increase the risk of cardiogenic shock. Thrombolytics may cause stroke and major bleeding while reducing mortality, and those who are treated will receive no additional benefits from nitrates [1].

Despite these therapeutic advances, coronary artery disease remained to be the foremost leading cause of death in both low- and middle income countries as well as high-income countries, contributed 11.8% and 17.3% of total deaths, respectively [2]. Researchers are evaluating the potential benefits and harms of add-on treatments like
vasodilators and positive inotropes on mortality [3]. Chinese herbal medicine (CHM) is another novel candidate as an add-on treatment.

1.2. Chinese Herbal Medicine for Treating Myocardial Infarction. In China, CHM is widely prescribed in both outpatient and inpatient settings [4]. Amongst community health clinics, 75% provide both BM and traditional Chinese medicine (TCM) treatments. TCM hospitals comprised 13.8% of all hospitals, and 90% of the BM hospitals are annexed with TCM departments [5]. Given the omnipresence of TCM services within the Chinese healthcare system, it is not uncommon for clinicians to prescribe CHM as an adjunct to BM treatment in the management of potentially life-threatening conditions including MI [6]. One of the most researched single herbs is *Radix Astragali*, which exerts its therapeutic effectiveness by inhibiting cardiac fibrosis, reducing infarct size, and increasing capillary and arteriole densities [7]. Commonly used Chinese proprietary medicines include Shexiangbaoxin tablets and Tongxinluo capsules. Shexiangbaoxin tablets are found to slow MI pathogenesis by inhibiting hypertrophy related metabolites [8]. On the other hand, Tongxinluo capsules act by promoting local blood supply and thus limit infarct size [9]. CHM injections based on sheng mai san are also widely prescribed. It reduces infarct size via the activation of protein kinase C, opening of the mitochondrial KATP channels, and lowering the concentration of 5-hydroxytryptamine, norepinephrine, methionine-enkephalin, and leucine-enkephalin [10, 11].

1.3. Synthesizing Chinese Herbal Medicine Trials: Focusing on Objective Outcomes. The average effect of these CHM formulae as an adjunct to BM could be estimated using random effect meta-analyses of randomized controlled trials (RCTs) [12]. One of the major caveats in conducting systematic reviews on CHM is that existing RCTs are often prone to high risks of bias, thus limiting their usefulness in elucidating treatment effectiveness [13]. However, results from a recent metaepidemiological study have provided an alternative perspective on this issue. It is suggested that objective outcomes are less susceptible to bias associated with inadequate allocation concealment and blinding [14, 15]. Accordingly, by focusing on objective outcomes like mortality, we may partially overcome limitations imposed by the relatively high risk of bias amongst CHM trials.

1.4. Aim of This Paper. Taking into account the methodological considerations above, we performed a systematic review and meta-analysis of RCTs on the efficacy and safety of CHM for MI as an add-on to BM treatment, with a focus on objective critical outcomes including death, recurrent myocardial infarction, and other post-MI cardiac consequences.

2. Methods

2.1. Criteria for Considering Studies for This Paper. We included RCTs comparing the efficacy and safety of CHM plus BM versus BM alone. CHM is defined as any preparation containing at least one herb or its extraction referenced in the 2010 Chinese Pharmacopeia [16]. We included RCTs which enrolled adult MI patients regardless of gender, age, ethnicity, or comorbidities. We focused on the primary outcomes of (i) mortality of cardiac origin and (ii) all-cause mortality. We also consider the following as secondary outcomes: (i) recurrence of MI and (ii) other nonfatal, post-MI cardiac outcomes including cardiac arrhythmia, heart failure, cardiac rupture, cardiogenic shock, and angina. Adverse events reported by authors were also summarized. We imposed no restrictions on language and publication status.

2.2. Search Methods for Identification of Studies. We searched 8 electronic databases since their inception to July 2010, including CENTRAL, MEDLINE, EMBASE, CINAHL, AMED, Chinese Biomedical Database (CBM), Chinese Medical Current Contents (CMCC), and Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS) (Figure 1). Search strategies are shown in Appendix 1 in the Supplementary Materials available online at http://dx.doi.org/10.1155/2013/675906.

2.3. Data Collection and Analysis

2.3.1. Selection of Studies, Data Extraction, and Risk of Bias Assessment. Two reviewers (Y. Qin and C. Mao) independently screened the titles and abstracts to assess their eligibility. Full texts of potentially eligible citations were retrieved for detailed examination. Selection discrepancies were settled through discussions between these two authors. The remaining disagreements were resolved by consulting another author (J. L. Tang). For included RCTs, comprehensive information on patients, CHM interventions, and baseline and control treatments, as well as outcomes, was extracted. Risks of bias amongst included RCTs were evaluated by the Cochrane collaboration’s risk of bias assessment tool [17]. The assessment composed of a description and a judgement for each entry in a risk of bias table, including (i) sequence generation, (ii) allocation sequence concealment, (iii) incomplete outcome data, (iv) selective outcome reporting, and (v) other potential sources of bias. Blinding was assessed for the primary outcome of all-cause morality.

2.3.2. Data Analysis. Analyses were conducted using Stata 11 and R software. Dichotomous efficacy outcomes were expressed as relative risk reduction (RRR) and relative risk (RR), while RR was used for adverse events. 95% confidence intervals (CIs) were calculated for all estimates. We performed random-effect meta-analysis separately for each outcome. For primary outcomes of all-cause mortality and cardiac death, funnel plots were drawn for assessing publication bias. In case of asymmetry, random trim and fill analysis were performed as a sensitivity analysis [18]. Tests for heterogeneity were performed with chi-squared tests, at a significance level of $P = 0.1$. $I^2$ statistic was calculated to estimate variation across studies. We regarded $I^2 < 25\%$ as an indicator of low heterogeneity level, 25–50% as moderate level, and higher than 50% as high level [19]. Heterogeneity
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Citations identified through electronic database search (n = 15866)
- From Chinese databases (n = 10856)
- From international databases (n = 5010)

Duplicates excluded (n = 3200)

Titles and abstracts screened (n = 12666)
- Excluded after review of titles and abstracts (n = 10006)
  - Did not report specified outcomes (n = 3201)
  - Not RCTs (n = 6805)

Full-text articles assessed for eligibility (n = 2660)
- Excluded after examining the full text (n = 2597)
  - Did not report specified outcomes (n = 1039)
  - Not RCTs (n = 1502)
  - Studies on patients without the diagnosis of MI (n = 56)

Articles included in this systematic review (n = 63)

Figure 1: Flow chart of literature search and study selection.

was explored with random-effect metaregression using baseline risk, mean age, route of drug administration (oral versus intravenous), and treatment duration as covariates, taking into account the sample size requirement of including not more than 1 covariate for every 10 studies [20]. We expected that higher baseline risk and mean age could be associated with a smaller effect [1], while intravenous administration and longer treatment duration could be associated with a larger effect.

3. Results

3.1. Literature Search. As shown in Figure 1, our search in electronic bibliographical databases yielded 12,666 citations after removal of duplicates, of which 2,660 were classified as potentially relevant and were subjected to a full-text assessment. A total of 65 RCTs published in 63 articles met the inclusion criteria. Details of these studies are presented in Table 1.

3.2. Study Characteristics. A total of 6,036 patients were enrolled in the CHM plus BM group, and 5,986 patients were allocated to the BM only group. The average size of the trials was 185 participants (ranging from 28 to 2735 participants per trial). Fifty trials reported treatment duration and the average duration was 68.9 days, ranging from 3 to 1440 days. Forty-nine trials reported the length of followup. The average follow-up length was 7.1 months, ranging from 0.1 to 84 months.

For diagnostic criteria, 36 (55.4%) studies applied the 1979 World Health Organization criteria, which enrolled patients with at least two of the following three presentations: chest pain or discomfort, an elevation in CK-MB levels, or an ECG with significant ST-segment elevations [84]. Four adopted criteria from the Chinese Society of Cardiology [85] and one used criteria from the European Society of Cardiology [86]. Twelve applied author-defined diagnostic criteria, and the remaining 12 did not report criteria used.

Thirty-one standardized Chinese herbal formulae were examined in 63 (96.9%) of the 65 included studies, while the other two studies used an individualized approach. 32 (50.0%) preparations were administered orally, 30 (46.9%) were prescribed as herbal injections, and 2 (3.12%) trials used both intravenous and oral treatments. Eight formulae were evaluated by three or more trials. In total, these formulae were assessed in 38 studies, constituting 58.5% of all included trials.

(i) Nine (13.8%) trials studied Shenmai injection, which contains ginsenoside, ginseng polysaccharide, Ophiopogon polysaccharides, and Ophiopogon flavonoids extracted from Panax ginseng and Ophiopogon japonicas.

(ii) Five (7.7%) evaluated Huangqi injection manufactured by extracting astragalosides from Radix Astragali.

(iii) Another five (7.7%) assessed Shexiangbaoxin tablets, which consisted of Moschus, Radix Ginseng, Borneolum Syntheticum, Venenum Bufonis, Cortex Cinnamomi, Calculus Bovis, and Styrax.

(iv) Four (6.2%) tested Shengmai injection, which is a mixture of extracts from Panax ginseng, Radix Ophiopogonis, and Schisandra chinensis Baill.

(v) Another four (6.2%) evaluated Tongxinluo capsules, consisting of Radix Ginseng, Scorpio, Hirudo, Eupolyphaga seu Steleophaga, Scolopendra, Peristomum Cicadae, Radix Paoniae Rubra, and Borneolum Syntheticum.

(vi) Three trials (4.6%) assessed Shenfu injection, which contains Ginsenoside and Aconitine extracted from Panax ginseng and Aconitum carmichaelii.

(vii) Another three evaluated Suxiao jiuxin pill (4.6%), consisting of Ligusticum chuanxiong Hort. and Borneolum syntheticum.
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<td>Treatment based on TCM syndrome differentiation + BM</td>
<td>BM</td>
<td>28</td>
<td>1</td>
</tr>
</tbody>
</table>

BM: routine biomedical treatment as defined by the investigators; In: injection; N/A: not reported.
*Two RCTs reported in one publication.
occurrence of fatal cardiogenic shock also favored combined treatment (RRR = 39%–45%). Pooled results also favor combined treatment procedure, the RRR remained to be significant (RRR = 32%–45%). Funnel plot indicates the presence of publication bias. After applying trim and fill procedure, the RRR remained to be significant (RRR = 29%, 95% CI = 16%–40%, Table 2). Ten RCTs reported death of cardiac origin, and pooled findings also favor combined treatment (RRR = 39%, 95% CI = 22%–52%). Funnel plot indicates the presence of publication bias. After applying trim and fill procedure, the RRR remained to be significant (RRR = 32%, 95% CI = 15%–46%).

Pooled results from another four RCTs reporting the occurrence of fatal cardiogenic shock also favored combined treatment (RRR = 28%, 95% CI = 5%–45%). Respectively nine, six, five, and three RCTs reported outcomes on sudden cardiac death, fatal myocardial reinfarction, fatal heart failure, and fatal cardiac arrhythmia. In these four comparisons, all pooled findings favored combined treatment (sudden cardiac death: RRR = 24%, 95% CI = 6%–45%; fatal cardiac reinfarction: RRR = 54%, 95% CI = 12%–81%; fatal heart failure: RRR = 52%, 95% CI = 9%–79%; fatal cardiac arrhythmia: RRR = 29%, 95% CI = 84%–222%), but the estimates were statistically insignificant. Except for fatal myocardial reinfarction ($I^2 = 37.3\%$), no significant heterogeneity existed in the comparisons mentioned above. However, given the small number of RCTs reporting this outcome, we were unable to explore heterogeneity using metaregression.

### 3.3. Risk of Bias

Among these 65 RCTs, only 7 were at low risk for bias for allocation sequence generation. Twelve were at high risk and the remaining RCTs did not report their sequence generation procedure clearly. All but one had high risk of bias in terms of allocation concealment and none of the included studies report the use of blinding. However, we regarded the risks of bias associated with lack of blinding and allocation concealment to be minimal, as the primary outcomes were of objective nature. Two of the included studies had high risk of bias for incomplete data and one for selective outcome reporting. Six are at high risk of bias due to other reasons. In summary, we consider the overall risk of bias amongst our included studies to be moderate (Figure 2). The detailed risk of bias assessment results is presented in Appendix 2 in the supplementary materials.

### 3.4. Effects of Interventions

#### 3.4.1. Impact on Fatal Outcomes

In this comparison (Table 2), a total of 44 RCTs reported total all-cause mortality. Pooled results demonstrated superiority of combined treatment in preventing all-cause mortality (RRR = 37%, 95% CI = 28%–45%). Funnel plot indicates the presence of publication bias. After applying trim and fill procedure (Figure 3), the RRR remained to be significant (RRR = 29%, 95% CI = 16%–40%, Table 2). Ten RCTs reported death of cardiac origin, and pooled findings also favor combined treatment (RRR = 39%, 95% CI = 22%–52%). Funnel plot indicates the presence of publication bias. After applying trim and fill procedure, the RRR remained to be significant (RRR = 32%, 95% CI = 15%–46%).

Pooled results from another four RCTs reporting the occurrence of fatal cardiogenic shock also favored combined treatment (RRR = 28%, 95% CI = 5%–45%). Respectively nine, six, five, and three RCTs reported outcomes on sudden cardiac death, fatal myocardial reinfarction, fatal heart failure, and fatal cardiac arrhythmia. In these four comparisons, all pooled findings favored combined treatment (sudden cardiac death: RRR = 24%, 95% CI = 6%–45%; fatal cardiac reinfarction: RRR = 54%, 95% CI = 12%–81%; fatal heart failure: RRR = 52%, 95% CI = 9%–79%; fatal cardiac arrhythmia: RRR = 29%, 95% CI = 84%–222%), but the estimates were statistically insignificant. Except for fatal myocardial reinfarction ($I^2 = 37.3\%$), no significant heterogeneity existed in the comparisons mentioned above. However, given the small number of RCTs reporting this outcome, we were unable to explore heterogeneity using metaregression.

#### 3.4.2. Impact on Nonfatal Cardiovascular Events

In this comparison (Table 2), a total of 11 RCTs reported overall, undifferentiated nonfatal heart events. Pooled results demonstrated superiority of combined treatment in preventing this outcome (RRR = 48%, 95% CI = 40%–56%). Twenty-three RCTs evaluated myocardial reinfarction, and the pooled result favors combined treatment (RRR = 52%, 95% CI = 39%–61%). The pooled results from 14 and 24 RCTs have also favored combined treatment, respectively, in preventing cardiogenic shock (RRR = 37%, 95% CI = 15%–53%) and in alleviating angina symptoms (RRR = 53%, 95% CI = 46%–61%). Three RCTs investigated nonfatal cardiac rupture as an outcome. The pooled finding supports combined treatment but the estimate was statistically insignificant (RRR = 56%, 95% CI = 67%–89%). No significant heterogeneity existed in all meta-analyses mentioned above.

Respectively, thirty and twenty-eight RCTs reported outcomes of cardiac arrhythmia and heart failure. In these two groups of studies, pooled findings all favored combined treatment, but high level of heterogeneity existed in both estimates (cardiac arrhythmia: RRR = 41%, 95% CI = 27%–52%, $I^2 = 76.2\%$; heart failure: RRR = 48%, 95% CI = 36%–58%, $I^2 = 47.9\%$).

