Osteopathic Medicine in Four Chronic Musculoskeletal Pain Diseases: An Observational Trial with Follow-Up

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Keywords

Chronic neck pain · Chronic low back pain · Chronic shoulder pain · Chronic knee pain · Osteopathic medicine

Abstract

Background and Aim: Patients with chronic musculoskeletal pain diseases (CMPDs) often use osteopathic medicine (OM), although the changes in patients with pain diseases are still insufficiently investigated. This study aimed to observe changes along and after OM in addition to routine care on pain, functioning, and quality of life in patients with four CMPDs. **Methods:** In this observational trial with follow-up, patients suffering from chronic neck pain (CNP, $n = 10$), chronic low back pain (CLBP, $n = 10$), chronic shoulder pain (CSP, $n = 10$), or chronic knee pain (CKP, $n = 10$) received up to six OM sessions in addition to routine care. **Results:** A total of 40 patients (73% female, mean age 47.7 ± 8.3 years, mean pain intensity 59.4 ± 12.5 mm, measured by a visual analog scale [VAS] 0–100 mm) were included. After 26 weeks, there was an improvement in the VAS pain score in the whole population (mean difference to baseline -33.1 mm [95% CI -40.5 to -25.7]), as well in the patients with the four diseases: CNP (-33.7 mm [-54.7 to -12.6]), CLBP (-28.2 mm [-47.9 to -8.4]), CSP (-32.4 [-46.8 to -18.0]), and CKP (-38.1 mm [-49.1 to -27.0]). Regarding disease-specific outcomes, we found improvements in CNP, as measured by the neck disability index (scale 0–50; mean difference -3.6 [-9.0 to 1.9]), CLBP, as measured by the low back pain rating scale (scale 0–60; -3.4

[-12.5 to 5.7]), CSP, as measured by the disabilities of the arm, shoulder and hand score (scale 0–100; -13.4 [-23.1 to -3.7]), and CKP, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (scale 0–96; -13.0 [-23.5 to -2.5]). These improvements persisted through week 52. No adverse events were observed. **Conclusion:** The study observed beneficial changes along and after the OM treatment in addition to routine care in patients with four different CMPDs. High-quality, multicenter randomized controlled trials are strongly needed to compare the effectiveness of OM and standard care interventions in treating CMPDs in the future. We have provided sufficient data for sample size calculations for these trials.

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Osteopathische Medizin in vier chronischen muskuloskeletalen Schmerzerkrankungen: Eine Beobachtungsstudie mit Follow-up

Schlüsselwörter

Chronische zervikale Schmerzen · Chronische lumbale Schmerzen · Chronische Schulterschmerzen · Chronische Kniebeschmerzen · Osteopathische Medizin

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Zusammenfassung

Hintergrund und Ziel: Patienten mit chronischen muskuloskeletalen Schmerzerkrankungen (CMPDs) nutzen oft osteopathische Medizin (OM), obwohl die Veränderungen bei Patienten mit Schmerzerkrankungen noch unzureichend untersucht sind. Ziel dieser Studie war es, Veränderungen während und nach der OM, in Ergänzung zur Routineversorgung, auf Schmerzen, Funktionsfähigkeit und Lebensqualität bei Patienten mit vier CMPDs zu beobachten. **Methoden:** In einer Beobachtungsstudie mit Follow-up erhielten Patienten, welche an chronischen zervikalen Schmerzen, (CNP, $n = 10$), chronischen lumbalen Schmerzen (CLBP, $n = 10$), chronischen Schulterschmerzen (CSP, $n = 10$), oder chronischen Knieschmerzen (CKP, $n = 10$) litten, bis zu sechs OM Behandlungen zusätzlich zur Routinebehandlung. **Ergebnisse:** Insgesamt wurden 40 Patienten (73% Frauen, mittleres Alter $47,7 \pm 8,3$ Jahre) mit einer mittleren Schmerzintensität von $59,4 \pm 12,5$ mm, gemessen auf einer Visuellen Analog Skala (VAS, 0–100 mm) eingeschlossen. Nach 26 Wochen bestand eine Verbesserung auf der VAS Schmerz in der Gesamtpopulation (mittlere Differenz zu Baseline $-33,1$ mm [95% KI $-40,5; -25,7$]), als auch bei den Patienten in allen vier Erkrankungen: CNP ($-33,7$ mm [$-54,7; -12,6$]), CLBP ($-28,2$ mm [$-47,9; -8,4$]), CSP ($-32,4$ [$-46,8; -18,0$]), und CKP ($-38,1$ mm [$-49,1; -27,0$]). Hinsichtlich krankheitsspezifischer Zielparmeter fanden wir Verbesserungen im CNP, gemessen mittels Neck Disability Index (Skala 0–50; mittlere Differenz $-3,6$ [$-9,0; 1,9$]), CLBP, gemessen mittels Low Back Pain Rating Scale (Skala 0–60; $-3,4$ [$-12,5; 5,7$]), CSP, gemessen mittels Disabilities of the Arm, Shoulder and Hand Score (Skala 0–100; $-13,4$ [$-23,1; -3,7$]) und CKP, gemessen mittels Western Ontario and McMaster Universities Osteoarthritis Index (Skala 0–96; $-13,0$ [$-23,5; -2,5$]). Die Verbesserungen hielten bis zur Woche 52 an. Es wurden keine unerwünschten Ereignisse beobachtet. **Schlussfolgerung:** Die Studie beobachtete positive Veränderungen während und nach der OM-Behandlung, in Ergänzung zur Routineversorgung, bei Patienten mit vier verschiedenen CMPDs. Qualitativ hochwertige, multizentrische randomisierte kontrollierte Studien sind dringend erforderlich, um die Wirksamkeit von OM-Behandlungen und Standardbehandlungen bei der Behandlung von CMPDs in Zukunft zu vergleichen. Wir haben ausreichende Daten für die Berechnung der Stichprobengröße für diese Studien zur Verfügung gestellt.