#### 3.4.3. Metaregression

We explored these heterogeneities by performing multivariate metaregression analyses using mean age, treatment duration, route of administration (oral versus intravenous), and baseline risk as covariates. None of the four covariates is significantly associated with cardiac arrhythmia (for baseline risk regression coefficient ($\beta$) = 0.46, $P = 0.41$; for mean age $\beta = 0.00$, $P = 0.96$; for duration of treatment $\beta = 0.00$, $P = 0.95$; for route of administration $\beta = 0.21$, $P = 0.63$), or heart failure (for baseline risk $\beta = 0.67$, $P = 0.39$;
<table>
<thead>
<tr>
<th>Events</th>
<th>No. of studies</th>
<th>No. of events/total no. CHM + BM group</th>
<th>BM group</th>
<th>Combined effect</th>
<th>Test for heterogeneity</th>
<th>Adjusted combined effect (trim and fill)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall (RR) (95% CI)</td>
<td></td>
<td>RRR (95% CI)</td>
<td>P value*</td>
<td>I² (P value)</td>
</tr>
<tr>
<td><strong>Fatal events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>44</td>
<td>308/5107/521/5112</td>
<td></td>
<td>0.63 (0.55–0.72)</td>
<td>&lt;0.001</td>
<td>37.47</td>
</tr>
<tr>
<td>Mortality of cardiac origin</td>
<td>10</td>
<td>142/2820/227/2796</td>
<td></td>
<td>0.61 (0.48–0.78)</td>
<td>&lt;0.001</td>
<td>11.66</td>
</tr>
<tr>
<td>Fatal myocardial reinfarction</td>
<td>6</td>
<td>20/2660/37/2687</td>
<td></td>
<td>0.46 (0.19–1.12)</td>
<td>0.086</td>
<td>7.98</td>
</tr>
<tr>
<td>Fatal cardiac arrhythmia</td>
<td>3</td>
<td>4/162/5/160</td>
<td></td>
<td>0.71 (0.16–3.22)</td>
<td>0.662</td>
<td>2.21</td>
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<tr>
<td>Fatal heart failure</td>
<td>5</td>
<td>8/410/18/444</td>
<td></td>
<td>0.48 (0.21–1.09)</td>
<td>0.078</td>
<td>0.06</td>
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<tr>
<td>Fatal cardiogenic shock</td>
<td>4</td>
<td>37/330/58/332</td>
<td></td>
<td>0.72 (0.55–0.95)</td>
<td>0.019</td>
<td>2.42</td>
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<tr>
<td>Sudden cardiac death</td>
<td>9</td>
<td>61/2775/81/2795</td>
<td></td>
<td>0.76 (0.55–1.06)</td>
<td>0.104</td>
<td>3.13</td>
</tr>
<tr>
<td><strong>Nonfatal events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated total heart events</td>
<td>11</td>
<td>209/2762/407/2761</td>
<td></td>
<td>0.52 (0.44–0.60)</td>
<td>&lt;0.001</td>
<td>8.99</td>
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<tr>
<td>Myocardial reinfarction</td>
<td>23</td>
<td>103/2377/215/2343</td>
<td></td>
<td>0.48 (0.39–0.61)</td>
<td>&lt;0.001</td>
<td>9.95</td>
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<tr>
<td>Cardiac arrhythmia</td>
<td>30</td>
<td>398/1730/640/1696</td>
<td></td>
<td>0.59 (0.48–0.73)</td>
<td>&lt;0.001</td>
<td>121.94</td>
</tr>
<tr>
<td>Heart failure</td>
<td>28</td>
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<td></td>
<td>0.52 (0.42–0.64)</td>
<td>&lt;0.001</td>
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<tr>
<td>Cardiac rupture</td>
<td>3</td>
<td>2/122/7/134</td>
<td></td>
<td>0.44 (0.11–1.67)</td>
<td>0.224</td>
<td>0.60</td>
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<tr>
<td>Cardiogenic shock</td>
<td>14</td>
<td>63/1015/110/1030</td>
<td></td>
<td>0.63 (0.47–0.85)</td>
<td>0.002</td>
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<tr>
<td>Angina</td>
<td>24</td>
<td>177/1047/297/1001</td>
<td></td>
<td>0.47 (0.39–0.56)</td>
<td>&lt;0.001</td>
<td>22.20</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated total events</td>
<td>2</td>
<td>43/2434/39/2436</td>
<td></td>
<td>1.16 (0.59–2.27)</td>
<td>0.664</td>
<td>2.19</td>
</tr>
<tr>
<td>Bleeding</td>
<td>9</td>
<td>81/706/81/745</td>
<td></td>
<td>0.97 (0.73–1.28)</td>
<td>0.816</td>
<td>4.89</td>
</tr>
</tbody>
</table>

*Test for overall effect; *chi-square test for heterogeneity.
BM: biomedical treatment; CHM: Chinese herbal medicine treatment; RR: relative risk; RRR: relative risk reduction; 95% CI: 95% confidence interval.
events. Beneﬁts in preventing heart failure and angina were
myocardial reinfarction, and the occurrence of total heart
lowering the risk of cardiogenic shock, cardiac arrhythmia,
analyses demonstrated that CHM is an effective add-on for
failure, and sudden cardiac death. For nonfatal outcomes, our
including myocardial reinfarction, cardiac arrhythmia, heart
of combined treatment on other reviewed fatal outcomes
than BM alone in lowering the risk of fatal cardiogenic
mortality.

for mean age $\beta = 0.02, P = 0.57$; for duration of treatment
$\beta = 0.00, P = 0.87$; for route of administration $\beta = 0.12, 
P = 0.77$).

3.4.4. CHM and BM versus BM Alone for MI: Adverse Events.
In this comparison (Table 2), nine RCTs reported bleeding as adverse events, but the pooled estimate was statistically insigniﬁcant (RR = 0.97, 95% CI = 0.73, 1.28). Two RCTs reported general, undifferentiated adverse events, pooled estimate is heterogeneous and statistically insigniﬁcant (RR = 1.16, 95% CI = 0.59, 2.27, $I^2 = 54.4\%$).

4. Discussion
This systematic review on the add-on effect of CHM on BM in
the treatment of MI summarized ﬁndings from 12,022
patients reported in 65 RCTs. The overall risk of bias amongst
included studies was moderate. Despite the lack of allocation
concealment and blinding in the majority of included trials, its
impact on risk of bias was less critical as we focused on
objective outcomes. Random-effect meta-analyses demonstrated that combined treatment is superior to BM alone in reducing the risk of all-cause mortality and death of cardiac origin. Funnel plots indicated the presence of publication bias for both outcomes, and trim and ﬁll procedures were conducted as sensitivity analyses. The directions of effect did not change after the adjustment, and the 95% CI of the estimates overlapped with the unadjusted values. The lower 95% CI boundary of the trim- and ﬁll-adjusted RRR for all-cause and cardiac mortality was 16% and 15%, respectively. Conservatively speaking, CHM appeared to offer a protective add-on effect against mortality after adjusting for the publication bias, a common problem amongst the clinical research literature on CHM [87].

Combined treatment is also found to be more effective than BM alone in lowering the risk of fatal cardiogenic shock. Our analyses did not demonstrate therapeutic beneﬁts of combined treatment on other reviewed fatal outcomes including myocardial reinfarction, cardiac arrhythmia, heart failure, and sudden cardiac death. For nonfatal outcomes, our analyses demonstrated that CHM is an effective add-on for lowering the risk of cardiogenic shock, cardiac arrhythmia, myocardial reinfarction, and the occurrence of total heart events. Beneﬁts in preventing heart failure and angina were
also observed but these ﬁndings are less robust given the
subjective nature of the outcome, and metaregression did not
shed light on potential sources of heterogeneity. We have
considered including allocation concealment and blinding as covariates in our metaregressions but numbers of trials with low risk in these domains are too small for conducting such analysis. The effect of combined treatment on these two outcomes would need to be further evaluated with methodologically stronger trials. In addition, more comprehensive reporting on BM treatment details and adverse events is expected in future studies, preferably with reference to the CONSORT statement.

Comprehensiveness of search is the major strength of this systematic review. The use of both international and Chinese databases allowed us to locate a much higher number studies compared to seven existing reviews on the topic [88]. We also attempted to synthesize results from trials evaluating heterogeneous CHM using random-effect model. This allowed us to estimate the average effect of adding CHM on top of conventional therapies [12]. The use of the trim and ﬁll method has also partly circumvented the problem of publication bias. Nevertheless, the robustness of our conclusion depends on the assumption that the objective nature of outcomes was less affected by two major sources of bias: allocation concealment and blinding. While this assumption is tested in metaepidemiological studies [89, 90], the generalizability of these ﬁndings warrants further investigations.

5. Conclusion
Based on RCTs of moderate quality, this systematic review demonstrated consistent, add-on beneﬁts of using CHM on top in BM treatment for preventing all-cause and cardiac mortality amongst MI patients. These ﬁndings are in line with the results from seven existing systematic reviews of smaller scope and lower methodological quality. This tentative conclusion warrants further scrutiny using rigorously designed RCT, and a more comprehensive approach in reporting BM treatment details and adverse events is warranted.

Authors’ Contribution
V. C. H. Chung and M. Chen are the co-ﬁrst authors of this paper.

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References


Review Article

Tuina-Focused Integrative Chinese Medical Therapies for Inpatients with Low Back Pain: A Systematic Review and Meta-Analysis

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Objective. To evaluate the effectiveness of Tuina-focused integrative Chinese medical therapies (TICMT) on inpatients with low back pain (LBP).

Methods. 6 English and Chinese databases were searched for randomized controlled trials (RCTs) of TICMT for in-patients with LBP. The methodological quality of the included RCTs was assessed based on PEDro scale. And the meta-analyses of TICMT for LBP on pain and functional status were conducted. Results. 20 RCTs were included. The methodological quality of the included RCTs was poor. The meta-analyses’ results showed that TICMT had statistically significant effects on pain and functional status, especially Tuina plus Chinese herbal medicine (standardised mean difference, SMD: 1.17; 95% CI 0.75 to 1.60 on pain; SMD: 1.31; 95% CI 0.49 to 2.14 on functional status) and Tuina plus acupuncture (SMD: 0.94; 95% CI 0.38 to 1.50 on pain; SMD: 0.53; 95% CI 0.21 to 0.85 on functional status). But Tuina plus moxibustion or hot pack did not show significant improvements on pain. And the long-term evidence of TICMT was far from sufficient.

Conclusions. The preliminary evidence from current studies suggests that TICMT might be effective complementary and alternative treatments for in-patients with LBP. However, the poor methodological quality of the included RCTs means that high-quality RCTs with long follow-up are warranted.

1. Introduction

Low back pain (LBP) and related disability are one of the major public health problems worldwide, which represent a great financial burden in the form of direct costs resulting from the loss of work and medical expenses, as well as indirect costs [1]. And the prevalence of LBP is quite high and increases according to the time span considered. The point prevalence of bothersome LBP has been estimated at 25%, whereas the 1-year prevalence has been estimated at 50% and the lifetime prevalence has been estimated at 85% [2–4]. Therefore, the adequate treatment of LBP is an important issue for patients, treating clinicians, and healthcare policy makers.

Tuina, a manual therapy in traditional Chinese medicine, emphasizes anatomy and physiology when used for neuromusculoskeletal disorders. Currently it is widely used for the treatment of LBP. Tuina procedures for LBP are combined soft-tissue manipulation with spinal manipulation. Soft-tissue manipulation is similar to massage, including stroking, kneading, and percussion. Spinal manipulation, on the other hand, is quite similar to mobilization and other adjustment techniques. These techniques can involve a manual procedure without thrust, during which a joint normally remains within its physiological range of motion. Alternatively, they can involve a manual procedure directed thrust to move a joint past the physiological range of motion, without exceeding the anatomical limit [5]. The clinical
practice guidelines have formed moderate recommendations of massage, mobilization, and manipulation for LBP [6, 7]. Some systemic reviews also concluded that these manual therapies might be beneficial for LBP [8–11]. But the evidence is only for single application of these manual therapies.

In the last decade, a mass of hospitals have adopted Tuina-focused integrative Chinese medical therapies (TICMT) in the management of LBP for better effectiveness in China, which consist of Tuina combined with other traditional Chinese medical therapies including Chinese herbal medicine, acupuncture, moxibustion, and hot pack. In addition, a number of clinical studies on TICMT have been rolled out and published [12]. However, the evidence from systematic reviews on TICMT for LBP is marginal. Therefore, we performed a systematic review of all currently available data and conducted quantitative meta-analyses of TICMT for in-patients with LBP to determine whether TICMT are effective complementary and alternative treatments for in-patients with LBP.

2. Methods

2.1. Search. The following electronic databases were searched from January 2001 to June 2012: PubMed, EMBASE, Cochrane Library, China Knowledge Resource Integrated Database (CNKI), Weipu Database for Chinese Technical Periodicals (VIP), and Wanfang Data. The first search terms were low back pain, lumbago, lumbar disc herniation, lumbar strain, backache, back pain, or dorsalgia. The second terms were Tuina, massage, mobilization, or spinal manipulation. The third search terms were acupunc-ture, electroacupuncture, herbal medicine, moxibustion, or hot pack, and the last search term was random. We combined these four terms for text word searches of titles and abstracts. No restrictions on publication status were imposed. The complete search strategies for each database were shown in Appendix A.

2.2. Study Selection. Randomized controlled trials (RCTs) of TICMT for in-patients with LBP were included. There were no limitations on the participant’s age, gender, or nationality. The included integrative therapies were Tuina combined with other traditional Chinese medical therapies including Chinese herbal medicine (herbal decoctions and herbal injections), acupuncture (manual acupuncture and electroacupuncture), moxibustion, and hot pack. Control treatments included any independent traditional Chinese medical therapy, placebo, waiting list controls, and integrative treatments without any manual therapy. The main outcomes of interest were pain and functional status.

Trials were excluded if any of the following were identified: (1) if the participants were outpatients; (2) if controlled treatment was an integrative therapy including any manual therapy. In this case, it would be impossible to evaluate the specific effect of Tuina combined with other traditional Chinese medical therapies; and (3) if the information about the outcome measures was not clearly reported.

2.3. Data Abstraction. Two authors extracted data independently according to predefined criteria including the first author, year of the study, the mean duration of LBP, sample size, the mean age of participants, the duration of treatments, the follow-up time, main outcome assessments, interventions of TICMT and control group, and the main conclusion (mean improvements). Any discrepancies were discussed until the authors reached consensus.

2.4. Methodological Quality Assessment. The methodological quality of RCTs was assessed independently by two authors by PEDro scale, which is based on the Delphi list and has been reported to have a fair to good reliability for RCTs of the physiotherapy in systematic reviews. This scale consists of 11 criteria being (1) study eligibility criteria specified, (2) random allocation of subjects, (3) concealed allocation, (4) measure of similarity between groups at baseline, (5) subject blinding, (6) therapist blinding, (7) assessor blinding, (8) less than 15% dropouts, (9) intention-to-treat analysis, (10) between-group statistical comparisons, and (11) point measures and variability data. Criteria (2)–(11) were used to calculate the PEDro score. Each criterion was scored as either 1 or 0 according to whether the criteria was met or not, respectively. The scores are summed and a higher score represents a better method-ological quality. A cut point of 6 on the PEDro scale was used to indicate high quality studies as this has been reported to be sufficient to determine high quality versus low quality in previous studies [33]. If additional data or clarification was necessary, we contacted the study authors. And disagreements were resolved by discussions among the authors.

2.5. Data Synthesis and Analysis. The mean change in outcome measures between the end of the final intervention and the baseline was used to assess the difference between TICMT group and control group in the meta-analyses. Standardised mean differences (SMDs) were used because the studies measured the outcomes based on different scales (e.g., VAS 0–10 and VAS 0–100). And SMDs and 95% confidence intervals (CIs) were calculated in the meta-analysis. In studies that involved more than one control group, the authors restricted our analyses to TICMT and each control group. Summary estimates of the treatment effect were calculated using the random effects model to account for the expected heterogeneity. Cochrane’s Q test and I² were used to assess statistical heterogeneity. The authors determined that there was considerable heterogeneity when Cochrane’s Q test result was determined with \( P < 0.10 \), and \( I^2 \) was above 75%. The Cochrane Collaboration software (Review Manager Version 5.0 for Windows; Copenhagen: The Nordic Cochrane Centre) was used for the meta-analyses. And the results of study characteristics are presented as mean ± standard deviation (SD) or the range of variation.
Figure 1: Study selection process. RCTs: randomized controlled trials and TICMT: Tuina-focused integrative Chinese medical therapies.

3. Results

3.1. Study Selection. We identified 953 records from English and Chinese databases. After the initial titles and abstracts screening, we excluded 904 because of a large number of duplicate records from three Chinese databases (CNKI, VIP, and Wanfang) and some reports did not met the inclusion criteria. We retrieved and reviewed 49 full articles. 20 RCTs were eligible [13–32]. In excluded studies, the trials were excluded due to outpatients (n = 13), duplicate publications (n = 2), unsuitable control intervention (n = 1), and unsuitable reports of the outcome (n = 13). And all RCTs were included in meta-analyses. The study selection process was summarized in Figure 1.

3.2. Study Characteristics. Twenty eligible studies included 2147 subjects with the mean age of 43. And all studies were conducted in China between 2005 and 2012. The disease duration ranged from 1 day to 10 years, and the study duration ranged from 3 days to 8 weeks. The time and session of Tuina treatment were 26.3 ± 4.4 minutes (ranging from 20 to 30 minutes) and 17.5 ± 10.5 (ranging from 3 to 42), respectively. In combined traditional Chinese therapies, the number of Chinese herbal medicine every day ranged from 1 to 3, and acupuncture points were 6.2 ± 3.1 (ranging from 1 to 10). The hot pack time ranged from 30 to 360 minutes. The follow-up time ranged from 4 to 24 weeks.

Of twenty RCTs, 7 RCTs assessed the effectiveness of Tuina plus Chinese herbal medicine for in-patients with LBP [13–19], 7 RCTs assessed the effect of Tuina plus acupuncture [20–26], 2 RCTs assessed the effect of Tuina plus hot pack [27, 28], and one assessed the efficacy of Tuina plus moxibustion [29]. The others assessed the effectiveness of
Tuina plus more than one Chinese medical therapy [30–32]. The control therapies contained Tuina, Chinese herbal medicine, acupuncture, moxibustion, traction, electromagnetic therapy, or integrated treatments (including Chinese herbal medicine plus traction, Chinese herbal hot pack plus traction, Chinese herbal hot pack plus electromagnetotherapy, and traction plus infrared radiation). In outcome assessments, visual analog scale (VAS) was used for pain, and the Oswestry disability index (ODI) or Japanese orthopaedic association score for low back pain (JOA) was used for functional status. The characteristics of all studies were summarized in Table 1.

3.3. Methodological Quality. The quality scores were presented in Table 2. The quality scores ranged from 5 to 8 points out of a theoretical maximum of 10 points. Although the predetermined cutoff 6 was exceeded by most studies included, it did not indicate that they were considered to be of high quality, because most of them (80% of studies) were at the limit of the cutoff with scores of 6. And there were serious flaws in concealed allocation (90% of studies), subjects blinded (100% of studies), therapists blinded (100% of studies), and assessors blinded (95% of studies). In addition, two studies were failed in random allocation, because the patients were randomly allocated by hospital record number. In other items on PEDro scale, the studies showed higher methodological quality involving measure of similarity between groups at baseline, less than 15% dropouts, intention-to-treat analysis, between-group statistical comparisons, and point measures and variability data.

3.4. Quantitative Data Synthesis

3.4.1. Effects of TICMT on Pain. Six RCTs tested the effectiveness of Tuina plus Chinese herbal medicine on pain for LBP compared with Tuina [13–15, 19], Tuina (or Chinese herbal medicine) [17], and Chinese herbal medicine plus traction [16]. And the meta-analysis showed favorable effects of Tuina plus Chinese herbal medicine on pain (n = 765; SMD: 1.17; 95% CI 0.75 to 1.60; P < 0.00001; heterogeneity: χ² = 42.05, I² = 86%; Table 3).

Five trials assessed the effect of Tuina plus acupuncture on pain for LBP versus Tuina [20], Tuina (or acupuncture) [22], electroacupuncture [23], traction [24], and electromagnetotherapy plus Chinese herb hot pack [25]. The meta-analysis showed superior effects of Tuina plus acupuncture on pain relief (n = 640; SMD: 0.94; 95% CI 0.38 to 1.50; P = 0.001; heterogeneity: χ² = 55.70, P < 0.00001, I² = 91%; Table 3). And one study tested the effectiveness of Tuina plus acupuncture and Chinese herbal medicine on pain for LBP compared with Tuina [31]. The meta-analysis also showed significant effects (n = 60; SMD: 1.61; 95% CI 1.03 to 2.20; P < 0.00001; Table 3).

One RCT tested the effectiveness of Tuina plus moxibustion on pain for LBP versus Tuina or moxibustion [29]. The meta-analysis did not shown favorable effects of Tuina plus moxibustion on pain reduction (n = 120; SMD: 0.42; 95% CI −0.17 to 1.02; P = 0.16; heterogeneity: χ² = 2.67, P = 0.10, I² = 63%; Table 3). In addition, Tuina plus hot pack did not show better effects on pain than Tuina (n = 120; SMD: −0.77; 95% CI −1.14 to −0.39; P < 0.0001; Table 3) [28].

3.4.2. Effects of TICMT on Functional Status. Two RCTs tested the effect of Tuina plus Chinese herbal medicine on functional status for LBP compared with Tuina [13, 18]. And the meta-analysis showed favorable effects of Tuina plus Chinese herbal medicine on functional status (n = 223; SMD: 1.31; 95% CI 0.49 to 2.14; P = 0.002; heterogeneity: χ² = 5.89, P = 0.02, I² = 83%; Table 4).

Two trials assessed the effect of Tuina plus acupuncture on functional status versus traction plus infrared radiation [21] or acupuncture [26]. Two studies maintained that in-patients in Tuina plus acupuncture group experienced more obvious improvements on functional status. And the meta-analysis also showed superior effects of Tuina plus acupuncture on functional status (n = 160; SMD: 0.53; 95% CI 0.21 to 0.85; P = 0.001; heterogeneity: χ² = 0.65, P = 0.42, I² = 0%; Table 4). In addition, Tuina plus Chinese herbal hot pack showed better effects on functional status than Tuina (n = 40; SMD, 2.82; 95% CI 1.92 to 3.72; P < 0.00001; Table 4) [27].

Two trials assessed the effect of Tuina plus more than one Chinese medical therapy on functional status for LBP versus traction plus Chinese herbal hot pack [30] and Tuina [32]. Tuina coupled with traction and Chinese herbal hot pack and Tuina coupled with acupuncture and moxibustion were, respectively, employed in two trials. And the meta-analysis showed favorable effects of Tuina plus more than one Chinese medical therapy on functional status (n = 203; SMD, 2.58; 95% CI 1.48 to 3.69; P < 0.00001; heterogeneity: χ² = 8.42, P = 0.004, I² = 88%; Table 4).

3.5. Long-Term Effects of TICMT. Three studies observed the long-term effect of TICMT for in-patients with LBP. But only one trial reported that TICMT group (Tuina plus acupuncture) experienced better improvements on functional status compared with acupuncture (recurrence rate, 6.2% versus 25.9%) [26]. The other two did not show detailed results [13, 22].

4. Discussion

In summary, there are encouraging results suggesting that TICMT has short-term effects on improving pain and functional status of in-patients with LBP, especially Tuina plus Chinese herbal medicine or acupuncture. But the quality of the included studies was generally poor. And Tuina plus hot pack or moxibustion did not show better effects on pain relief, which might be explained by the fact that there are relatively fewer eligible studies. In addition, the studies of long-term effects of TICMT were extremely insufficient. Consequently, interpretation of these positive findings should be caution.
## Table 1: Randomized controlled trials evaluating the effect of Tuina-focused integrative Chinese medical therapies (TICMT) for low back pain (LBP).

<table>
<thead>
<tr>
<th>First authors, yr</th>
<th>Mean duration of LBP</th>
<th>Sample size, mean age (yr)</th>
<th>Duration weeks</th>
<th>Follow-up weeks</th>
<th>Main outcome assessments</th>
<th>TICMT group (EG) intervention*</th>
<th>Control group (CG) intervention*</th>
<th>Main conclusion (mean improvements)</th>
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<tbody>
<tr>
<td>Huang (2008) [14]</td>
<td>1–13 days</td>
<td>100 42</td>
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<td>—</td>
<td>Pain VAS (0–10)</td>
<td>Tuina (25 min/21 sessions) plus CHM (1/21 sessions)</td>
<td>Tuina (25 min/21 sessions)</td>
<td>EG (5.78) &gt; CG (4.79)</td>
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<tr>
<td>Su (2008) [15]</td>
<td>NR</td>
<td>120 40</td>
<td>3 days</td>
<td>—</td>
<td>Pain VAS (0–10)</td>
<td>Tuina (30 min/3 sessions) plus CHM (1/3 sessions)</td>
<td>Tuina (30 min/3 sessions)</td>
<td>EG (4.90) &gt; CG (0.55)</td>
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<td>NR</td>
<td>96 &gt;16</td>
<td>4</td>
<td>—</td>
<td>Pain VAS (0–10)</td>
<td>Tuina (30 min/24 sessions) plus CHM (2/24 sessions)</td>
<td>CHM (2/24 sessions)</td>
<td>EG (8.15) &gt; CG (5.99)</td>
</tr>
<tr>
<td>Wen (2010) [17]</td>
<td>4–20 days</td>
<td>120 NR</td>
<td>3</td>
<td>—</td>
<td>Pain VAS (0–100)</td>
<td>Tuina plus CHM (NR) plus Traction plus infrared radiation (15 min/24 sessions)</td>
<td>EG (21.40) &gt; CG1 (12.20) EG (21.40) &gt; CG2 (11.10)</td>
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<td>36 mo</td>
<td>184 58</td>
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<td>ODI</td>
<td>Tuina (28 sessions) plus injection CHM (1/28 sessions)</td>
<td>Tuina (28 sessions)</td>
<td>EG (51.20) &gt; CG (28.20)</td>
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<td>Tuina (7 sessions) plus CHM (1/7 sessions)</td>
<td>Tuina (7 sessions)</td>
<td>EG (7.86) &gt; CG (6.32)</td>
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<td>Pain VAS (0–10)</td>
<td>Tuina (20 min/14 sessions) plus electroacupuncture (4 AP/14 sessions)</td>
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<td>EG (5.51) &gt; CG (4.45)</td>
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<td>Chen (2007) [21]</td>
<td>15.9 mo</td>
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<td>JOA (0–29)</td>
<td>Tuina (25 min/7 sessions) plus acupuncture (3–8 AP/8 sessions)</td>
<td>Traction plus infrared radiation (30 min/14 sessions)</td>
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<td>105 41</td>
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<td>(1) Tuina (7 sessions) plus acupuncture (1 AP/7 sessions)</td>
<td>(2) Acupuncture (1 AP/7 sessions)</td>
<td>EG (4.84) &gt; CG1 (4.32) EG (8.74) &gt; CG2 (4.11)</td>
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**Table 1**: Continued.

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<tr>
<th>First authors, yr</th>
<th>Mean duration of LBP</th>
<th>Sample size, mean age (yr)</th>
<th>Duration weeks</th>
<th>Follow-up weeks</th>
<th>Main outcome assessments</th>
<th>TICMT group (EG) intervention*</th>
<th>Control group (CG) intervention*</th>
<th>Main conclusion (mean improvements)</th>
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</thead>
<tbody>
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<td>He (2010) [23]</td>
<td>1 day–10 yr</td>
<td>180 38</td>
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<td>Tuina (6 sessions) plus electroacupuncture (10 AP/10 sessions)</td>
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<td>EG (3.65) &gt; CG (3.17)</td>
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<td>Ke (2011) [24]</td>
<td>&gt;7 days</td>
<td>60 20–65</td>
<td>7</td>
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<td>Pain VAS (0–10)</td>
<td>Tuina (7 sessions) plus electroacupuncture (4–6 AP/7 sessions)</td>
<td>Traction (7 sessions)</td>
<td>EG (4.53) &gt; CG (3.14)</td>
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<td>15</td>
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<td>Pain VAS (0–10)</td>
<td>Tuina (30 min/15 sessions) plus acupuncture (3–5 AP/7 sessions)</td>
<td>Electromagnetic therapy (20 min/1 sessions) plus Chinese herbal hot pack (25 min/15 sessions)</td>
<td>EG (4.70) &gt; CG (1.70)</td>
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<td>2-3</td>
<td>12</td>
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<td>Tuina (20 min/14–21 sessions) plus acupuncture (8–9 AP/14–21 sessions)</td>
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<td>EG (12.70) &gt; CG (10.60)</td>
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<td>Tuina (20 sessions) plus Chinese herbal hot pack (30 min/40 sessions)</td>
<td>Tuina (20 sessions)</td>
<td>EG (11.32) &gt; CG (5.23)</td>
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<td>20</td>
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<td>Tuina (20 sessions) plus hot pack (360 min/20 sessions)</td>
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<td>90 31</td>
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<td>—</td>
<td>Pain VAS (0–10)</td>
<td>Tuina (30 sessions) plus moxibustion (3 AP/30 sessions)</td>
<td>Tuina (30 sessions) (1) Tuina (30 sessions) (2) Moxibustion (3 AP/30 sessions)</td>
<td>EG (3.51) &gt; CG1 (3.21) EG (3.51) &gt; CG2 (1.79)</td>
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<td>100 44</td>
<td>10</td>
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<td>EG (11.1) &gt; CG2 (4)</td>
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</table>

VAS: Visual analog scale; ODI: the Oswestry disability index; CHM: Chinese herbal medicine; NR: no reported; JOA: Japanese orthopaedic association score for low back pain; yr: year; mo: month; h: hour; AP: acupuncture point.

*Intervention dose: number of intervention time/number of sessions, number of acupuncture points/number of sessions, or number of Chinese herbal medicine every day/number of sessions.
<table>
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<tr>
<th>Study</th>
<th>Eligibility criteria</th>
<th>Random allocation</th>
<th>Concealed allocation</th>
<th>Similar at baseline</th>
<th>Subjects blinded</th>
<th>Therapists blinded</th>
<th>Assessors blinded</th>
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0: does not meet the criteria; 1: meets the criteria.
Table 3: Forest plots of the effect of Tuina-focused integrative Chinese medical therapies (TICMT) on pain of in-patients with low back pain. Box in the line for each study: the mid-point of the box represents the mean effect estimate, which area shows the weight given to the study, and the line represents the confidence intervals of the mean effect estimate. The diamond below these studies represents the overall effect. The vertical line, which corresponds to the value 0 in the plot, is the line of no effect. Note that it says favours TICMT to the right of the vertical line and favours control therapy to the right of the vertical line.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>TICMT Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control therapy Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. mean difference IV, random, 95% CI</th>
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<td>5.8%</td>
<td>1.81 (1.34, 2.29)</td>
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<td>50</td>
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<td>50</td>
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<td>2.12</td>
<td>24</td>
<td>5.6%</td>
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<td>5.9%</td>
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<td>21.4</td>
<td>7.95</td>
<td>40</td>
<td>12.2</td>
<td>8.89</td>
<td>40</td>
<td>5.8%</td>
<td>1.34 (0.85, 1.83)</td>
</tr>
<tr>
<td>You and Zhou 2012 [19]</td>
<td>7.86</td>
<td>1.22</td>
<td>120</td>
<td>6.32</td>
<td>1.23</td>
<td>120</td>
<td>6.2%</td>
<td>1.25 (0.98, 1.53)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>383</td>
<td>382</td>
<td>41.3%</td>
<td>1.17 (0.75, 1.60)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.28; Chi² = 42.05, df = 6 (P &lt; 0.00001); I² = 86% Test for overall effect: Z = 5.38 (P &lt; 0.00001)</td>
<td></td>
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<tr>
<td>1.1.2 Tuina plus acupuncture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>He et al. 2010 [23]</td>
<td>3.65</td>
<td>1.62</td>
<td>81</td>
<td>3.17</td>
<td>1.64</td>
<td>79</td>
<td>6.2%</td>
<td>0.29 (−0.02, 0.60)</td>
</tr>
<tr>
<td>Ke and Li 2011 [24]</td>
<td>4.53</td>
<td>1.02</td>
<td>60</td>
<td>3.14</td>
<td>1.09</td>
<td>60</td>
<td>6.0%</td>
<td>1.31 (0.91, 1.70)</td>
</tr>
<tr>
<td>Liu et al. 2008 [22]</td>
<td>4.84</td>
<td>1.19</td>
<td>35</td>
<td>4.32</td>
<td>1.05</td>
<td>35</td>
<td>5.8%</td>
<td>0.46 (−0.02, 0.93)</td>
</tr>
<tr>
<td>Liu et al. 2008 [22]</td>
<td>4.84</td>
<td>1.19</td>
<td>35</td>
<td>4.11</td>
<td>1.27</td>
<td>35</td>
<td>5.8%</td>
<td>0.59 (−0.02, 1.07)</td>
</tr>
<tr>
<td>Pang et al. 2006 [20]</td>
<td>5.51</td>
<td>1.58</td>
<td>60</td>
<td>4.45</td>
<td>1.55</td>
<td>60</td>
<td>6.1%</td>
<td>0.67 (0.30, 1.04)</td>
</tr>
<tr>
<td>Yang et al. 2011 [25]</td>
<td>4.7</td>
<td>0.95</td>
<td>50</td>
<td>1.7</td>
<td>1.49</td>
<td>50</td>
<td>5.7%</td>
<td>2.38 (1.87, 2.90)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>321</td>
<td>319</td>
<td>35.7%</td>
<td>0.94 (0.38, 1.50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.44; Chi² = 55.70, df = 5 (P &lt; 0.00001); I² = 91% Test for overall effect: Z = 3.27 (P = 0.001)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1.1.3 Tuina plus hot pack</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuan et al. 2010 [28]</td>
<td>3.65</td>
<td>1.78</td>
<td>60</td>
<td>4.85</td>
<td>1.3</td>
<td>60</td>
<td>6.1%</td>
<td>−0.77 (−1.14, −0.39)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>60</td>
<td>60</td>
<td>6.1%</td>
<td>−0.77 (−1.14, −0.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable Test for overall effect: Z = 4.04 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1.1.4 Tuina plus moxibustion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu 2010 [29]</td>
<td>3.51</td>
<td>2.33</td>
<td>30</td>
<td>1.79</td>
<td>2.31</td>
<td>30</td>
<td>5.7%</td>
<td>0.73 (0.21, 1.26)</td>
</tr>
<tr>
<td>Liu 2010 [29]</td>
<td>3.51</td>
<td>2.33</td>
<td>30</td>
<td>3.21</td>
<td>2.44</td>
<td>30</td>
<td>5.8%</td>
<td>0.12 (−0.38, 0.63)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>60</td>
<td>60</td>
<td>11.5%</td>
<td>0.42 (−0.17, 1.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.12; Chi² = 2.67, df = 1 (P &lt; 0.10); I² = 63% Test for overall effect: Z = 1.40 (P = 0.16)</td>
<td></td>
<td></td>
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<tr>
<td>1.1.5 Tuina plus more than one Chinese medical therapy</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2011 [31]</td>
<td>5.98</td>
<td>1.42</td>
<td>30</td>
<td>3.4</td>
<td>1.72</td>
<td>30</td>
<td>5.6%</td>
<td>1.61 (1.03, 2.20)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>30</td>
<td>30</td>
<td>5.6%</td>
<td>1.61 (1.03, 2.20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable Test for overall effect: Z = 5.38 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>854</td>
<td>851</td>
<td>100.0%</td>
<td>0.91 (0.54, 1.28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.55; Chi² = 202.56, df = 16 (P &lt; 0.00001); I² = 92% Test for overall effect: Z = 4.83 (P = 0.00001)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Our positive results concur with some relevant clinical guidelines and systematic reviews. The clinical guideline from the United States in 2007 found the moderate-quality evidence to support the efficacy of massage and spinal manipulation for the management of LBP [6]. The clinical guidelines from Belgium in 2006 [4] and United Kingdom in 2009 [7] also found the moderate-quality evidence for spinal manipulation and recommended offering a maximum of 9 sessions of spinal manipulation over a period of up to 12 weeks. And the systematic review including 13 RCTs
concluded that massage might be beneficial for subacute and chronic nonspecific LBP, and the massage also showed the long-term effect (at least 1 year) [8]. Some systematic reviews [34–36] and clinical guidelines [6, 7] also found the evidence to support the efficacy of acupuncture with respect to improvements on pain and function. In addition, there were some recommendations of herbal medicines for LBP in systematic reviews [37, 38] and clinical guidelines [3, 6]. Although the evidence is only for single application of these therapies for LBP, they partly supported the efficacy of TICMT for the management of LBP. Comparing with these systematic reviews and clinical guidelines, there were some key strong points in our systematic review. We assessed the integrated effect of TICMT for LBP by the qualitative review and quantitative meta-analyses for the first time. Although TICMT were widely used for the in-patients with LBP in Chinese hospitals, the evidence from systematic reviews was marginal. We, on the other hand, separately assessed the effect of Tuina plus Chinese herbal medicine, Tuina plus acupuncture, Tuina plus moxibustion, Tuina plus hot pack, and Tuina plus more than one Chinese medical therapy. And the outcomes of interest contained pain and functional status. So our systematic review provided stronger evidence of TICMT for LBP.