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Introduction

Low back pain, neck pain, and chronic musculoskeletal pain diseases (CMPDs) in general lead to a large disease burden globally, and CMPDs constitute one of the leading causes of ill health [1, 2]. The 12-month prevalence of chronic knee pain (CKP) among patients aged 50 years and older treated by general practitioners was reported to be 25.3% [3]. In a German cross-sectional study ($n = 2,510$ participants), the 3-month prevalence was 25% for chronic low back pain (CLBP), 18% for chronic neck pain (CNP), 11% for chronic shoulder pain (CSP) in the right shoulder, and 9% for CSP in the left shoulder [4]. These CMPDs are recommended to be treated by a multimodal regime, including analgesics, educational interventions, exercise, and manual treatments [5–13]. However, long-term medication with analgesics might result in adverse events, and there is growing interest in non-pharmacological treatment options, including treatments originating from complementary and integrative medicine [14–17].

Osteopathic medicine (OM) is a component of complementary and integrative medicine. In an Australian adult population, OM was reported to be used by 4.6% of the patients within the last 12 months ($n = 1,067$ interviews) [18]. Patients seek OM mostly for pain symptoms not only in the lower back (36%) and neck (15%) but also in the shoulder (7%) [19]. OM relies on manual contact for diagnosis and treatment and emphasizes the structural and functional integrity of the body, including skeletal, arthrodiagonal, and myofascial structures and related vascular, lymphatic, and neural elements [20]. These structures include the musculoskeletal, visceral, and so-called craniosacral system. In Europe, OM is commonly administered by nonphysicians (in Germany, often physiotherapists and “Heilpraktiker” [healing practitioners]) or physicians as a diagnosis-related and individualized treatment (osteopathic manipulative treatment) and additionally offers self-training instructions for postural improvement. There is some evidence that OM might be effective in treating CMPDs. Previous studies have indicated that OM is effective in relieving pain in patients with CNP [21], relieving pain and improving function in patients with CLBP [22, 23], and relieving shoulder pain [24, 25]. Further, unpublished randomized controlled trials (RCTs) suggest beneficial effects of OM for shoulder pain [26] and knee pain [27].

However, until now, to the best of the authors’ knowledge, a prospective observation of six routine OM treatments in patients with various CMPDs; outcomes for pain, quality of life, disease-specific function; restrictions in activities of daily living (ADL); and the utilization of additional therapies over a long follow-up period has not been published.

The aims of this observational trial with follow-up were to assess data on pain, functioning, and quality of life in patients suffering from CNP, CLBP, CSP, or CKP, who received OM in addition to German physician routine care setting, and to investigate the study feasibility. A further aim was to provide sufficient data for sample size calculations for future RCTs.

Methods

Study Design and Setting

The observational trial with follow-up included 40 adult patients, with 10 patients in each of the four groups of CMPDs (CNP, CLBP, CSP, or CKP). The outcomes were assessed after 12, 26, and 52 weeks. The study was performed at the outpatient clinic for Integrative Medicine of the Charité – Universitätsmedizin in Berlin, Germany.

Patients

Patients were recruited by the website of the outpatient department for integrative medicine and the intranet of Charité – Universitätsmedizin Berlin. Patients between 30 and 65 years of age with a clinical diagnosis of CNP, CLBP, CSP, or CKP (disease duration with the specific pain of at least 12 weeks) and an average visual analog scale (VAS) score for pain intensity (0–100 mm, 0 = no pain, 100 = worst imaginable pain) of at least 40 mm within the last 7 days with respect to the diagnosis were included. The main exclusion criteria were a history of OM treatment within the last 12 months; musculoskeletal pain due to known malignant diseases, infections, a previous accident, known or suspected primary or secondary bone tumor, known vascular anomaly, peripheral or central neurological symptoms, rheumatic diseases, or the presence of implants/endoprostheses in the respective body region; a body mass index higher than 30; the intake of centrally acting analgesics; and the presence of pregnancy or lactation.

Exposure

After inclusion, the patients received six individualized diagnosis-related OM treatment sessions that lasted 45 min each, with 3- to 4-week intervals (during 26 weeks), in addition to routine care. An on-demand dose of 500 mg paracetamol up to four times daily was provided in the first 26 weeks. The patients were discouraged from taking analgesics other than paracetamol. No changes were made to the other conventional or complementary therapy regimens received by the patients. The diagnostics method, treatment strategy, and treatment interval were intentionally made to be the same as those usually used in our outpatient clinic for integrative medicine. At the beginning of each session, a short anamnesis and physical examination were performed to determine the OM treatment strategy for the respective session. For the treatment techniques performed for the musculoskeletal, visceral, and craniosacral systems, the patients were treated in a standing, sitting, or lying position with or without active participation. Postural and ergonomic advice was included. The OM treatment was administered by a medical doctor who specialized in orthopedic surgery (G.R.), completed a 5-year part-time OM training program (1,350 h), holds an MSc degree in osteopathy, and had long-term experience in OM treatment.

Outcome Parameters

All parameters were measured at baseline and after 12, 26, and 52 weeks using standardized questionnaires, including validated

patient-reported outcome measurements. Because this is an exploratory study, no primary outcome parameters were determined. All patients rated their average perceived pain in the respective body region within the last 7 days using a VAS [28]. For all CMPDs, the minimal clinically important difference (MCID) between baseline and 26 weeks (after 6 treatments) was considered to be 15 mm [29, 30]. The criteria for a substantial clinical benefit (SCB) was considered to be 26.5 mm [31]. Health-related quality of life was measured by the 12-item short form health survey (SF-12), with an MCID of 5 points [32–35].