4.1. Limitations of the Review. There are several limitations in our study. First, the distorting effects of publication and location bias on systematic reviews and meta-analyses are well documented [39, 40]. We are confident that our search strategy located all relevant studies. However, some degree of uncertainty remains. Another possible source of bias is that more negative trials of TICMT for in-patients with LBP may be never published in the peer-reviewed literature.
Evidence-Based Complementary and Alternative Medicine

4.2. The Possible Rationale of TICMT for LBP. Assuming that TICMT were beneficial for LBP, the complex interplay of both physical and mental modes may provide a possible rationale. The manual therapy delivered to soft and connective tissues may induce local biochemical changes that modulate local blood circulation, improve muscle flexibility, intensify the movement of lymph, and soften adherent connective tissue, which may alternately improve reuptake of local nociceptive and inflammatory mediators [41, 42]. These effects may subsequently influence neural activity at the spinal cord segmental level, thereby modulating the activities of cerebral cortex that improve pain and dysfunction due to LBP [43]. In addition, manual therapy may impact the primary afferent neurons from paraspinal tissues, the motor control system, and pain processing [44]. Chinese herbal medicine and acupuncture may strengthen the effectiveness of these manual therapies in local blood circulation and nociceptive and inflammatory mediators, because isolated components of the Chinese herbs have anti-inflammatory, antilipidemic, antioxidant, and immune modulation properties [45]. And the acupuncture also works through the central nervous system by stimulating the production of endorphins and neurotransmitters that modulate nociception and other involuntary bodily functions, or through the gate control theory of pain, in which the nociceptive input is inhibited in the central nervous system in the presence of another type of input [46–48]. It also stimulates vascular and immunomodulatory factors involved as mediators of inflammation [49].

5. Conclusion

Twenty RCTs were analyzed in our systematic review, evaluating TICMT in management of LBP. The findings from the current studies suggest that TICMT might be effective complementary and alternative treatments for in-patients with LBP. However, the poor quality of the included studies and the shortage of long-term effects of TICMT suggest that the positive evidence is underpowered. Consequently, future studies should adhere to high-quality RCTs with long follow-up for demonstrating the effectiveness of TICMT for in-patients with LBP.

Appendices

A. Search Strategies

A.1. PubMed Publication Date from 2001/01/01 to 2012/06/30, Randomized Controlled Trial

(1) ((((((low back pain [Title/Abstract]) OR back pain [Title/Abstract]) OR backache [Title/Abstract]) OR dorsalgia [Title/Abstract]) OR lumbago [Title/Abstract]) OR lumbar disc herniation [Title/Abstract]) OR lumbar sprain [Title/Abstract].

(2) (((Tuina [Title/Abstract]) OR massage [Title/Abstract]) OR mobilization [Title/Abstract]) OR spinal manipulation [Title/Abstract].

(3) (((acupuncture [Title/Abstract]) OR electroacupuncture [Title/Abstract]) OR herbal medicine [Title/Abstract]) OR moxibustion [Title/Abstract]) OR hot pack [Title/Abstract].

(4) ((1) AND (2)) AND (3).

A.2. EMBASE Publication Date from 2001/01/01 to 2012/06/30

(1) (low back pain OR backache OR back pain OR dorsalgia OR lumbago OR lumbar disc herniation OR lumbar sprain).ti.

(2) (Tuina OR massage OR mobilization OR spinal manipulation).ti.

(3) (acupuncture OR electroacupuncture OR herbal medicine OR moxibustion OR hot pack).ti.

(4) (random OR randomly OR randomized controlled trial OR RCT).ab.

(5) (((1) AND (2)) AND (3)) AND (4).

(6) (low back pain OR backache OR back pain OR dorsalgia OR lumbago OR lumbar disc herniation OR lumbar sprain).ab.

(7) (Tuina OR massage OR mobilization OR spinal manipulation).ab.

(8) (acupuncture OR electroacupuncture OR herbal medicine OR moxibustion OR hot pack).ab.

(9) (((6) AND (7)) AND (8)) AND (4).

A.3. Cochrane Library Publication Date from 2001/01/01 to 2012/06/30

(1) (“low back pain” OR “back pain” OR “backache” OR “dorsalgia” OR “lumbago” OR “lumbar disc herniation” OR “lumbar sprain” in title/abstract/keywords) AND (“Tuina” OR “massage” OR “mobilization” OR “spinal manipulation” in title/abstract/keywords) AND (“acupuncture” OR “electroacupuncture” OR “herbal medicine” OR “moxibustion” OR “hot pack” in title/abstract/keywords).
A.4. Chinese Databases including China Knowledge Resource Integrated Database (CNKI) Publication Date from 2001/01/01 to 2012/06/30

(1) (low back pain [Title] OR back pain [Title] OR lumbar disc herniation [Title] OR lumbar sprain [Title]).

(2) (Tuina [Title] OR massage [Title] OR mobilization [Title] OR spinal manipulation [Title]) AND (1).

(3) (acupuncture [Title] OR electroacupuncture [Title] OR herbal medicine [Title] OR moxibustion [Title] OR hot pack [Title]) AND (2).

(4) random [Abstract] AND (3).


(8) random [Abstract] AND (7).

A.5. Weipu Database for Chinese Technical Periodicals (VIP) Publication Date from 2001/01/01 to 2012/06/30

(1) (((low back pain [Title] OR back pain [Title] OR lumbar disc herniation [Title] OR lumbar sprain [Title]) AND (Tuina [Title] OR massage [Title] OR mobilization [Title] OR spinal manipulation [Title])) AND (acupuncture [Title] OR electroacupuncture [Title] OR herbal medicine [Title] OR moxibustion [Title] OR hot pack [Title])) AND random [Abstract].


A.6. Wanfang Data Publication Date from 2001/01/01 to 2012/06/30

(1) (Title = low back pain OR back pain OR lumbar disc herniation OR lumbar sprain) AND (Title = Tuina OR massage OR mobilization OR spinal manipulation) AND (Title = acupuncture OR electroacupuncture OR herbal medicine OR moxibustion OR hot pack) AND (Abstract = random).

(2) (Abstract = low back pain OR back pain OR lumbar disc herniation OR lumbar sprain) AND (Abstract = Tuina OR massage OR mobilization OR spinal manipulation) AND (Abstract = acupuncture OR electroacupuncture OR herbal medicine OR moxibustion OR hot pack) AND (Abstract = random).

Evidence-Based Complementary and Alternative Medicine

Acknowledgments

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References


[13] B. J. Liang, “Clinical observation on effectiveness of huohua decoction in combination with tuina in treating 25 cases of


Research Article

Chinese Patent Medicine Liu Wei Di Huang Wan Combined with Antihypertensive Drugs, a New Integrative Medicine Therapy, for the Treatment of Essential Hypertension: A Systematic Review of Randomized Controlled Trials

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2 Department of Gastroenterology, Guang’anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China
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Objectives. To assess the beneficial and adverse effects of Liu Wei Di Huang Wan (LWDHW), combined with antihypertensive drugs, for essential hypertension. Methods. Five major electronic databases were searched up to August 2012 to retrieve any potential randomized controlled trials designed to evaluate the clinical effectiveness of LWDHW combined with antihypertensive drugs for essential hypertension reported in any language, with main outcome measures as blood pressure. The quality of the included studies was assessed with the Jadad scale and a customized standard quality assessment scale. Results. 6 randomized trials were included. The methodological quality of the trials was evaluated as generally low. The pooled results showed that LWDHW combined with antihypertensive drugs was more effective in blood pressure and the scale for TCM syndrome and symptom differentiation scores compared with antihypertensive drugs alone. Most of the trials did not report adverse events, and the safety is still uncertain. Conclusions. LWDHW combined with antihypertensive drugs appears to be effective in improving blood pressure and symptoms in patients with essential hypertension. However, the evidence remains weak due to the poor methodological quality of the included studies.

1. Introduction

Hypertension is one of the most prevalent and important public health concerns in both developed and developing countries [1–3]. Several studies have demonstrated that successful long-term treatment of hypertension has a significant impact on morbidity and mortality for cardiovascular disease (CVD) and stroke. However, only 53% of patients treated for hypertension had blood pressure actually controlled to ≤140/90 mmHg [4]. Considering these data and the seriousness of the effects of hypertension on the individual and society as a whole, both economically and socially, physicians must look for more effective and alternative ways to achieve the target blood pressure as quickly as possible. Can integrative medicine contribute to combat hypertension more effectively?

Integrative medicine is a relatively new discipline which attempts to combine complementary and alternative medicine (CAM) with Western medicine [5]. As Western medicine has been developed based on the scientific method, integrative medicine, therefore, combines the latest modern scientific advances with the most profound perspectives of CAM to regain and preserve health [6]. In China, the integrative medicine mainly refers to the integrated traditional Chinese and Western medicine. Traditional Chinese medicine (TCM), including herbal medicine and acupuncture, is one of the most important parts in CAM. TCM has long been used in the treatment of a wide variety
of illnesses including hypertension [7, 8]. Much of the past literature reflects clinical observations made by physicians in their offices. More recently, with more and more reports of the significance of disease-syndrome combination [9], there are also large numbers of controlled studies based on the use of combination of TCM and Western medicine in the treatment of hypertension [10–14].

Liu Wei Di Huang Wan (LWDHW), a traditional Chinese patent medicine containing six commonly used herbs (Rehmanniae radix, pulp of Cornus, yam, Poria cocos, Alisma orientalis, and Cortex moutan), is widely used to treat hypertension-related signs and symptoms in clinical practice for centuries in China. Recent research showed that LWDHW could lower blood pressure. The mechanism of the prescription maybe related to enriching yin and nourishing kidney in TCM. Biochemically, LWDHW also showed good effect in decreasing the concentrations of ET and vWF in plasma, increasing the content of NO and protecting the function of kidney with essential hypertension [15, 16].

Our previous studies have showed that kidney deficiency syndrome is one of the most important pathogenesis of essential hypertension in TCM, which could be well treated by LWDHW [17]. LWDHW combined with antihypertensive drugs, a new integrative medicine therapy, has been widely used as an alternative and effective method for treating essential hypertension in China currently. A large number of clinical studies reported the clinical effect of LWDHW and LWDHW combined with antihypertensive drugs ranging from case reports and case series to controlled observational studies and randomized clinical trials (RCTs) until now. However, there is no a critically appraised evidence such as systematic reviews or meta-analyses on potential benefit and safety of LWDHW combined with antihypertensive drugs for essential hypertension to justify their clinical use and their recommendation. Understanding the effect of LWDHW combined with antihypertensive drugs on blood pressure, hypertension-related signs and symptoms, quality of life (QoL), and cardiovascular risk factors could be valuable for essential hypertension management. The present paper aims to evaluate the beneficial and harmful effects of LWDHW combined with antihypertensive drugs for treatment of essential hypertension in randomized trials.

2. Methods

2.1. Database and Search Strategies. The literature searches were conducted in Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (August, 2012). All of those searches ended on 10 August, 2012. Ongoing registered clinical trials were searched in the website of Chinese clinical trial registry (http://www.chictr.org/) and international clinical trial registry by the US national institutes of health (http://clinicaltrials.gov/). The following search terms were used individually or combined: “essential hypertension”, “hypertension,” “Liu Wei Di Huang Wan,” “Liu Wei Di Huang Pill,” “clinical trial,” and “randomized controlled trial.” The bibliographies of the included studies were searched for additional references.

2.2. Inclusion Criteria. All the randomized controlled trials (RCTs) of all the prescriptions based on “Liu Wei Di Huang Wan” combined with antihypertensive drugs compared with antihypertensive drugs in patients with hypertension were included. There were no restrictions on population characteristics, language, and publication type. The primary outcome measure was blood pressure (BP), and the secondary outcome measure was the scale for TCM syndrome and symptom differentiation (TCM-SSD) scores. The criteria “significant effective, effective, or not effective” was also included in the outcome measurement. Duplicated publications reporting the same groups of participants were excluded.

2.3. Data Extraction and Quality Assessment. Two authors conducted the literature searching (X. J. Xiong, K. W. Yao), study selection (X. J. Xiong, B. Feng), and data extraction (X. J. Xiong, X. Du) independently. The extracted data included authors, title of study, year of publication, study size, age and sex of the participants, details of methodological information, name and component of Chinese herbs, treatment process, details of the control interventions, outcomes (e.g., blood pressure), and adverse effects for each study. Disagreement was resolved by discussion and reached consensus through a third party (J. Wang). The methodological quality of trials was assessed using the 6 criteria 6 election bias (study design, confounders, blinding, data collection methods, withdrawals, and dropouts) to follow 3 categories: Category A (strong quality): four strong ratings with no weak ratings above. Category B (moderate quality): less than four strong ratings and one weak rating. Category C (weak quality): two or more weak ratings. The quality of included trials were assessed according to the Cochrane Handbook of Systematic Reviews of Interventions (Chapter 8.5) to address the following five criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.

2.4. Data Synthesis. Revman 5.1 software provided by Cochrane Collaboration was used for data analyses. Dichotomous data were expressed as relative risk (RR) and continuous outcomes as weighted mean difference (WMD), both with 95% confidence intervals (CI). Meta-analysis was performed if the intervention, control, and outcome were the same or similar. The statistical heterogeneity was presented as significant when *I*^2^ is over 50% or *P* < 0.1. In the absence of significant heterogeneity, we pooled data using a fixed-effect model (*I*^2^ < 50%), otherwise we used random effects model (*I*^2^ > 50%) [24].

3. Result

3.1. Description of the Included Trials. After primary search of 5 databases, 340 trials were screen out from electronic
Table 1: Characteristics and methodological quality of the included studies.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Sample</th>
<th>Diagnosis standard</th>
<th>Intervention</th>
<th>Control</th>
<th>Course (week)</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang 2007 [19]</td>
<td>68</td>
<td>Hypertension diagnostic criteria (unclear)</td>
<td>LWDHW plus nifedipine controlled release tablet</td>
<td>Nifedipine controlled release tablet</td>
<td>4</td>
<td>BP</td>
</tr>
<tr>
<td>Chen et al. 2008</td>
<td>97</td>
<td>CGMH-2005</td>
<td>LWDHW plus captopril</td>
<td>captopril</td>
<td>8</td>
<td>BP; adverse effect</td>
</tr>
<tr>
<td>Zhang et al. 2004</td>
<td>78</td>
<td>1993 WHO—ISH GMH</td>
<td>LWDHW plus enalapril</td>
<td>enalapril</td>
<td>7</td>
<td>BP; TCM-SSD</td>
</tr>
<tr>
<td>Zhou et al. 2003</td>
<td>100</td>
<td>1999 WHO—ISH GMH</td>
<td>LWDHW plus nifedipine controlled release tablet</td>
<td>Nifedipine controlled release tablet</td>
<td>18</td>
<td>BP; TCM-SSD</td>
</tr>
<tr>
<td>Hu et al. 1994</td>
<td>50</td>
<td>Hypertension diagnostic criteria (unclear); TCM diagnostic criteria (unclear)</td>
<td>LWDHW plus nifedipine</td>
<td>nifedipine</td>
<td>10</td>
<td>BP</td>
</tr>
</tbody>
</table>


The interventions of all the trials [18–23] included LWDHW combined with antihypertensive drugs as shown in Table 1. The controls included antihypertensive drugs alone. The total treatment duration ranged from 4 weeks to 18 weeks. All of the 6 trials used the blood pressure (BP) as the main outcome measure. Other outcome measures include the scale for TCM syndrome and symptom differentiation (TCM-SSD). Adverse effect was described in details. Three classes were used to evaluate treatment effects, including significant effective, effective, ineffective according to BP and TCM-SSD.

3.2. Methodological Quality of Included Trials. The methodological quality of all the included RCTs was assessed to be of general low according to the predefined quality assessment criteria as shown in Table 2. The randomized allocation of participants, allocation concealment and double-blind were not mentioned in all the six trials. Only one trial [18] has reported drop-out. None of trials had a pre-trial estimation of sample size, which indicated the lack of statistical power to ensure appropriate estimation of the therapeutic effect.
Table 2: Quality assessment of the included randomized controlled trials.

<table>
<thead>
<tr>
<th>Included trials</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants personnel and outcome assessors</th>
<th>Incomplet outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai 2004 [18]</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
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<tr>
<td>Zhang 2007 [19]</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
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<tr>
<td>Chen et al. 2008 [20]</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
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<tr>
<td>Zhang et al. 2004 [21]</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
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<tr>
<td>Zhou et al. 2003 [22]</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Hu et al. 1994 [23]</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 3: Analyses of blood pressure.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Intervention (n/N)</th>
<th>Control (n/N)</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LWDHW plus sustained-release nifedipine versus sustained-release nifedipine</td>
<td>1  90/93</td>
<td>52/61</td>
<td>5.19 (1.35, 20.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>LWDHW plus captopril versus captopril</td>
<td>1  45/49</td>
<td>43/48</td>
<td>1.31 (0.33, 5.20)</td>
<td>0.70</td>
</tr>
<tr>
<td>LWDHW plus enalapril versus enalapril</td>
<td>1  35/42</td>
<td>23/36</td>
<td>2.83 (0.98, 8.15)</td>
<td>0.05</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>3  170/184</td>
<td>118/145</td>
<td>2.77 (1.37, 5.57)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

All the trials did not mention follow up. We have tried to contact the authors for further detailed information about the article, but regrettably no information could be got till now.

3.3. Effect of the Interventions

3.3.1. Blood Pressure. Three trials [18, 20, 21] used blood pressure decrease to measure the outcome: significant effective (diastolic blood pressure decreased by 10 mmHg reaching the normal range, or diastolic blood pressure has not yet returned to normal, but has been reduced ≥20 mmHg), effective (diastolic blood pressure decreased to less than 10 mmHg reaching the normal range, or diastolic blood pressure decreased by 10–19 mmHg, but did not reach the normal range, or systolic blood pressure decreased ≥30 mmHg), and ineffective (not to meet the above standards). The trial showed significant difference between treatment and control group on the three criteria outcome measurement (RR: 2.77 (1.37, 5.57); P = 0.004). Five trials 19-21, 23-24 compared the effectiveness using the blood pressure value, and significant difference was found between treatment and control group in systolic blood pressure (WMD: −9.31 (−10.75, −7.86); P < 0.00001) and diastolic blood pressure (WMD: −6.27 (−7.69, −4.86); P < 0.000001) (Tables 3, 4, and 5).

3.3.2. TCM-SSD Scores. Two trials [21, 22] used the TCM-SSD scores to measure the outcome: significant effective (The main symptoms such as headache, dizziness, palpitations, insomnia, tinnitus, and irritability disappear, or TCM-SSD scores reduced rate ≥70%), effective (the main symptoms relieved, or 70% > TCM-SSD scores reduced rate ≥30%), and ineffective (the main symptoms do not change, or TCM-SSD scores reduced rate <30%). There is only one trial [21] who reported the TCM-SSD scores decrease. The meta-analysis showed there is significant beneficial effect on the combination group compared to the antihypertensive drugs using alone (RR: 3.04 1.10, 8.38; P = 0.03) (Table 6). The other trial [22] reported that after 18 weeks of treatment, the scores of main symptoms in hypertension, including headache, insomnia, amnesia, waist soreness, and tinnitus, decreased significantly. As we cannot obtain more details of the TCM-SSD scores, so we cannot get the analysis of comparison between groups (Table 6).

3.3.3. Other Outcomes. One trial [18] showed that after 8 weeks of treatment, the serum level of ET decreased and NO increased in both groups with significant difference in LWDHW plus sustained-release nifedipine group compared to sustained-release nifedipine group. One trial [19] showed that after 4 weeks of treatment, β2-MG reduced significantly in treatment group compared to control group. One trial [20] showed that significant difference was found between treatment and control group in BUN and Cr after 8 weeks of treatment. One trial [22] reported that significant difference was found between treatment and control group in IgG and C3 after 18 weeks of treatment. One trial [23] showed that IgG and C3 decreased in the treatment group.

3.4. Sensitivity Analysis, Subgroup Analysis, and Publication Bias. The number of trials was too small to conduct any sufficient additional analysis of sensitivity, subgroup, and publication bias.

3.5. Adverse Effect. Only one trial mentioned the adverse effect [20]. It mentioned adverse effect such as dry cough during the course. It may be related to the adverse effect of captopril.
4. Discussion

This paper included 6 randomized trials and a total of 555 participants. Liu Wei Di Huang Wan combined with antihypertensive drugs, a new integrative medicine therapy, showed significant benefit on decreasing blood pressure and improving symptoms and signs as compared with conventional treatment for essential hypertension. However, due to the low-quality methodology and potential publication bias, a definite conclusion of the beneficial effectiveness of LWDHW combined with antihypertensive drugs in treating essential hypertension could not be drawn. The positive findings should be interpreted conservatively due to the following facts.

All the six trials included had improper study design or method used, such as lack of randomization or allocation concealment. No trials reported randomization procedure clearly and only mentioned that “patients were randomized into two groups”. So, it is hard to judge whether randomization was conducted properly and really. All the trials haven’t mentioned allocation concealment and double-blind. Therefore, it is possible that some of the trials are not true RCTs. And two trials including Cai 2004 and Zhang 2007 [18, 19], only have one author. It is impossible for an RCT to be done properly in terms of randomization and allocation concealment by one doctor totally. Publication bias could also be a factor. We have tried to take all measures to contact authors to get further information either by telephone or email. Unfortunately, no replies and informations was got. Subsequently, no clear conclusion could be made from these trials.

Adverse effect was reported by Chen et al. in 2008 [20] as only dry mouth. The adverse effect was not severe, and it spontaneously recovered without special treatment. The other 5 trials did not report any adverse effects and these were not significantly different between the two treatments. Therefore, due to the limited and inadequate evidence provided by the eligible trials, conclusions about the safety of LWDHW combined with antihypertensive drugs cannot be made from this paper. Large-scale clinical trials with long-term followup were warranted to assess the safety of new integrative medicine therapy properly.

Syndrome is a classification according to subjective symptom and objective sign collected by physician through inspection, auscultation-olfaction, interrogation and palpation [25]. Syndrome differentiation is the basic rule in TCM. Failure to apply syndrome differentiation to clinical trials may result in treatments being ineffectve or even harmful, and failure to evaluate the real efficacy of TCM. In this paper, only one trial [23] reported the TCM diagnostic criteria but without further details. The rest five trials [18–22] did not report TCM diagnostic criteria. If syndrome differentiation in TCM was considered into the studies properly, the positive effects could be enhanced.

5. Conclusions

In conclusion, because of the unclear methodological quality of these including trials, a definite conclusion on efficacy and safety associated with Liu Wei Di Huang Wan combined with antihypertensive drugs cannot be drawn from this paper.

<table>
<thead>
<tr>
<th>Trials</th>
<th>WMD (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LWDHW plus sustained-release nifedipine versus sustained-release nifedipine</td>
<td>1</td>
<td>−10.00 (−11.76, −8.24)</td>
</tr>
<tr>
<td>LWDHW plus nifedipine controlled release tablet versus nifedipine controlled release tablet</td>
<td>1</td>
<td>−10.50 (−24.07, 3.07)</td>
</tr>
<tr>
<td>LWDHW plus captopril versus captopril</td>
<td>1</td>
<td>−9.00 (−13.66, −4.34)</td>
</tr>
<tr>
<td>LWDHW plus nifedipine controlled release tablet versus nifedipine controlled release tablet</td>
<td>1</td>
<td>−8.00 (−11.35, −4.65)</td>
</tr>
<tr>
<td>LWDHW plus nifedipine versus nifedipine</td>
<td>1</td>
<td>−3.00 (−10.91, 4.91)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>5</td>
<td>−9.31 (−10.75, −7.86)</td>
</tr>
</tbody>
</table>

Table 4: Analyses of systolic blood pressure.

<table>
<thead>
<tr>
<th>Trials</th>
<th>WMD (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LWDHW plus sustained-release nifedipine versus sustained release nifedipine</td>
<td>1</td>
<td>−7.00 (−8.74, −5.26)</td>
</tr>
<tr>
<td>LWDHW plus nifedipine controlled release tablet versus nifedipine controlled release tablet</td>
<td>1</td>
<td>−2.25 (−11.90, 7.40)</td>
</tr>
<tr>
<td>LWDHW plus captopril versus captopril</td>
<td>1</td>
<td>−6.75 (−11.26, −2.24)</td>
</tr>
<tr>
<td>LWDHW plus nifedipine controlled release tablet nifedipine controlled release tablet</td>
<td>1</td>
<td>−4.00 (−7.23, −0.77)</td>
</tr>
<tr>
<td>LWDHW plus nifedipine versus nifedipine</td>
<td>1</td>
<td>−6.00 (−14.46, 2.46)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>5</td>
<td>−6.27 (−7.69, −4.86)</td>
</tr>
</tbody>
</table>

Table 5: Analyses of diastolic blood pressure.
Before recommending Liu Wei Di Huang Wan combined with antihypertensive drugs as an alternative treatment measure in hypertensive patients, more rigorous trials with high quality are needed to give high level of evidence.

**Author’s Contribution**

J. Wang, K. Yao, X. Yang, B. Feng, X. Du, and P. Wang contributed equally to this paper. All the authors contributed to the writing of this paper.

**Conflicts of Interests**

The authors declare that they have no conflict of interests.

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**References**


Research Article

Results of a 2-Week Inpatient Stay at the Department for Internal and Integrative Medicine: An Observational Study

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Introduction. The Department for Internal and Integrative Medicine in Essen utilizes mind/body medical elements in order to empower patients with chronic diseases to better cope with their symptoms and to adopt a healthy lifestyle. This study explored the influence and predictors of a 2-week integrative treatment program on patients’ quality of life.

Methods. This observational study was conducted with inpatients as part of the quality assurance program. Patients’ quality of life, psychological symptoms, and health locus of control were measured on admission and discharge and again 3, 6, and 12 months after discharge. Regression analyses were conducted to determine the factors predicting improved quality of life.

Results. Data from 2486 inpatients treated in 2001–2004 were included (80% female, mean age 53.9 ± 14.3 years). Response rates decreased to 50% at 12 months. Small-to-moderate effects were found on patients’ quality of life, anxiety, and depression. Patients’ internal locus of control significantly increased. Improved quality of life was mainly predicted by lower baseline scores.

Conclusion. Results of this study suggest that a 2-week inpatient treatment might sustainably reduce patients’ symptoms and increase their quality of life; however, conclusions are only preliminary. More research is needed to enable the effectiveness to be judged conclusively.

1. Introduction

Integrative treatment approaches are becoming increasingly important. This is especially the case in treating chronic diseases; long-term conditions that develop slowly over time often progress in severity and rarely can be cured [1]. Treating such diseases, including musculoskeletal, cardiovascular, digestive, and metabolic disorders, uses up nearly 80% of nations’ health budgets and imposes immense individual burdens [2–4]. Chronic diseases impair physical and mental health and reduce one’s ability to carry out activities of daily living [5]. For example, studies have shown that physical illness is an important risk factor for anxiety and depression [6, 7] and that depression is a risk factor for physical illness [8].

Although much progress has been made to date in drug development and medical technology, patients and their psychosocial needs are less often involved in the therapeutic process. Despite the effect that psychological health and lifestyle factors are known to have on health and disease in patients with chronic health conditions [9], few change their lifestyles [10]. Empowering patients to adopt healthy lifestyles may enhance the effects of any treatments received and reduce future health risks.

The Department for Internal and Integrative Medicine at Kliniken Essen-Mitte, the University of Duisburg-Essen’s academic teaching hospital, was established in 1999. The Clinic combines conventional medicine, complementary medicine, and Mind/Body therapies to treat patients with chronic diseases [11, 12]. The Mind/Body therapies were added specifically to promote patients’ active participation in their care. Mind/Body therapies are defined as “practices that focus on the interactions between the brain, mind, body, and behaviour, with the intention of using the
mind to affect physical functioning and promote health” [13]. Such therapies include lifestyle education: seeking to enhance patients’ capacity for self-care through such elements as exercise, good nutrition, relaxation, and self-help [12, 14, 15]. Although Mind/Body programs are not overtly psychotherapeutic, aspects of cognitive behavioural therapy are used to enhance patients’ ability to cope with their condition, and its impact on daily life, and to live a healthy lifestyle. Research shows such programs’ effectiveness for conditions including coronary heart disease [16–18], inflammatory bowel disease [19, 20], and cancer [21]. Patients’ control beliefs are also considered key in ensuring long-term treatment effectiveness [22]. Patients who have an internal locus of control (believe that they are able improve their own health) should use active coping strategies more often than other patients.

This observational study was conducted to explore the influence of a 2-week integrative treatment program on patients’ quality of life, psychological symptoms, and locus of control and to determine the factors predicting improved quality of life.

### 2. Methods

#### 2.1. Design and Patients
This observational study was conducted at the Department for Internal and Integrative Medicine in Essen [11], Germany, as part of its ongoing quality assurance program. The Clinic was established as a model clinic in 1999 to treat patients with chronic diseases of rheumatological, gastrointestinal, pulmonological, and cardiovascular origin, including those with chronic pain syndromes. Referrals come from specialist and general practitioners, with treatment costs being met by statutory health insurance and many private health insurance companies. The quality assurance program evaluates the Clinic’s therapeutic results and cost-effectiveness on behalf of the North Rhine-Westphalia federal state government. Previous partial publication of these results [16, 22] omitted the first year of evaluation [22] and specific patient subgroups [23]. Data on the Clinic’s cost-effectiveness are not reported here.

All patients admitted to the Clinic between January 2001 and January 2004 received detailed study information and were invited to participate in this study. Patients who were willing to participate signed informed consent forms. Participants received questionnaires on their admission to (ADM) and discharge from (DIS) a 2-week inpatient hospital stay, with further questionnaires at 3-(FU3), 6-(FU6), and 12 month (FU12) intervals after discharge.

#### 2.2. Intervention
Patients received two weeks of integrative inpatient hospital treatment; following individual treatment plans developed from extensive anamneses by physicians, nurses, and mind/body therapists. Treatments included conventional diagnostic and interventional medical approaches, including physiotherapy, and the use of complementary techniques. The latter included the use of traditional medicine (Traditional Chinese Medicine, acupuncture, cupping, leeching, etc.) and classical naturopathy (hydrotherapy, thermotherapy, manual therapy, massage, phytotherapy, exercise, nutritional therapy, and fasting). Patients also received several mind/body therapy sessions, focusing on exercise, stress-reduction, diet, and self-help, to empower them to adopt healthy lifestyles. These sessions were based on Harvard Medical School’s Benson-Henry Institute for Mind/Body Medicine Program [24] and the University of Massachusetts’ Mindfulness-Based Stress Reduction Program [25, 26]. Elements of cognitive restructuring were also added in this study [27, 28].

#### 2.3. Outcome Measures
The following were used to evaluate patients’ postintervention change.

#### 2.4. Primary Outcome Measure

##### 2.4.1. Health Related Quality of Life (SF-36)
Patients’ health-related quality of life was assessed using the short form 36 of the health survey questionnaire (SF-36) [29]. This tool measures individuals’ quality of life on eight dimensions and two main component scales (physical, mental). It has proven validity and reliability [29]. Each scale ranges from 0 to 100, with higher scores indicating higher quality of life. In this study, only the main component summaries were analysed; comparing the outcome with age- and gender-matched values from the German general population [30, 31]. The differences found are presented as z-scores, with 0 representing the mean and 1 the standard deviation of the population. The SF-36 assesses quality of life by means of daily living activities, making its use inappropriate in a hospital setting. The SF-36 was, therefore administered at ADM, FU3, FU6, and FU12, but not at discharge, in this study.

#### 2.5. Secondary Outcome Measures

##### 2.5.1. Anxiety and Depression (HADS)
Changes in patients’ psychological symptoms were measured using the Hospital Anxiety and Depression Scale (HADS). This tool has 14 items, scored on 4 point Likert scales [32]. Higher scores indicate more severe symptoms. For both dimensions, cut-off scores have been introduced to indicate possible sub-syndromal (≥8) or clinically relevant (≥11) anxiety or depression [33]. Study patients completed the HADS at admission, discharge, and followup.

##### 2.5.2. Health Locus of Control (GKÜ)
Patients’ health locus of control was measured using the GKÜ (German abbreviation for Gesundheitsbezogene Kontrollüberzeugungen) [34, 35] a short version in German of the Multidimensional Health Locus of Control Questionnaire (MHLC) [36]. The GKÜ is a 9-item questionnaire which assesses three dimensions of patients’ control beliefs: internal, external-social, and external-fatalistic. The more internal control patients perceive, the more they feel able to influence their health. By contrast, the more control that patients attribute to others...
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(external-social), or to luck or destiny (external-fatalistic), the less they feel able to influence their health. The GKÜ was originally devised for use with patients with cancer, but has since been adapted for use with other patients, such as those with back pain [37]. A previous study reported problems with one item on the GKÜ [38]. A factor analysis undertaken with the present study data showed that this item loaded on two factors equally. It was therefore deleted from the analysis [38]. Patients completed the GKÜ at admission, discharge, and followup.

2.5.3. Satisfaction with Health and Life in General (FLZ). Patients’ satisfaction with their health and lives in general was measured using two 5-point Likert items from the Life Satisfaction Questionnaire (Fragebogen zur Lebenszufriedenheit, FLZ) [39] at admission, discharge, and followup. The scale used ranged from 1 = very dissatisfied to 5 = very satisfied, with higher scores indicating patients’ greater satisfaction with their health and lives in general.