In addition, for each diagnosis group, a disease-specific outcome parameter, listed below, was measured. In patients with CNP, neck function was assessed by the neck disability index (NDI, scores ranging from 0 to 50, MCID of 3.0 points, SCB of 8.4 points) [31, 36, 37]. In patients with CLBP, pain was evaluated with the pain subscale of the low back pain rating scale (scores ranging from 0 to 60, MCID of 1.2 points) [38–40]. In patients with CSP, upper extremity function was assessed by the disabilities of the arm, shoulder and hand questionnaire (DASH, scores ranging from 0 to 100, MCID of 8 points in the total score) [41–43]. In addition, the DASH includes an optional questionnaire module for sports/music that does not influence the DASH total score. In patients with CKP, knee function was evaluated by two outcome measurements, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, total scores ranging from 0 to 96, MCID of 10 points in the total score) [44–47] and the Lequesne index (total scores ranging from 0 to 24, MCID of a 40% change in each score) [48–51].

Furthermore, the following parameters related to the respective CMPD with respect to the last 4 weeks were assessed: days with restrictions in activities of daily living (ADL), analgesic intake (reported as the number of patients taking analgesics), and the use of additional therapies. Furthermore, treatment expectations (“highly effective,” “effective,” “slightly effective,” “not effective”) and outcome expectations (“healing,” “substantial improvement in symptoms,” “modest improvement in symptoms,” “no improvement”) were rated by the study physician and by the patients. In addition, parameters related to the safety of OM, including therapy-related adverse events and serious adverse events, were evaluated.

Statistical Analysis

As this was an observational trial with follow-up, no sample size calculation was performed. A total of 10 patients per CMPD group was considered sufficient to achieve the objectives of the study. The collected data were evaluated descriptively: mean values, SDs, medians, and interquartile ranges, additionally in non-normally distributed data, and frequencies and percentages for the entire group and by CMPD group. The pre- and posttreatment outcome parameters were exploratively compared by mean differences. All confidence intervals were two-sided. The results are presented descriptively. The evaluation was carried out according to the intention-to-treat principle with the full analyses set and without the substitution of missing values. The statistical analysis was performed using SAS software, version 9.4 [52], and R, version 3.6.3 [53].

Results

Patients

Among the 91 eligible patients, 40 were enrolled (as planned, with 10 patients in each of the 4 CMPD groups, CNP, CLBP, CSP, and CKP) between June 2015 (first pa-

Fig. 1. Recruitment, treatment, and follow-up of patients with chronic neck pain, chronic low back pain, chronic shoulder pain, and chronic knee pain.

tient included) and January 2017 (last patient included) (Fig. 1). The group of patients with CLBP was complete first (January 2016), followed by the groups CNP (July 2016), CKP (October 2016), and finally CSP (January 2017). Two patients (one with CLBP and one with CSP) did not return the questionnaires after 52 weeks. There were no other patients lost to follow-up. To return the questionnaires one reminder had to be sent to 22 patients after 12 weeks, 19 patients after 26 weeks, and 21 patients after 52 weeks. During the entire study period, a total of 34 patients had to be reminded to return the questionnaires. Apart from that, the questionnaires were mostly well accepted and carefully completed.

At baseline, the mean age of all the patients ($n = 40$) was 47.7 ± 8.3 years (mean $\pm$ SD) (Table 1), with a range from 30 to 62 years. Twenty-nine patients (72.5%) were female, and the mean duration of the specific CMPD symptoms was 9.0 ± 10.3 years. At least one nondrug treatment for the respective CMPD within the last 6

weeks was reported by 26 patients (65%). In the past, 24 patients (60.0%) had received OM, 10 (25.0%) of whom received OM specifically for the respective CMPD. Analgesics for the respective CMPD were taken within the last 6 weeks by 20 patients (50.0%). The mean VAS score for pain was 59.4 ± 12.5 mm, the mean SF-12 physical component scale (SF-12 PCS) score was 39.2 ± 8.0 , and the mean SF-12 mental component scale (SF-12 MCS) score was 48.6 ± 9.2 . Regarding OM treatment expectations, the study physician mostly expected OM to be “effective” (55.0%) and “slightly effective” (40.0%), whereas the patients mostly expected it as “effective” (50.0%) and “highly effective” (47.5%). With respect to the outcome expectations, the study physician tended to report “substantial improvement in symptoms” (37.5%) or “modest improvement in symptoms” (62.5%), whereas the patients tended to report “substantial improvement in symptoms” (80.0%). For the duration of symptoms, restrictions in ADL, and pain intensity, as measured by the