2.5.4. Demand on Medical Services. The study questionnaire also asked patients to record how many doctors’ visits they had made during the previous month. Patients were also asked, at admission and 12-month followup, how many days they had been admitted for hospital inpatient treatment and how many days they had missed work (where appropriate) over the previous year.

2.5.5. Improvement in Disease-Related Symptoms. At discharge and each followup, patients compared their main disease-related symptoms with before they entered treatment, using a 5-point Likert scale that ranged from “much worse” to “much improved.”

2.5.6. Statistical Analysis. All analyses were based on full data sets with no missing data. Baseline comparisons and comparisons between responders and non-responders were conducted using t-tests for independent groups, for parametric data, and x²-tests for nonparametric data. Responders were defined as patients who returned their questionnaires at given time points, with nonresponders being those who failed to do so.

Repeated analyses of variance (ANOVA) were used to analyse the study’s primary and secondary outcome measures as appropriate. Residuals were checked visually for normal distribution. The homogeneity of variance was tested using a Mauchly test for sphericity. Cases of nonsphericity were corrected using a Greenhouse-Geisser correction. The estimated differences between the time points, from the ANOVA analyses, and their 95% Confidence Intervals, were reported for each outcome. Effect size Cohen’s d (the estimated differences from the ANOVA analyses divided by the standard deviation of patients’ admission scores) was also given. Changes in patients’ disease-related symptoms were explored solely descriptively.

Analyses were conducted in the following order to determine the factors influencing the study’s primary outcome measure: (1) bivariate correlations were used to explore possible links between patients’ sociodemographic characteristics, their scores at admission and their outcome at discharge and followup. (2) Factors with significant correlations (r ≥ 0.1) were entered as possible predictors into the regression analysis. Patients’ age and gender were automatically included in each regression. (3) Linear forward stepwise regression analysis with linear outcome and linear or dichotomous regressors was then conducted.

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) (Version 20.0, IBM, USA). The significance level was set at α = 5%. An automatic Bonferroni correction was applied for the posthoc comparison of the main ANOVA effects.

3. Results

3.1. Patients’ Characteristics. The study’s response rates are shown in Figure 1. Of the 2804 patients treated between January 2001 and January 2004, 2486 agreed to participate in the study on admission. The initial response rate of 87.5% on discharge, diminished to 61.3%, 57.7%, and 48.2% at 3, 6 and 12 months’ followup. The numbers of patients included in the analyses are shown in each of the following tables. Since only complete patients’ data sets were included in the
analyses, a missing score at any time point led to exclusion of this patient’s data.

Table 1 shows patients’ sociodemographic and clinical characteristics on admission. The study sample consisted mainly of women in their mid-50s; most of whom had not been educated to A-level standard. Men more often reported being in a relationship, with more education, more frequent absenteeism from work over the past year and lower expectations of improvement from their inpatient stay than women.

More than two thirds of the patients experienced a chronic pain condition, with back pain, headache, fibromyalgia and arthritis being the most frequently cited causes for admission. More than half of the study patients were diagnosed as severely affected by their disease conditions, with few being seen as only slightly affected.

Most patients had high expectations of complementary medicine’s effectiveness, with more than 80% expecting some improvement and few expecting none.

The following results compare responders’ and non-responders’ sociodemographic and clinical characteristics to indicate potential response bias, illustrate the primary and secondary outcomes for patients with complete data sets, and present the regression analysis, for patients with complete data sets, to determine the factors associated with improvements in their quality of life after inpatient treatment.

3.2. Comparison of Responders and Nonresponders. An eighth of patients (12.5%) were lost to followup between admission and discharge. More than a third (38.7%) had withdrawn within three months of discharge (FU3), the time of the biggest withdrawal. Table 2 shows the significant differences found between responders and nonresponders.

Table 2 shows that responders stayed longer in hospital, experienced less psychological symptoms, and scored more highly on the mental health component summary of the SF-36 than non-responders. Responders’ levels of internal locus of control were also higher at baseline, and their external-fatalistic control beliefs lower, than nonresponders’. Three months posttreatment, responders’ results also outstripped non-responders’ with regard to their satisfaction with their life in general and perceived improvements in their symptoms at discharge.

3.3. Primary Outcome Measure

3.3.1. Health-related Quality of Life (SF-36). The physical (PCS) and mental component (MCS) summaries of patients’ SF-36 scores increased from admission to FU3; remaining relatively stable thereafter, see Table 3. Repeated ANOVA analyses showed a significant time effect on both the PCS ($P < 0.0001$) and the MCS ($P < 0.0001$). Patients’ physical (PCS) and mental component summaries (MCS) were found to be significantly higher at FU3, FU6 and FU12, when compared to admission. No statistical differences were found between patients’ follow-up measurements. The effect sizes for patients’ PCS and MCS summaries were small to moderate. Altogether 41.3% and 44.3% had increased their PCS and MCS summaries respectively by more than five points from discharge onwards; a clinically important improvement in their quality of life [29].

Compared to age- and gender-matched data from a normative German population, patients’ PCS was $z = −1.49$ and their MCS $z = −0.97$ at admission; below the average of the corresponding norms. At FU3, study patients’ PCS was $z = −1.01$ and their MCS $= −0.47$; an improvement of 0.5z.

3.4. Secondary Outcome Measures

3.4.1. Anxiety and Depression (HADS). ANOVA analyses revealed significant time effects on patients’ anxiety ($P < 0.0001$) and depression ($P < 0.0001$) scores. Post-hoc analysis found patients’ scores to be significantly lower on discharge and at followup than on admission. Although HADS-A and HADS-D increased on followup, they were still significantly lower than on admission. The effect sizes for anxiety and depression were moderate on discharge and small at followup, see Table 3.

The proportion of patients with cut-off scores $>8$ (indicating subsyndromal anxiety or depression) and $>11$ (indicating a clinically relevant disorder) were relatively high on admission ($HADS_A ≥ 8$: 61.1%; $HADS_A ≥ 11$: 35.5%; $HADS_D ≥ 8$: 46.5%; $HADS_D ≥ 11$: 22.4%). These scores were lower on both discharge ($HADS_A ≥ 8$: 34.5%; $HADS_A ≥ 11$: 14.3%; $HADS_D ≥ 8$: 22.0%; $HADS_D ≥ 11$: 9.4%) and followup. At FU12, 33% less patients showed signs of subsyndromal or clinically relevant anxiety or depression, compared to admission ($HADS_A ≥ 8$: 42.3%; $HADS_A ≥ 11$: 22.1%; $HADS_D ≥ 8$: 31.9%; $HADS_D ≥ 11$: 16.8%).

3.4.2. Health Locus of Control (GKÜ). Significant changes were found for all three scales of the GKÜ over time (all $P < 0.001$). Discharge and follow-up scores were significantly higher for internal and significantly lower external-social control beliefs, compared to admission (see Table 3). Follow-up scores were also higher for external-fatalistic beliefs.

The ratio of patients’ internal to external control beliefs, suggesting a perceived shift in control beliefs, also increased significantly over time ($P < 0.001$), with all follow-up scores being significantly higher than on admission.

3.4.3. Satisfaction with Health and Life in General (FLZ). Patients’ satisfaction scores are shown in Table 3. ANOVA analysis showed significant time effects ($P < 0.001$), with increases in satisfaction with health found throughout the follow-up period, compared to baseline. Patients’ satisfaction with their lives in general was higher than their satisfaction with their health, on average. The ANOVA results also showed significant time effects for patients’ satisfaction with their lives in general ($P < 0.001$), with significant differences found between baseline and all follow-up measurements. The increase in the latter, however, was only marginally.

3.4.4. Demand on Medical Services. In the posttreatment year (FU12), employed patients’ absenteeism from work fell by
### Table 1: Sociodemographic and clinical data of patients at admission.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Female</th>
<th>Male</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete sample size</strong></td>
<td>(N = 2486)</td>
<td>1994</td>
<td>492</td>
<td></td>
</tr>
<tr>
<td><strong>Age (M ± SD; range)</strong></td>
<td>53.9 ± 14.3; 16–91</td>
<td>53.87 ± 14.3</td>
<td>54.8 ± 14.5</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Family status (% in relationship/married)</strong></td>
<td>(N = 2438)</td>
<td>58.1</td>
<td>54.9</td>
<td>71.2</td>
</tr>
<tr>
<td><strong>Education (% with A-level and higher)</strong></td>
<td>(N = 2414)</td>
<td>26.3</td>
<td>24.0</td>
<td>35.8</td>
</tr>
<tr>
<td><strong>Number of doctors consultations within the past 4 weeks (M ± SD; range)</strong></td>
<td>(N = 2241)</td>
<td>3.9 ± 3.4; 0–25</td>
<td>3.8 ± 3.2</td>
<td>4.2 ± 3.9</td>
</tr>
<tr>
<td><strong>Days of sick leave in the past 12 months (M ± SD; range)</strong></td>
<td>(N = 881)</td>
<td>25.9 ± 56.3; 0–365</td>
<td>23.6 ± 49.2</td>
<td>33.3 ± 74.7</td>
</tr>
<tr>
<td><strong>Days admitted to hospitals within the past year (M ± SD; range)</strong></td>
<td>(N = 914)</td>
<td>21.4 ± 19.3; 2–70</td>
<td>21.2 ± 20.0</td>
<td>22.2 ± 19.1</td>
</tr>
<tr>
<td><strong>Length of stay at the hospital in days (M ± SD; range)</strong></td>
<td>(N = 2486)</td>
<td>14.6 ± 3.6; 4–54</td>
<td>14.7 ± 3.6</td>
<td>14.1 ± 3.4</td>
</tr>
<tr>
<td><strong>Expectancy of improvement (%)</strong></td>
<td>(N = 2398)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Very much</td>
<td>44.8</td>
<td>48.2</td>
<td>31.7</td>
<td></td>
</tr>
<tr>
<td>(ii) Somewhat</td>
<td>37.4</td>
<td>35.5</td>
<td>45.0</td>
<td></td>
</tr>
<tr>
<td>(iii) Unsure</td>
<td>16.6</td>
<td>15.3</td>
<td>21.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(iv) Not so much</td>
<td>1.0</td>
<td>0.7</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>(v) Not at all</td>
<td>0.3</td>
<td>0.4</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td><strong>Major admission diagnosis (%)</strong></td>
<td>(N = 2486)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Arthritis</td>
<td>6.7</td>
<td>7.2</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>(ii) Fibromyalgia</td>
<td>10.8</td>
<td>13.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>(iii) Headache</td>
<td>11.3</td>
<td>12.1</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>(iv) Hypertension</td>
<td>3.4</td>
<td>2.7</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>(v) IBD (Crohn, Colitis)</td>
<td>4.9</td>
<td>3.9</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>(vi) IBS</td>
<td>3.0</td>
<td>3.3</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>(vii) Ischemic cardiac disease</td>
<td>1.2</td>
<td>0.5</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>(viii) Lung diseases</td>
<td>5.5</td>
<td>5.7</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>(ix) Osteoarthritis</td>
<td>9.9</td>
<td>10.5</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>(x) Spinal Pain</td>
<td>18.8</td>
<td>18.2</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>(xi) Pain, others</td>
<td>10.9</td>
<td>10.5</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>(xii) Others</td>
<td>13.7</td>
<td>12.5</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td><strong>Physician rated severity of disease (%)</strong></td>
<td>(N = 2486)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very severe</td>
<td>6.5</td>
<td>6.8</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>49.3</td>
<td>52.4</td>
<td>36.7</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>39.1</td>
<td>37.2</td>
<td>46.8</td>
<td></td>
</tr>
<tr>
<td>Slight</td>
<td>4.2</td>
<td>3.1</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>0.9</td>
<td>0.5</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

M: mean; SD: standard deviation. For several variables, data were inconclusive. For work absenteeism, only scores from patients with full-time or part-time employment were entered.

3.4.5. Improvement of Disease-Related Symptoms. On discharge, almost 80% of the study patients rated their health as at least somewhat improved, with some 60% continuing to do so 12 months later. In contrast, at FU12, a fifth of patients (20%) saw their health as worse than before admission.

3.4.6. Predictors of Improvement in the Primary Outcome Measure. All of patients’ socio-demographic and clinical admission data with significant correlations of $r \geq 0.1$ were entered into the predictor analysis, to determine the factors influencing the changes found in their SF36 physical (PCS) and mental (MCS) component summaries at 3-month followup. The resulting analysis showed that change in patients’ PCS score at FU3 was predicted by their PCS score on admission ($\beta = -0.33$), their internal control beliefs on admission ($\beta = 0.13$), age ($\beta = -0.11$), their MCS score on admission ($\beta = 0.13$), a main diagnosis of a pain versus a...
nonpain condition ($\beta = -0.09$) and being employed ($\beta = 0.09$) (all $P < 0.05$). Patients’ MCS at FU3 was predicted by their MCS score on admission ($\beta = -0.55$), a higher educational level ($\beta = 0.07$), and their satisfaction both with life in general ($\beta = 0.15$), and with health ($\beta = 0.06$) on admission (all $P < 0.05$).

4. Discussion

4.1. Summary of the Results. This observational study investigated changes occurring in patients with chronic conditions following a 2-week inpatient integrative program. The latter combined conventional medicine, complementary medicine and Mind/Body therapies aimed at empowering patients to adopt a healthy lifestyle. The results revealed a small-to-moderate, but sustained improvement in patients’ perceived quality of life, with regard to both its physical and mental health aspects. Patients also reported reduced anxiety and depression, as measured on the Hospital Anxiety and Depression Scale (HADS). At the same time, patients’ internal locus of control increased and their external-social control beliefs diminished. On the other hand, patients’ external-fatalistic control beliefs rose significantly over time. Patients’ satisfaction with their health and lives in general increased. Employed patients reported fewer days’ absenteeism and all patients made fewer doctors’ visits during the posttreatment year. Altogether, patients reported substantial benefit from their two weeks of integrated inpatient treatment.

4.2. Comparisons with the Literature. The above results are in line with those of other studies into the effectiveness of inpatient treatments that include naturopathy and Traditional Chinese Medicine [40–48]. Patients in these other observational trials also showed improved symptoms and health, as well as improved quality of life. The effect sizes were also comparable between these studies, for example, Melchart et al. [47] found effects around $d = 0.5$ for changes to patients’ PCS and MCS after 6 months, changes only marginally larger than those found in the present study. More than two fifths of the patients in the present study (42%) reported improvements of >5 points in the SF-36, which is considered clinically relevant [49]. The effect sizes for the HADS anxiety and depression scales were moderate on discharge and small on followup, although the frequency with which patients scored above the cut-offs for subsyndromal and clinically relevant anxiety and depression each fell by almost a third (33%).

Patients with chronic conditions often suffer from comorbid psychological disorders. Falls in the levels of anxiety and depression that patients reported in this study, following their inpatient treatment may reflect improvements in their overall health. They may also reflect the impact of the psychosocial approaches used in the Mind/Body therapy element of the treatment received.

The regression analysis conducted showed that the change in the SF-36 physical component summary was predicted by patients’ PCS score on admission. Patients with lower PCS scores on admission benefited most, perhaps because they began with very low scores and thus had more room to improve. The effect might also reflect a regression to the mean.