Table 1. Baseline characteristics of study participants

	Total (n = 40)	Neck pain (n = 10)	Low back pain (n = 10)	Shoulder pain (n = 10)	Knee pain (n = 10)
Sex, female	29 (72.5)	7 (70.0)	7 (70.0)	7 (70.0)	8 (80.0)
Age, years	47.7±8.3	49.2±4.8	45.3±8.1	47.2±9.7	49.1±10.3
Profession, employed	30 (75.0)	8 (80.0)	8 (80.0)	7 (70.0)	7 (70.0)
Duration of the specific CMPD symptoms, years	9.0±10.3	11.4±11.7	6.8±6.1	5.7±4.5	12.2±15.1
	5.3 [8.0]	8.5 [5.0]	4.5 [7.8]	5.3 [7.1]	6.5 [11.3]
Restrictions in ADL, days	14.6±11.1	14.5±11.8	20.6±10.3	14.2±10.6	9.2±10.2
	15.0 [20.5]	9.0 [21.2]	22.5 [13.2]	12.5 [17.2]	4.5 [18.8]
Use of physical therapy last 4 weeks	13 (32.5)	4 (40.0)	3 (30.0)	6 (60.0)	0
Physical therapy in the past for the respective CMPD	33 (84.6)	9 (90.0)	7 (77.8)	10 (100)	7 (70.0)
Osteopathy in the past	24 (60.0)	8 (80.0)	4 (40.0)	6 (60.0)	6 (60.0)
For the respective CMPD	10 (25.0)	4 (40.0)	3 (30.0)	0	3 (30.0)
For other disease	17 (42.5)	5 (50.0)	2 (20.0)	6 (60.0)	4 (40.0)
CMPD-related analgesics intake (last 4 weeks)	20 (50.0)	5 (50.0)	4 (40.0)	8 (80.0)	3 (30.0)
Medications for other diagnoses	30 (75.0)	6 (60.0)	6 (60.0)	9 (90.0)	9 (90.0)
Visual analogue scale pain (0–100 mm)*	59.4±12.5	62.3±10.8	62.0±14.8	57.3±14.8	56.0±9.4
	57.2 [11.0]	60.0 [18.8]	57.5 [10.8]	55.2 [13.8]	57.0 [9.8]
SF-12					
Physical Component Scale (0–100)**	39.2±8.0	36.9±8.5	39.6±8.1	38.8±6.4	41.8±9.1
Mental Component Scale (0–100)**	48.6±9.2	42.9±10.3	51.7±9.0	47.2±7.4	52.5±7.7
	50.8 [14.7]	40.0 [17.9]	54.7 [7.4]	47.8 [10.6]	55.0 [8.2]
NDI (0–50)*	–	15.1±5.9	–	–	–
Low Back Pain Rating Scale (0–60)* (n = 9)	–	–	19.3±4.7	–	–
DASH (0–100)*	–	–	–	55.7±13.4	–
WOMAC total score (0–96)*	–	–	–	–	22.4±13.7
Lequesne index of severity (0–24)*	–	–	–	–	5.3±3.7

Data are presented as mean ± SD, median [IQR], or n (%). *Lower values indicate better status. **Higher values indicate better status; in cases of non-normal distribution median and IQR are additionally reported. ADL, activities of daily living; CMPD, chronic musculoskeletal pain disease; DASH, Disabilities of Arm, Shoulder and Hand; NDI, Neck Disability Index Score; IQR, interquartile range; SF-12, 12-item Short Form Health Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

VAS, we found distinct differences between the mean and median values.

Exposure

The interventions were performed as described in the Methods. Regarding adherence to the OM interventions, *n* = 39 patients underwent all 6 treatments. One patient with CNP underwent only one intervention because of personal reasons but did not drop out of the study and returned all questionnaires throughout the 52 weeks of follow-up.

Outcomes

VAS Pain

In the whole study population, pain intensity, as measured by the VAS, improved after 12 weeks and approximately three OM sessions (mean difference to baseline –29.3 mm [–35.7 to –23.0]) with a clinically stable improvement after 26 weeks and 6 treatments (mean difference to baseline –33.1 mm [–40.5 to –25.7]). The im-

provements had a substantial clinical benefit (SCB criteria change of 26.5 mm reached, Table 2). The largest improvement after 26 weeks was observed in CKP (mean difference to baseline –38.1 mm [–49.1 to –27.0]), and the lowest was observed in CLBP (–28.2 mm [–47.9 to –8.4]). Improvements persisted through the follow-up conducted at week 52 (mean difference to baseline –34.9 [–42.4 to –27.5]) (Fig. 2).

Health-Related Quality of Life with SF-12

After 12 weeks, there was a tendency to an overall improvement in the SF-12 PCS score, with a mean difference to baseline of 4.9 (1.9–7.9), but not in the SF-12 MCS score (0.08 [–2.2 to 3.8]). Similarly, after 26 weeks, the SF-12 PCS score mean difference to baseline (6.9 [4.2–9.5]) but not the SF-12 MCS score (–0.02 [–3.1 to 3.0]) improved (Table 2). The improvement in SF-12 PCS score after 26 weeks was clinically important (MCID 5 points) and persisted through week 52 (mean difference to baseline 6.7 [3.7–9.7]) (Fig. 3).

Table 2. Subjective pain, health-related quality of life, and disease-specific outcomes, comparison baseline to 12 and 26 weeks

	N	Baseline, mean (95% CI)	N	At 12 weeks, mean (95% CI)	N	12 weeks vs. baseline, mean difference (95% CI)	N	At 26 weeks, mean (95% CI)	N	26 weeks vs. baseline, mean difference (95% CI)
Total population										
VAS pain (0–100 mm)*, MCID 15 mm	40	59.4 (55.4 to 63.4)	40	30.1 (23.7 to 36.4)	40	–29.3 (–35.7 to –23.0)	40	26.3 (18.8 to 33.8)	40	–33.1 (–40.5 to –25.7)
SF-12 PCS (0–100)**, MCID 5	40	39.2 (36.7 to 41.8)	39	44.2 (41.5 to 46.9)	39	4.9 (1.9 to 7.9)	40	46.1 (43.4 to 48.8)	40	6.9 (4.2 to 9.5)
SF-12 MCS (0–100)**	40	48.6 (45.7 to 51.5)	39	49.2 (45.6 to 52.7)	39	0.8 (–2.2 to 3.8)	40	48.6 (45.1 to 52.0)	40	–0.02 (–3.1 to 3.0)
By chronic musculoskeletal pain disease VAS pain, SF-12, and disease specific outcomes										
Chronic neck pain (CNP)										
VAS pain	10	62.3 (54.6 to 70.0)	10	27.7 (14.8 to 40.6)	10	–34.6 (–49.6 to –19.6)	10	28.7 (11.4 to 46.0)	10	–33.7 (–54.7 to –12.6)
SF-12 PCS	10	36.9 (30.8 to 42.9)	9	43.3 (35.0 to 51.6)	9	6.5 (–2.7 to 15.7)	9	43.9 (38.0 to 49.8)	9	7.0 (1.4 to 12.7)
SF-12 MCS	10	42.9 (35.6 to 50.3)	9	42.9 (31.7 to 54.1)	9	1.5 (–8.0 to 11.0)	9	43.5 (33.5 to 53.6)	9	0.6 (–5.7 to 6.9)
NDI (0–50)*, MCID 3.0	10	15.1 (10.9 to 19.3)	10	11.7 (7.3 to 16.1)	10	–3.4 (–7.2 to 0.4)	9	11.7 (5.2 to 18.2)	9	–3.6 (–9.0 to 1.9)
Chronic low back pain (CLBP)										
VAS pain	10	62.0 (51.4 to 72.6)	10	37.1 (18.7 to 55.5)	10	–24.9 (–43.6 to –6.3)	10	33.8 (12.3 to 55.3)	10	–28.2 (–47.9 to –8.4)
SF-12 PCS	10	39.6 (33.8 to 45.4)	10	43.3 (36.9 to 49.7)	10	3.7 (–3.0 to 10.4)	10	45.0 (37.8 to 52.1)	10	5.4 (–0.1 to 10.9)
SF-12 MCS	10	51.7 (45.3 to 58.2)	10	50.1 (41.5 to 58.6)	10	–1.7 (–6.0 to 2.6)	10	50.4 (42.7 to 58.1)	10	–1.4 (–8.7 to 6.0)
Low back pain rating scale (0–60)*, MCID 1.2	9	19.3 (15.7 to 22.9)	10	16.0 (7.4 to 24.6)	9	–1.9 (–9.6 to 5.8)	10	15.4 (6.5 to 24.3)	9	–3.4 (–12.5 to 5.7)
Chronic shoulder pain (CSP)										
VAS pain	10	57.3 (46.6 to 67.9)	10	31.6 (18.8 to 44.5)	10	–25.6 (–38.7 to –12.5)	10	24.9 (10.2 to 39.5)	10	–32.4 (–46.8 to –18.0)
SF-12 PCS	10	38.8 (34.2 to 43.3)	10	42.1 (37.6 to 46.6)	10	3.3 (–1.4 to 8.1)	10	47.9 (42.9 to 52.9)	10	9.1 (4.9 to 13.3)
SF-12 MCS	10	47.2 (41.9 to 52.5)	10	48.2 (42.5 to 53.8)	10	0.9 (–5.3 to 7.2)	10	47.5 (42.1 to 52.8)	10	0.2 (–4.3 to 4.8)
DASH disability/symptom (0–100)*, MCID 8	10	55.6 (46.1 to 65.2)	10	42.5 (32.5 to 52.5)	10	–13.2 (–20.2 to –6.1)	9	42.2 (33.3 to 51.1)	9	–13.4 (–23.1 to –3.7)
DASH sport/music (0–100)*	3	68.8 (6.6 to 130.9)	3	60.4 (36.7 to 84.1)	3	–8.3 (–47.4 to 30.7)	3	56.3 (25.2 to 87.3)	3	–12.5 (–105.7 to 80.7)
DASH work (0–100)*	10	48.8 (31.1 to 66.4)	10	48.8 (31.1 to 66.4)	10	0	9	41.0 (17.2 to 64.8)	9	–8.3 (–18.2 to 1.6)
Chronic knee pain (CNP)										
VAS pain	10	56.0 (49.3 to 62.8)	10	23.9 (11.8 to 36.1)	10	–32.1 (–41.6 to –22.5)	10	17.9 (5.1 to 30.8)	10	–38.1 (–49.1 to –27.0)
SF-12 PCS	10	41.8 (35.2 to 48.3)	10	47.9 (42.8 to 53.0)	10	6.2 (–1.0 to 13.4)	10	47.7 (41.4 to 54.0)	10	5.9 (–2.1 to 13.9)
SF-12 MCS	10	52.5 (47.0 to 58.0)	10	54.9 (50.7 to 59.2)	10	2.4 (–5.0 to 9.8)	10	53.0 (46.6 to 59.3)	10	0.5 (–8.8 to 9.7)
WOMAC, total score (0–96)*, MCID 10	9	22.4 (11.9 to 33.0)	10	12.5 (5.2 to 19.8)	9	–12.1 (–23.4 to –0.8)	10	10.7 (1.2 to 20.2)	9	–13.0 (–23.5 to –2.5)
WOMAC, pain (0–20)*	9	6.1 (4.0 to 8.2)	9	3.2 (1.4 to 5.0)	9	–3.3 (–5.4 to –1.2)	10	2.4 (0.2 to 4.6)	9	–4.1 (–6.2 to –2.0)
WOMAC, stiffness (0–8)*	9	2.2 (0.6 to 3.8)	10	1.9 (1.1 to 2.7)	9	–0.4 (–2.3 to 1.4)	10	1.7 (0.3 to 2.9)	9	–0.7 (–2.7 to 1.4)
WOMAC, physical function (0–68)*	9	14.1 (6.4 to 21.9)	10	7.4 (2.1 to 12.7)	9	–8.3 (–16.4 to –0.2)	10	6.6 (0.2 to 13.0)	9	–8.2 (–15.3 to –1.2)
Lequesne, index of severity (0–24)*, MCID 40%	9	5.3 (2.4 to 8.1)	10	3.2 (1.2 to 5.1)	9	–2.1 (–4.7 to 0.6)	10	3.2 (0.7 to 5.6)	9	–2.7 (–4.9 to –0.5)
Lequesne, pain (0–8)*	9	3.0 (1.3 to 4.7)	10	1.6 (0.5 to 2.7)	9	–1.4 (–3.0 to 0.1)	10	1.7 (0.3 to 3.1)	9	–1.7 (–3.1 to –0.3)
Lequesne, max. distance walked (0–8)*	9	0.4 (–0.1 to 1.0)	10	0.4 (–0.1 to 0.9)	9	0.0 (–0.4 to 0.4)	10	0.3 (–0.2 to 0.8)	9	–0.2 (–0.6 to 0.1)
Lequesne, ADL (0–8)*	9	1.8 (0.9 to 2.8)	10	1.2 (0.4 to 1.9)	9	–0.6 (–1.6 to 0.3)	10	1.2 (0.4 to 1.9)	9	–0.8 (–1.6 to 0.0)