For the MCS at baseline, the link was reversed. The higher patients’ MCS scores were on admission, the more their PCS scores improved at followup. Patients’ pain diagnoses, age, and employment status also proved important in this study. Patients who had nonpain diagnoses were younger and were employed were more responsive, perhaps because

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders at DIS (M ± SD)</th>
<th>Nonresponders at DIS (M ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay at the hospital (in days)</td>
<td>14.8 ± 5.2</td>
<td>13.3 ± 5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Internal control beliefs (GKÜ)</td>
<td>3.0 ± 0.9</td>
<td>2.9 ± 0.9</td>
<td>0.034</td>
</tr>
<tr>
<td>External-fatalistic control beliefs (GKÜ)</td>
<td>2.2 ± 0.9</td>
<td>2.4 ± 0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>7.4 ± 4.2</td>
<td>8.1 ± 4.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders at FU3 (M ± SD)</th>
<th>Nonresponders at FU3 (M ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay at the hospital (in days)</td>
<td>14.8 ± 3.0</td>
<td>14.3 ± 4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>External-fatalistic control beliefs (GKÜ)</td>
<td>2.2 ± 0.9</td>
<td>2.2 ± 0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>7.3 ± 4.1</td>
<td>7.9 ± 4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental component summary (SF-36)</td>
<td>40.2 ± 12.9</td>
<td>38.7 ± 12.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Satisfaction with life in general</td>
<td>3.4 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Subjective health change at discharge (in %)

(i) Much improved                             | 33.2                        | 25.7                          | 0.001 |
(ii) Somewhat improved                         | 47.4                        | 52.4                          |       |
(iii) The same                                 | 15.8                        | 16.5                          |       |
(iv) Somewhat worse                            | 2.7                         | 3.9                           |       |
(v) Much worse                                 | 0.9                         | 1.5                           |       |

DIS: discharge; FU3: 3-month followup; M: mean; SD: standard deviation.
<table>
<thead>
<tr>
<th>Outcome (Questionnaire)</th>
<th>No. of patients</th>
<th>ADM</th>
<th>DIS</th>
<th>FU3</th>
<th>FU6</th>
<th>FU12</th>
<th>Estimated differences* to admission (M; 95% CI)</th>
<th>Estimated effect sizes* (Cohen's d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component summary (SF-36)</td>
<td>(N = 796)</td>
<td>32.9 ± 10.2</td>
<td>37.4 ± 11.7</td>
<td>37.4 ± 12.1</td>
<td>38.0 ± 12.3</td>
<td></td>
<td>5.0; −4.4 to 4.2</td>
<td>4.2; 3.5 to 4.8</td>
</tr>
<tr>
<td>Mental component summary (SF-36)</td>
<td>(N = 796)</td>
<td>39.6 ± 12.8</td>
<td>44.7 ± 12.6</td>
<td>44.8 ± 12.4</td>
<td>45.1 ± 12.7</td>
<td></td>
<td>4.1; 4.9; 4.9; 4.6; 3.8 to 5.4</td>
<td>0.38</td>
</tr>
<tr>
<td>Psychological symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety (HADS-A)</td>
<td>(N = 850)</td>
<td>9.0 ± 4.3</td>
<td>5.7 ± 3.9</td>
<td>6.9 ± 4.4</td>
<td>6.8 ± 4.6</td>
<td>−2.9;</td>
<td>−3.2 to −2.5</td>
<td>−1.7; 2.0 to −1.3</td>
</tr>
<tr>
<td>Depression (HADS-D)</td>
<td>(N = 853)</td>
<td>7.1 ± 4.1</td>
<td>4.4 ± 3.6</td>
<td>5.8 ± 4.3</td>
<td>5.9 ± 4.4</td>
<td>−2.7;</td>
<td>−3.0 to −2.4</td>
<td>−1.6 to −0.9</td>
</tr>
<tr>
<td>Satisfaction with health (FLZ)</td>
<td>(N = 865)</td>
<td>2.2 ± 0.9</td>
<td>—</td>
<td>2.7 ± 1.0</td>
<td>2.7 ± 1.0</td>
<td>2.8 ± 1.0</td>
<td>−0.4 to 0.5</td>
<td>0.5 to 0.7</td>
</tr>
<tr>
<td>Satisfaction with life in general (FLZ)</td>
<td>(N = 868)</td>
<td>3.5 ± 0.9</td>
<td>—</td>
<td>3.6 ± 0.9</td>
<td>3.6 ± 0.9</td>
<td>3.6 ± 0.9</td>
<td>−0.1 to 0.2</td>
<td>0.1 to 0.2</td>
</tr>
<tr>
<td>Control beliefs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control belief internal (GKÜ)</td>
<td>(N = 893)</td>
<td>3.0 ± 0.9</td>
<td>3.6 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>3.3 ± 1.0</td>
<td>0.6; 0.5 to 0.6</td>
<td>0.3; 0.3 to 0.4</td>
</tr>
<tr>
<td>Control belief external-social (GKÜ)</td>
<td>(N = 881)</td>
<td>2.8 ± 1.0</td>
<td>2.7 ± 1.0</td>
<td>2.6 ± 1.0</td>
<td>2.6 ± 1.0</td>
<td>2.6 ± 1.0</td>
<td>−0.1; −0.2 to −0.1</td>
<td>−0.2 to −0.2</td>
</tr>
<tr>
<td>Control belief external-fatalistic (GKÜ)</td>
<td>(N = 877)</td>
<td>2.1 ± 0.8</td>
<td>2.1 ± 0.8</td>
<td>2.2 ± 0.9</td>
<td>2.2 ± 0.8</td>
<td>2.3 ± 0.8</td>
<td>0.0; 0.0</td>
<td>0.1 to 0.2</td>
</tr>
<tr>
<td>Ratio internal/external (GKÜ)</td>
<td>(N = 876)</td>
<td>1.3 ± 0.8</td>
<td>1.6 ± 1.0</td>
<td>1.6 ± 1.0</td>
<td>1.6 ± 1.0</td>
<td>1.6 ± 1.0</td>
<td>0.4; 0.3</td>
<td>0.2 to 0.3</td>
</tr>
<tr>
<td>Demand of medical services</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days of sick leave</td>
<td>(N = 264)</td>
<td>18.9 ± 36.0</td>
<td>8.3 ± 13.1</td>
<td>−10.5; −14.9 to −6.1</td>
<td>−1.0; −0.8 to 6.1</td>
<td>−0.26</td>
<td>−0.26</td>
<td></td>
</tr>
<tr>
<td>Number of doctors' visits</td>
<td>(N = 703)</td>
<td>3.7 ± 3.2</td>
<td>2.3 ± 2.5</td>
<td>2.3 ± 3.0</td>
<td>2.8 ± 3.1</td>
<td>−1.4; −1.7 to −1.2</td>
<td>−1.3; −1.5 to −1.0</td>
<td>−1.3 to −0.7</td>
</tr>
<tr>
<td>Days admitted to a hospital</td>
<td>(N = 202)</td>
<td>23.2 ± 20.3</td>
<td>25.9 ± 21.3</td>
<td>2.7; −0.8 to 6.1</td>
<td>−0.13</td>
<td>−0.13</td>
<td></td>
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</tr>
<tr>
<td>Subjective health change (%)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>(i) Much improved</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) Somewhat improved</td>
<td>30.8</td>
<td>24.8</td>
<td>23.7</td>
<td>27.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iii) The same</td>
<td>49.0</td>
<td>38.3</td>
<td>35.4</td>
<td>31.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iv) Somewhat worse</td>
<td>16.0</td>
<td>25.7</td>
<td>23.4</td>
<td>22.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(v) Much worse</td>
<td>3.1</td>
<td>7.0</td>
<td>8.8</td>
<td>9.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| ADM: admission; DIS: discharge; FU3: 3-month follow-up; M: mean; SD: standard deviation; CI: confidence interval; * estimation from repeated measurement ANOVA. #Effect size calculation was based on estimated differences. $The number of patients included in the analyses may be smaller due to missing data at any measurement time-point, leading to their exclusion within the repeated measurement ANOVA.
they had shorter disease histories and were potentially less impaired than those unable to work. Comparable results have been found for patients with low back pain [50, 51]. Together, these variables explained 12.4% of the variance found, suggesting minor predictive power.

For improvements in patients’ MCS scores, lower MCS scores at admission, higher levels of satisfaction with health and life in general and a higher level of education proved significant. Higher degrees of satisfaction might be linked to greater levels of openness and appreciation which, together with higher levels of education, might incline patients towards psychosocial Mind/Body interventions. All of the selected factors, taken together, explained 24.4% of the MCS change variance found.

An internal locus of control proved the only significant factor predicting change in patients’ PCS scores, but did not influence their MCS scores. Improvements in patients’ physical health were perhaps linked to an increased probability of adopting a healthy lifestyle in patients with a more internal locus of control. Adequate exercise, nutrition, and relaxation are certainly considered important to overall health and mortality [52–54]. Further research is needed to explore the link between patients’ locus of control and their actual behaviours, given that neither external-social nor external-fatalistic control beliefs predicted any study outcomes. Although patients’ external-fatalistic control beliefs increased during inpatient treatment, which was contrary to expectations, this change may reflect the questionable discriminative power of the tool used. The Mind/Body program offered at the Department for Internal and Integrative Medicine, based on similar programs used elsewhere, draws on patients’ acceptance of their health situations. Accepting patients might be mistakenly seen to have high external-fatalistic control beliefs because the questionnaire used cannot distinguish between these two variables. The study data provide no conclusive evidence about this matter. Further studies are therefore needed to evaluate the relationship between patients’ locus of control and their acceptance of their health situations. Data on patients’ posttreatment demands on medical services was also inconclusive, although there was some suggestion of falls in absenteeism and the number of doctors’ visits made.

4.3. Limitations of the Study. This study’s findings are weakened by its observational design; the lack of a control group renders the effects indivisible from nonspecific effects. There may also have been some selection bias, as 11.3% of all treated patients chose not to participate in the study. Another problem resulted from the followup response rate the loss of 50% of the patients at 12 months generating much missing data. Whilst other quality assurance programs have experienced similar response rates [41, 42], some have lost only 25% of their participants [47]. The followup losses experienced in the present study may mean that the reported results reflect a bias in patients’ response behaviours. To detect such a bias, responders’ and nonresponders’ sociodemographic and baseline characteristics were compared. Non-responders were found to have shorter clinic stays (potentially reducing delivery of the study discharge questionnaire), more external-fatalistic control beliefs, higher depression scores and less mental health than responders. They also cited less symptomatic improvement on discharge then responders. Taken together, these comparisons suggest that patients with more disadvantageous control beliefs, greater psychological symptoms and less benefit from treatment were more often lost to followup. The reported effects might therefore be an overestimation and, in part, reflect regression to the mean.

Since neither the patients nor the program has changed for the most part, these data, retrieved about 10 years ago, are still valid and the results generalizable to current conditions. The Clinic still provides internal and external quality assurance program, but with other quality indices.

4.4. Future Research. This study’s results suggest that patients experience benefit from receiving two weeks of integrative inpatient treatment, but more research is needed to confirm and extend them. Future studies should use more rigorous designs, such as randomised controlled trials, to explore links between patients’ sociodemographic, clinical characteristics and selected outcome measures, delving into the nature of and mechanisms behind these links. They should also focus on ways to enhance patient compliance.

5. Conclusion
The results of this study suggest that a 2-week inpatient treatment might sustainably reduce patients’ somatic and psychological symptoms and increase their quality of life; however, conclusions are limited by the observational study design and a high withdrawal rate. Increases in patients’ quality of life were predicted by several variables; the most important being low quality of life at admission. More research is needed for conclusive judgment of integrated inpatient treatment programs’ effectiveness and modes of action.

Conflict of Interests
All authors declare no conflict of interests.

Acknowledgments
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References


Evidence-Based Complementary and Alternative Medicine


Research Article

Clinical Pathways Based on Integrative Medicine in Chinese Hospitals Improve Treatment Outcomes for Patients with Acute Myocardial Infarction: A Multicentre, Nonrandomized Historically Controlled Trial

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Objective. To determine the impact of an integrative medicine clinical pathways (CPs) on the length of in-hospital stay and on outcomes for patients with acute myocardial infarction (AMI). Methods. A multicenter nonrandomized controlled trial enrolling 197 consecutive patients with AMI at eight urban TCM hospitals was conducted between 1 January 2010 and 31 October 2010. These patients were enrolled in the interventional group after the CPs had been implemented. The control group included 405 patients with AMI from eight hospitals; these patients were treated between 1 January 2008 and 31 December 2009, before the CPs were implemented. Outcome measures were the length of hospital stay, costs of medical care, and major cardiovascular events (MACEs) during hospitalization. Results. Compared with the control group, the patients in the intervention group had a shorter length of hospital stay (9.2 ± 4.2 days versus 12.7 ± 8.6 days, P < 0.05), and reduced healthcare costs in hospital (46365.7 ± 18266.9 versus 52866.0 ± 35404.4, P < 0.05). There were statistically significant differences in MACE during the hospitalization period (2.5% versus 6.9%, P = 0.03). Conclusion. These data suggest that the development and implementation of the clinical pathways based in Integrative Medicine could further improve quality of care and outcome for patients with AMI.

1. Introduction

Acute myocardial infarction (AMI) is a serious cardiovascular disease and is a leading cause of death worldwide. In recent years, the AMI incidence and mortality has decreased significantly in America because early reperfusion and drug treatment has been standardized [1]. However, it is estimated that with further economic development, aging of the population, and changes in diet and physical activity in China, the absolute number of AMI events and deaths will increase dramatically in the next two decades [2]. There is also a discrepancy between guideline recommendations and
the current AMI management in most Chinese hospitals [3]. Therefore, strong evidence-based initiatives to improve patient management will be critical to address this challenge.

TCM has been practiced for thousands of years, and it has made great contributions to peoples’ health and wellbeing. Epidemiological data has suggested that Chinese herbal preparations may be beneficial in reducing the mortality from AMI, and TCM treatment was shown to help improve the quality of life for AMI patients [4]. TCM hospitals have the ability to perform reperfusion and to use drugs appropriately, and they are also making progress in their effort to follow the Clinical Guidelines. However, there are still situations that arise when using TCM to treat patients with AMI, including a lack of standardized TCM syndrome diagnosis, the need for syndrome differentiation and treatment standardization, and clinical skills in reperfusion and standardized drug treatment, which require further improvement [5].

Clinical pathways (CPs), also known as critical pathways, are management plans that display goals for patients and provide the sequence and timing of actions necessary to achieve these goals with optimal efficiency. As competition in the healthcare industry has increased, CPs have been widely implemented as a method to reduce variation in care and potentially improve healthcare quality. Cardiovascular medicine in particular is an area in which CPs have been used extensively [6]. The evidence-based Integrative Medicine CPs, developed to improve the quality of healthcare, was based on published guidelines and the best research evidence from TCM and Western medicine [7]. Previous research has suggested that CPs may help to reduce costs while improving the quality of care for AMI patients [8]. However, the effectiveness of Integrative Medicine CPs on improving AMI management is unclear.

In previous studies, we developed CPs based on standardized therapy for AMI Integrative Medicine. The standardized management included thrombolysis therapy, primary percutaneous coronary intervention (PCI), antiplatelet and anti-ischemic therapy, and TCM therapy (such as Astragalus injection and compound Danshen dripping pills) to benefit Qi and to activate blood. A small single-center trial suggested that the CPs could reduce the length of the hospital stay and in-hospital health care costs for patients with AMI who underwent PCI [9]. The purpose of this study is to assess further the influence of the Integrative Medicine CPs on care quality and outcomes among AMI patients in TCM hospitals, in a multicenter nonrandomized controlled trial.

2. Methods

2.1. Study Design and Setting. This trial is a multicenter, nonrandomized retrospective study in eight hospitals (Guangdong Provincial Hospital of TCM; Shuguang Hospital of Shanghai University of TCM; Yueyeyang Hospital of Integrated Medicine of Shanghai University of TCM; Oriental Hospital of Beijing University of TCM; Jiangsu Provincial Hospital of TCM; 3rd Affiliated Hospital of Guangxi College of TCM; Wuyi Hospital of TCM of Jiangmen city; Zhongshan Hospital of TCM) (Figure 1). This study (2008GL-35) was approved by the Ethical Committee of Guangdong Provincial Hospital of Chinese Medicine.

2.2. Study Patients. Inclusion criteria for this study included patients with acute myocardial infarction (onset of chest pain ≤ 24 h) admitted to emergency, and ages ranging from 18 to 80 years old who agreed to emergency reperfusion therapy (including intravenous thrombolysis or PCI). Exclusion criteria included serious mechanical complications (such as left ventricular free wall rupture, ventricular septal perforation, papillary muscles, and adjacent chordal rupture), concomitant diseases with aortic dissection, acute pulmonary embolism, severe liver failure, renal failure, mental illness, malignancy, hematopoietic tumor, nervous system primary diseases, and pregnancy or lactation [10].

In our preliminary study, we found that Qi deficiency and blood stasis were the main TCM syndromes for AMI [11]. In order to implement the AMI CPs conveniently in all hospitals, we considered Qi deficiency and blood stasis as the basic syndrome occasionally accompanied with Phlegm, Yin-deficiency or Yang-deficiency of a single TCM syndrome element. The diagnostic criteria of the Qi deficiency and blood stasis were based on the TCM standard of coronary heart disease, which was formulated by the Cardiovascular Society of the National Association of Integrative Medicine [12].

Sample size was calculated using PEMS 3.1 for Windows software (Sichuan University, Chengdu). The length of in-hospital stay was considered to be one of the most important factors in the calculation of sample size. The standard deviation (SD) of the length of in-hospital stay for the conventional treatment group was 6 days [13], and it was considered clinically significant when the length of in-hospital stay was reduced by 4 days. If \( \alpha = 0.05 \), power = 0.90, and \( \beta = 0.10 \), the estimated total sample size is 256 patients. Taking into account a 15% dropout rate, the total sample size is 294 patients.

In the study protocol, the planned sample size was 240 consecutive patients who were enrolled into the intervention groups after pathway implementation. There were 450 consecutive patients, admitted to the eight hospitals between 1 January 2008 and 31 December 2009, prior to CP implementation, who were included as a historical control group. The Guangdong Provincial Hospital of TCM planned to enroll 100 patients for the intervention group and 100 patients for the control group. Additionally, each of the other 7 hospitals planned to enroll 20 patients for the intervention group and 50 patients for the control group.

2.3. Intervention. The patients in the historical control group received conventional management determined by a physician, which included Western medicine and nonstandardized TCM therapy. The patients in the intervention group were treated according to the standardized management plan as determined by the CPs. The Western medical treatment consisted of reperfusion therapy and aspirin, clopidogrel, low molecular weight heparin (LMWH), \( \beta \) receptor blocker, and angiotensin-converting enzyme inhibitors (or angiotensin II receptor blocker), according to the 2007 updated guidelines.
for the management of patients with ST-segment elevation myocardial infarction (STEMI) [14].

For Qi deficiency and blood stasis, the standard TCM technique performed in the intervention group was 30 mL Astragalus injection (Astragalus, Zhengda Qingchunbao pharmaceutical company) mixed with 250 mL 5% glucose, which was infused intravenously once per day, and 10 particles of compound Danshen dripping pills (Salvia, Pseudoginseng, Borneol, Tasly Group) 3 times a day. Instead of Astragalus injection, Gualou Xiebai Banxia Tang (Trichosanthes 15 g, Bulbus allii macrostemonis 20 g, Pinelliae 15 g) was administered to patients with cold-phlegm syndrome, Wen Dan Tang (Poria 15 g, Dried tangerine peel 10 g, Pinellia 15 g, Caulis bambusae in taenia 15 g, Fructus aurantii 15 g) was administered for patients with heat-phlegm syndrome, 30 mL Shen Mai injection (Ginseng, Radix, Zhengda Qingchunbao pharmaceutical company) mixed with 5% glucose injection infusion was administered for Yin-deficiency, and 30 mL Shenfu (tuber, red ginseng, Sanjiu Ya pharmaceutical company) in 5% glucose intravenous infusion was administered for Yang-deficiency. All the treatments were administered for 1 week.

2.4. Outcome Measures. The primary outcome was the length of the in-hospital stay. Discharge standard, for patients to be discharged from the hospital with stable life signs (hemodynamic, electrocardiogram, and cardiac function) and without the symptoms of myocardial ischemia, was determined according to “Clinical pathways of ST-segment elevation myocardial infarction” (2009 version) by the Medical Administration of the Ministry of Health [15]. The secondary outcome was the major cardiovascular events (MACE) and economic evaluation during the period of hospitalization. MACE is defined as death, nonfatal myocardial infarction, stent thrombosis or target vessel revascularization. Total medical costs include treatment costs, operation costs, drug costs, nursing costs, inspection fees, and bed charges. All data were analyzed using SPSS 17.0 (IBM Corporation, Armonk). Measurement data were presented as mean ± ST. Count data were presented as the frequency and constituent ratio, and analyzed using the chi-square test or the exact test exact probability method. For measurement data, two samples were compared using the Mann-Whitney U test. The statistical tests used were two-sided tests, and $P < 0.05$ was considered a statistically significant difference.

3. Results

Between 1 January 2010 and 31 October 2010, a total of 250 consecutive patients fulfilling the inclusion criteria were initially evaluated as the intervention group, and 53 patients were excluded because of severe mechanical complications or severe liver failure and renal failure. A total of 450 patients admitted to eight hospitals from 1 January 2008 to 31 December 2009 were screened for the historical control group, and 45 patients were excluded because of severe mechanical complications or concomitant diseases. As a result, there were 197 patients enrolled into the intervention group and 405 patients enrolled into the historical control group.

3.1. Clinical Features in the Intervention and Historical Control Groups. Of the 602 patients, 514 (85%) were admitted for ST-segment elevation myocardial infarction (STEMI) and 71
Table 1: Demographic and clinical features of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group (n = 197)</th>
<th>Historical control group (n = 405)</th>
<th>χ² (Z)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>149 (75.6)</td>
<td>308 (76.0)</td>
<td>0.01</td>
<td>0.91</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63.42 ± 11.87</td>
<td>63.89 ± 13.20</td>
<td>−0.49</td>
<td>0.63</td>
</tr>
<tr>
<td>Hypertension</td>
<td>109 (55.3)</td>
<td>214 (52.8)</td>
<td>0.33</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37 (18.8)</td>
<td>55 (13.6)</td>
<td>2.77</td>
<td>0.10</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>58 (29.4)</td>
<td>65 (16.0)</td>
<td>5.88</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous coronary disease</td>
<td>14 (7.1)</td>
<td>22 (5.4)</td>
<td>0.66</td>
<td>0.42</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>20 (10.2)</td>
<td>34 (8.4)</td>
<td>0.01</td>
<td>0.93</td>
</tr>
<tr>
<td>Current smoker</td>
<td>106 (53.8)</td>
<td>196 (48.4)</td>
<td>4.96</td>
<td>0.03</td>
</tr>
<tr>
<td>Family history of coronary disease</td>
<td>16 (8.1)</td>
<td>65 (16.0)</td>
<td>10.13</td>
<td>0.00</td>
</tr>
<tr>
<td>Clinical pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>176 (89.3)</td>
<td>338 (87.1)</td>
<td>0.61</td>
<td>0.44</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>21 (10.7)</td>
<td>50 (12.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac function (Killips classification)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level I</td>
<td>99 (64.7)</td>
<td>275 (69.1)</td>
<td>−0.96</td>
<td>0.34</td>
</tr>
<tr>
<td>Level II</td>
<td>31 (20.3)</td>
<td>70 (17.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level III</td>
<td>10 (6.5)</td>
<td>23 (5.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level IV</td>
<td>13 (8.5)</td>
<td>30 (7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous thrombolysis</td>
<td>8 (4.1)</td>
<td>27 (6.7)</td>
<td>1.64</td>
<td>0.20</td>
</tr>
<tr>
<td>Emergency PCI</td>
<td>189 (95.9)</td>
<td>378 (93.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>64 (34.0)</td>
<td>102 (30.0)</td>
<td>−0.37</td>
<td>0.72</td>
</tr>
<tr>
<td>Two branch</td>
<td>56 (29.8)</td>
<td>116 (34.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three branch</td>
<td>65 (34.6)</td>
<td>122 (35.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis &lt; 50%</td>
<td>3 (1.6)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent implantation</td>
<td>1.19 ± 0.63</td>
<td>1.25 ± 0.90</td>
<td>−0.11</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Values are given as number of patients (%) or mean ± SD.

3.2. Drug Treatments. Comparing the main Western medicine drug treatments in both groups, there were no statistically significantly differences among antiplatelet therapy (aspirin, clopidogrel), beta receptor blockers, ACEI (or ARB), and nitrate (P > 0.05). However, the prescribing frequency of low molecular weight heparin (LMWH) and statins in the intervention group was higher in the intervention group than in control group (P < 0.05; Table 2).

The rate of Chinese medicine decoction use in the treatment group was significantly higher than in the control group (P < 0.01). There were also significant differences among Compound Danshen dripping pills, Qi-benefitting agents, and blood-activating agents (P < 0.05). The frequency of injections benefitting Qi was higher in the treatment group than in the control group, whereas injections...
promoting blood circulation had a lower frequency in the treatment group compared to the control group (Table 3).

3.3. The Average Length of In-Hospital Stay. The length of in-hospital stay showed a skewed distribution in both groups, and therefore a nonparametric test was used. The average length of stay in the treatment group was 3.5 days less than that of the control group, which was statistically significant \((P < 0.01; \text{Table 4})\).

3.4. The Total In-Hospital Costs. The average hospitalization costs had a skewed distribution in both groups, so a nonparametric test was used. In the intervention group, the average total in-hospital charges were ¥48047.3 when it was adjusted by the price index, which reduced to ¥4820.00 compared with the control group. There were statistically significant differences between intervention groups and control groups. \((P < 0.01; \text{Table 5})\).

3.5. The Incidence of Major Cardiovascular Events (MACEs). The major adverse events of death, nonfatal myocardial infarction, stent thrombosis, and target vessel revascularization (TVR) occurred in 2.5% of patients (5 of 197) in the intervention group and in 6.9% (28 of 405) of those in the control group during hospitalization \((P = 0.03; \text{Table 6})\). Three patients in the intervention group died due to cardiac shock, and 22 patients died in the historical control group due to cardiac shock (10 patients), severe heart failure (4 patients), ventricular fibrillation (5 patients), and multiple organ dysfunction syndrome (3 patients). The majority of MACE incidents were death during hospitalization (1.5% versus 5.4%, \(P = 0.03\)). There was no statistical difference in nonfatal myocardial reinfarction, stent thrombosis, and TVR between two groups (Table 6).

4. Discussion

The number of patients in China who develop and present to hospitals with acute coronary syndrome will increase in the near future. China's fee-for-service payment system has resulted in a rapid cost increase, inefficiencies, poor quality, unaffordable health care, and an erosion of medical ethics [16], and improvement of patient management, together with health system reform, is urgently required. CPs are management plans that specify goals for patients and provide the sequence and timing of the actions necessary to achieve these goals with optimal efficiency. Several areas for improving patient care using CPs have been identified, including increasing the use of guideline-recommended medications, reducing variation in care, targeting the use of cardiac procedures, and reducing the length of the hospital stay [17]. Therefore, the Ministry of Health in China has encouraged the implementation of CPs in cardiovascular disease to control medical cost and to improve healthcare quality.

To standardize the AMI treatment-based integrative medicine in TCM hospitals, we conducted this study and evaluated the efficacy of CPs in eight TCM hospitals. In our study, there were more patients with hyperlipidemia or who were current smokers, and fewer patients with a family history of coronary disease in the intervention group than in the historical control group. These data indicate that, with diet and lifestyle changes in China, smoking and hyperlipidemia have emerged as key risk factors leading to AMI, especially for younger people.

4.1. Length of in-Hospital Stay. A previous epidemiological study showed that the average length of hospital stay was from 11.6 to 13.7 days in China for the patients with AMI who were admitted to hospital within 12 h after onset of chest pain [13]. Our trial indicated that the average length of stay in the treatment group (after implementation of CPs) was 3.5 days less than the control group \((9.2 \pm 4.2 \text{ days versus } 12.7 \pm 8.6 \text{ days}, P < 0.01)\). The length of the hospital stay after AMI depends on many factors, including department policies, insurance coverage, age, and patients’ complications. However, the length of the hospital stay depended more on the damaged myocardium duration of recovery because there were few changes in the medical policy and insurance coverage from 2008 to 2010, and there are no statistical differences in age, cardiac function, and other clinical characteristics between the interventional and historical groups. In this study, we consistently followed the hospital discharge standards, which ensured that the patients would be discharged from hospitals in a stable condition. Therefore, the reduction in the length of stay observed in this study is attributed to the potential improvement of healthcare quality and the decreased variation in care conferred by the use of CPs.
guidelines and to close the gap between the practice and the
to improve health providers' adherence to published AMI
tively, which revealed that CPs have the potential capacity
were lower than in the historical control group, respectively
or statin
usage rate of these therapies in TCM hospitals, data has
occur in patients with AMI. Despite the increased
mechanism of accelerating cardiac function recovery
using Qi-benefitting and blood-activating compounds. Also,
ical. Our study showed that, after the price index adjustment,
the total medical expenditure during hospitalization in the
intervention group was reduced compared to the historical
group. This suggested that the CPs based on integrative
medicinal could decrease the cost of hospitalization through
reduction in the length of a patient's in-hospital stay and in
the potential overprescription of drugs and diagnostic tests.

4.2. Total In-Hospital Medical Costs. China's current strategy
to improve payment for health services has made some
positive changes; however, the rapid increase in health expendi-
ture and inappropriate treatment concerning individuals
and governments resulting from China's fee-for-service
payment and a price schedule that overpays for drugs and
high-technological diagnostics tests has led providers to
overprescribe drugs and diagnostic tests [18]. Control of the
high out-of-pocket healthcare payments when patients have
inadequate insurance coverage in many parts of China is crit-
cal. The study showed that, after the price index adjustment,
the total medical expenditure during hospitalization in the
intervention group was reduced compared to the historical
group. This suggested that the CPs based on integrative
medicinal could decrease the cost of hospitalization through
reduction in the length of a patient's in-hospital stay and in
the potential overprescription of drugs and diagnostic tests.

4.3. Health Providers’ Compliance with the Guideline. Despite
strong evidence for the benefits of AMI patient management
using antiplatelet agents, LMWH and lipid-lowering ther-
pies, reports from the CPACS study indicated that physician
compliance with guideline recommendations and sustained
use of medical therapy remains suboptimal [19]. Statins
and LMWH are effective in reducing mortality and serious
coronary events in patients with AMI. Despite the increased
usage rate of these therapies in TCM hospitals, data has
shown a lower prescribing rate in TCM hospitals than in
Western Medicine hospitals [20]. Our results demonstrate
that the use rates of LMWH (100% versus 89%) or statin
lipid-lowering drugs (100% versus 96%) in the intervention
group were higher than in the historical control group, respec-
tively, which revealed that CPs have the potential capacity
to improve health providers' adherence to published AMI
guidelines and to close the gap between the practice and the
guideline. However, the prescribing frequency of β receptor
blockers and ACE inhibitors were not as high as expected in
the intervention group (81% and 82%, resp.). These findings
are not unique to TCM hospitals; data from CPACS has
consistently demonstrated that β receptor blockers and ACE
inhibitors are not being used as often or as long as they
should be, which reflects the physicians' fears that these drugs
may lead to dynamic deterioration in patients with cardiac
shock, acute heart failure, or low blood pressure [19].

4.4. Management of TCM after Reperfusion Therapy. TCM
plays an important role in the current treatment of AMI
especially in TCM hospitals. In the past 10 years, blood-
activating had emerged as a main TCM method for treating
patients with AMI, thus leading to wide prescribing of
Chinese medicine intravenous preparations that are clinical
blood-activating agents [5]. As a result, there is more usage
of blood-activating intravenous agents in the historical group
(63%), as shown in Table 3. However, in our previous study
that related the distribution and evolution of syndrome
elements during the perireperfusion period, we found that
reperfusion treatments play a vital role in activating circula-
tion in the TCM theory, and that Qi deficiency and blood
stasis are the main syndromes after reperfusion therapy
[11]. An analysis of 5284 patients with coronary artery
disease indicated that the top two TCM patterns were blood
stasis (79.3%) and Qi deficiency (56.5%) [21]. Therefore,
Qibenefitting and blood activating should become the main
TCM treatment, replacing blood-activating alone. In this
study, Qibenefitting intravenous agents (e.g., Astragalus,
Shen Mai injection and Shenfu injection) and compound
Danshen dripping pills were used as the standardized TCM
management after reperfusion. Thus, it is reasonable that
the rate of use of these agents in intervention group are
higher than in the historical group (P < 0.01). Other trials
indicated that Astragalus injection was effective in reversing
left ventricular remodeling and improving left ventricular
function in patients with AMI [22], and that Salvia miltior-
rhiza extract (the main ingredients of compound Danshen
dripping pills) affords protection against isoproterenol-
induced myocardial infarction [23], which demonstrated the
possible mechanism of accelerating cardiac function recovery
using Qi-benefitting and blood-activating compounds. Also,
CPs application based on integrative medicine guarantees an
increase in the standardized usage of TCM therapy (97% versus
84%).

4.5. Major Adverse Cardiac Events. Despite wide implement-
tion of CPs in cardiovascular disease, no controlled study
has shown that CPs could reduce the incidence of the death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>N</th>
<th>( \bar{x} \pm s )</th>
<th>M</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total charges (¥)</td>
<td>Intervention</td>
<td>197</td>
<td>48047.3 ± 18929.4</td>
<td>44198.7</td>
<td>1.83</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>405</td>
<td>52866.0 ± 35404.4</td>
<td>46157.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total charges adjusted by price index (¥)</td>
<td>Intervention</td>
<td>197</td>
<td>46365.7 ± 18266.9</td>
<td>42651.7</td>
<td>2.94</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>405</td>
<td>52866.0 ± 35404.4</td>
<td>46157.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Individual and combined outcome measure of MACE occurrence during hospitalization.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group</th>
<th>Historical group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3 (1.5)</td>
<td>22 (5.4)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1 (0.5)</td>
<td>1 (0.2)</td>
<td>0.55*</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1 (0.5)</td>
<td>2 (0.5)</td>
<td>1.0*</td>
</tr>
<tr>
<td>TVR</td>
<td>0 (0)</td>
<td>3 (0.7)</td>
<td>0.56*</td>
</tr>
<tr>
<td>Total</td>
<td>5 (2.5)</td>
<td>28 (6.9)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Using the exact probability method; MI: myocardial infarction; TVR: target vessel revascularization.
or MACE in patients with AMI. Our research indicated that, compared with the historical group, the incidence of death and MACE during hospitalization was lower in the intervention group compared to the control group (1.5% versus 5.4%, 2.5% versus 6.9%, resp., \( P < 0.05 \)). The reasons for this encouraging outcome are complex. Multiple factors including an increase in prescribing drugs, recommended by AMI guidelines, standardized use of TCM based on Qi-benefitting and blood-activating, and a decrease in the variation in care attributed to an improvement in healthcare.

5. Conclusions

Integrative medicine treatment, combining TCM and conventional medicine, has been the most representative characteristic for patients with coronary heart disease in China, especially those in TCM hospitals. We found that, in the current era of published treatment guidelines, implementation of the CPs based on the standardized therapies of integrative medicine could further improve guideline compliance and overall quality of care by reducing the length of stay and medical cost for patients with AMI in Chinese hospitals.

6. Limitations of This Study

Although our study revealed the potential improvements in patient outcome by the development and implementation of CPs for AMI patients in China, there are several limitations of the study. First, the duration of the study period was short because of budget limitations, which leaves uncertainty in the long-term outcome of patients with AMI. Second, this study used a nonrandomized retrospective trial design, which may not fully reflect the improvement of CPs on the quality of health care due to potential changes in insurance coverage or policy. Therefore, multicenter large-scale randomized studies are needed to assess prospectively the differential effects of CPs based on integrative medicine versus CPs only based on western medicine.

Conflict of Interests

None of authors received funding or research grants from the relevant drug manufacturers in this research. The authors declare that they have no conflict of interests.

Author’s Contribution

All authors contributed substantially to one or more of the following activities: study design, study conduct, data analysis, interpretation of data, and writing of the manuscript.

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