* Lower values indicate better status. ** Higher values indicate better status. ADL, activities of daily living; DASH, Disabilities of Arm, Shoulder and Hand; Lequesne, Index of Severity for Osteoarthritis of the Knee; max., maximum; MCID, minimal clinically important difference (numbers without unit are given in points); NDI, Neck Disability Index Score; SF-12 PCS, 12-item Short Form Health Survey Physical Component Scale; SF-12 MCS, 12-item Short Form Health Survey Mental Component Scale; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Fig. 2. Visual analog scale (VAS) pain through 52 weeks in all four chronic musculoskeletal pain diseases. Values are means and 95% CIs.

Fig. 3. Estimated mean scores of the 12-item Short Form Health Survey (SF-12) Physical Component Scale (PCS) and Mental Component Scale (MCS) over 52 weeks. Values are means and 95% CIs.

Fig. 4. Estimated mean scores for Neck Disability Index, Low Back Pain Rating Scale, Disabilities of Arm, Shoulder and Hand Score, and Western Ontario and McMaster Universities Osteoarthritis Index through 52 weeks in the according diagnosis group. Values are means and 95% CIs.

Disease-Specific Outcomes

All disease-specific outcomes showed at least a tendency toward improvement over time in the respective study populations of 10 patients (Table 2; Fig. 4).

Among the CNP patients, we found clinically relevant (MCID 3.0 points) improvements in the NDI score from baseline to 12 weeks (mean difference [95% CI] -3.4 [-7.2 to 0.4]) and versus 26 weeks (-3.6 [-9.0

Table 3. Number of days with restrictions in activities of daily living within the last 4 weeks, for total study population and for each chronic musculoskeletal pain disease

	N	Baseline, mean (95% CI)	N	At 12 weeks, mean (95% CI)	12 weeks vs. baseline, mean difference (95% CI)	N	At 26 weeks, mean (95% CI)	26 weeks vs. baseline, mean difference (95% CI)	N	At 52 weeks, mean (95% CI)	52 weeks vs. baseline, mean difference (95% CI)
Total study population	40	14.6 (11.1 to 18.2)	40	7.8 (5.3 to 10.3)	-6.8 (-10.1 to -3.5)	40	6.0 (3.3 to 8.7)	-8.6 (-11.8 to -5.5)	38	5.4 (2.7 to 8.0)	-8.8 (-12.1 to -5.4)
Neck pain	10	14.5 (6.1 to 22.9)	10	7.3 (0.5 to 14.1)	-7.2 (-16.5 to 2.1)	10	6.6 (-0.0 to 13.2)	-7.9 (-13.0 to -2.8)	10	7.8 (1.4 to 14.2)	-6.7 (-12.8 to -0.6)
Low back pain	10	20.6 (13.2 to 28.0)	10	9.6 (3.6 to 15.6)	-11.0 (-18.3 to -3.7)	10	8.6 (0.6 to 16.6)	-12.0 (-22.0 to -2.0)	9	4.8 (-2.0 to 11.6)	-15.9 (-25.6 to -6.2)
Shoulder pain	10	14.2 (6.6 to 21.8)	10	9.8 (4.3 to 15.3)	-4.4 (-10.1 to 1.3)	10	5.8 (0.0 to 11.6)	-8.4 (-15.4 to -1.4)	9	6.7 (-1.3 to 14.6)	-6.0 (-11.7 to -0.3)
Knee pain	10	9.2 (1.9 to 16.5)	10	4.5 (1.4 to 7.6)	-4.7 (-11.6 to 2.2)	10	2.9 (0.5 to 5.3)	-6.3 (-12.5 to -0.1)	10	2.3 (0.0 to 4.6)	-6.9 (-13.9 to 0.1)

to 1.9]). For patients with CLBP, a clinically relevant (MCID 1.2 points) improvement in the low back pain rating scale was observed after 12 weeks (-1.9 [-9.6 to 5.8]) and after 26 weeks (-3.4 [-12.5 to 5.7]). In the ten patients with CSP, a clinically relevant (MCID 8 points) functional improvement in the DASH disability/symptom score was found from baseline to 12 weeks (-13.2 [-20.2 to -6.1]) and to 26 weeks (-13.4 [-23.1 to -3.7]). Only $n = 3$ patients filled out the questionnaires for the optional sport/music score. In the patients with CKP, a clinically relevant improvement in function (MCID 10 points) according to the WOMAC total score was observed after 12 weeks (-12.1 [-23.4 to -0.8]), and additional improvement was observed after 26 weeks (-13.0 [-23.5 to -2.5]). After 26 weeks, we observed a tendency for improvements in the WOMAC subscale scores for pain (-4.1 [-6.2 to -2.0]), stiffness (-0.7 [-2.7 to 1.4]), and physical function (-8.2 [-15.3 to -1.2]). Some improvements were also observed in the Lequesne index of severity after 12 weeks (-2.1 [-4.7 to 0.6]) and 26 weeks (-2.7 [-4.9 to -0.5]). The observed improvement, 39.6%, did not reach the MCID (40%).

After 52 weeks, the improvements in the disease-specific parameters persisted in the CLBP (low back pain rating scale score mean [95% CI] 15.4 [2.5–28.2]), CSP (DASH disability/symptom score 38.3 [29.4–47.2]), and CKP groups (WOMAC total score 10.3 [2.1–18.5]) but not in the CNP group (NDI 13.8 [8.4–19.2]) (Fig. 4).

Restrictions in Activities of Daily Living, Analgesics Intake, and the Use of Additional Therapies for CMPDs over the Last 4 Weeks

The number of days with restrictions in ADL over the last 4 weeks decreased from baseline to 12 weeks (overall mean of 14.6 vs. 7.8 days) and decreased further to 26 weeks for the whole study population and within every CMPD group. Only the CNP and CSP groups did not show additional improvement after 52 weeks (Table 3). The number of patients taking analgesics decreased in the whole study population from baseline to 26 weeks (Table 4). In the patients with CNP and CLBP, the number of patients taking analgesics remained unchanged from baseline to 26 weeks. The reduction in analgesic intake remained fairly low (overall by 18.4 percentage points) through 52 weeks. With regard to the respective CMPD, in the whole population, the number of patients undergoing physical therapy decreased from $n = 13$ (32.5%) at baseline to $n = 7$ (17.5%) at 12 weeks but increased again to $n = 12$ (30.0%) at 26 weeks (Table 4). The number of patients who used additional complementary medicine decreased from baseline to 26 weeks from $n = 12$ (30.0%) to $n = 8$ (20.0%). Additionally, the

Table 4. Number of patients using additional medical aid for the respective musculoskeletal pain disease

	Baseline (<i>n</i> = 40)*	At 12 weeks (<i>n</i> = 40)*	At 26 weeks (<i>n</i> = 40)*	At 52 weeks (<i>n</i> = 38)*
Patients taking analgesics (<i>n</i> = 40, last week)**	20 (50.0)	13 (32.5)	10 (25.0)	12 (31.6)
Ibuprofen	15 (37.5)	9 (22.5)	6 (15.0)	7 (18.4)
Diclofenac	4 (10.0)	3 (7.5)	4 (10.0)	2 (5.2)
Metamizol	4 (10.0)	4 (10.0)	2 (5.0)	2 (5.2)
Paracetamol	0	1 (2.5)	0	1 (2.6)
Flupirtin	1 (2.5)	0	0	0
Indometacin	0	0	0	1 (2.6)
Patients taking analgesics per diagnosis group				
Neck pain (<i>n</i> = 10)	5 (50.0)	5 (50.0)	5 (50.0)	5 (50.0)
Low back pain (<i>n</i> = 10, <i>n</i> = 9 after 52 weeks)	4 (40.0)	3 (30.0)	4 (40.0)	1 (11.1)
Shoulder pain (<i>n</i> = 10, <i>n</i> = 9 after 52 weeks)	8 (80.0)	5 (50.0)	1 (10.0)	3 (30.3)
Knee pain (<i>n</i> = 10)	3 (30.0)	0	1 (10.0)	3 (30.0)
Patients using non-drug therapy (last 4 weeks)**				
Use of physical therapy**	13 (32.5)	7 (17.5)	12 (30.0)	10 (26.3)
Physiotherapy	10 (25.0)	4 (10.0)	5 (12.5)	4 (10.5)
Exercise	0	0	0	2 (5.3)
Massage	3 (7.5)	4 (10.0)	4 (10.0)	2 (5.3)
Thermotherapy	6 (15.0)	4 (10.0)	5 (12.5)	4 (10.5)
Other	6 (15.0)	1 (2.5)	5 (12.5)	5 (13.2)
Use of complementary medicine**	12 (30.0)	10 (25.0)	8 (20.0)	10 (26.3)
Homeopathy	1 (2.5)	1 (2.5)	1 (2.5)	0
Autogenic training	0	0	0	2 (5.3)
Yoga	7 (17.5)	3 (7.5)	1 (2.5)	5 (13.2)
Ayurveda	0	1 (2.5)	0	0
Herbal therapy	1 (2.5)	1 (2.5)	0	1 (2.6)
Biofeedback	0	0	0	0
Bioresonance	0	0	0	0
Feldenkrais	0	0	0	1 (2.6)
Hypnotherapy	0	0	0	0
Meditation	4 (10.0)	0	1 (2.5)	2 (5.3)
Cupping	1 (2.5)	0	1 (2.5)	0
Sessions with a healer	1 (2.5)	0	0	0
Tai Qi	1 (2.5)	0	0	0
Other	6 (15.0)	4 (10.0)	5 (12.5)	5 (13.2)
Visiting a physician**	24 (60.0)	9 (22.5)	9 (22.5)	9 (23.7)
General practitioner	10 (25.0)	4 (10.0)	3 (7.5)	4 (10.5)
Rheumatologist	0	0	0	1 (2.6)
Orthopedic surgeon	12 (30.0)	5 (12.5)	6 (15.0)	7 (18.4)
Neurologist	3 (7.5)	1 (2.5)	1 (2.5)	0
Surgeon	2 (5.0)	0	0	0
Other physician	6 (15.0)	2 (5.0)	3 (7.5)	2 (5.3)
Visiting a complementary medicine provider**	4 (10.0)	4 (10.0)	4 (10.0)	6 (15.8)
Physician for homeopathy	1 (2.5)	1 (2.5)	1 (2.5)	0
Physician for anthroposophical medicine	0	0	0	0
Chinese medicine physician	1 (2.5)	2 (5.0)	0	2 (5.3)
Physician for naturopathy	0	0	1 (2.5)	0
Osteopath	1 (2.5)	0	1 (2.5)	3 (7.9)
Healing practitioner	2 (5.0)	0	0	1 (2.6)

Data are presented as *n* (%). * Percent are reported as valid percent. ** More than one answer possible.

number of patients visiting another physician decreased from *n* = 24 (60.0%) at baseline to *n* = 9 at 12, 26, and 52 weeks. The number of patients visiting a complementary medicine provider remained at *n* = 4 (10.0%) from baseline to 26 weeks and increased to *n* = 6 at 52 weeks.

Safety

No adverse events were observed.

Discussion

In this observational trial with follow-up, we observed beneficial changes along and after the OM treatment in addition to Germans' physician routine care in patients with CMPDs. Furthermore, in a homogeneous research environment, the course of 4 CMPDs during and after OM treatments could be followed across diagnoses. Six OM sessions were associated with a substantial clinical

improvement in pain intensity in patients with CMPD. Moreover, we observed clinically relevant disease-specific improvements in all CMPD groups except for the CKP group. Furthermore, we observed fewer restrictions in ADL, lower rate of use of analgesics and of additional therapies, and a clinically relevant improvement in the SF-12 PCS score but not in the SF-12 MCS score. Improvements with substantial clinical benefits were observed after only 3 OM treatments over 12 weeks, but additional benefits were observed after 26 weeks and 6 OM treatments. At 52 weeks, the improvements remained, including those in overall pain, the SF-12 PCS score, restrictions in ADL, and disease-specific parameters for CLBP, CSP, and CKP, but not CNP. No adverse events were reported after OM treatment. Apart from the reminders to return the questionnaires, the study was straightforward to conduct, and patients with CLBP and CNP appeared to be the easiest to recruit into the study. Furthermore, patients showed high study adherence.

The study observed beneficial changes after OM in addition to routine care in patients with CMPDs. These results are supported by those of an observational study [54] from the United States of America (USA) focusing on the outcomes per OM office visit. In the prospective part of the study (299 office visits), patients' perceptions of the symptoms after the treatment were assessed. Immediately after 92% of the office visits for OM, patients reported feeling better or much better, and after <2% of the office visits, they reported feeling worse; after 7 days (last follow-up), 72% of the patients reported feeling better or much better, and 6% reported feeling worse. The authors observed a short-term symptom relief after OM. Our study results included several validated patient-reported measurements and observed pain and functional improvements in patients with CMPDs. Furthermore, after 52 weeks, we found indications for lasting improvements. For future research, long-term follow-ups should be considered. Further, the inclusion of patients with different CMPD provides the opportunity to compare the symptom development of patients with different diagnoses under OM treatment. We must be aware that the mode of application of OM might differ across settings in Germany and the USA in accordance with the different training systems. For future comparisons of study results between the two countries, uniform OM definitions and standards are indispensable.

Though we observed improvements in CMPDs, there is some conflicting evidence regarding OM for CMPDs. A systematic review [55] investigated OM for various types of musculoskeletal pain and found no convincing evidence that it is effective. A more recent meta-analysis [56] that included 19 RCTs found some evidence suggesting that OM may be effective in treating patients suffering from neck pain and low back pain. Regarding CNP, a me-

ta-analysis [21] that included 3 RCTs ($n = 123$ patients) found moderate-quality evidence for significant and clinically relevant effectiveness of OM in relieving pain, as measured by a 100-point scale (mean difference -13.04 [95% CI -20.64 to -5.44]). A more recent RCT [57] reported that OM might be effective in reducing pain intensity in adult violinists and violists with CNP. For CLBP, a meta-analysis [21] that investigated the effectiveness of OM found moderate-quality evidence for a significant intergroup difference in favor of OM regarding pain, as measured by a 100-point scale (-14.93 [95% CI -25.18 to -4.68]) based on 7 studies ($n = 769$ patients), and functional status, as measured using the standard mean difference in a random-effects model (mean difference, -0.32 [95% CI -0.58 to -0.07]) based on 7 studies ($n = 771$ patients). The results of a recent meta-analysis [23] strengthen the evidence, and OM was more effective than control interventions in pain reduction (effect size -0.59 [95% CI -0.81 to -0.36], $p < 0.001$) and in improving functional status (effect size -0.42 [-0.68 to -0.15], $p = 0.002$). Further, two RCTs investigated OM in patients with CLBP. One RCT [58] ($n = 66$) compared 5 OM and 5 sham OM interventions and found a clinically relevant improvement in pain and function between groups, in favor of OM. Another RCT [59] ($n = 39$) investigated two different OM approaches in 10 sessions in addition to exercise and found improvements in pain, function, and general health in both groups.

To further interpret our results, we used the MCID and SCB with respect to baseline. For pain, after 26 weeks, we observed an SCB in the whole population and in each of the four CMPD groups for pain. For the NDI, we considered the MCID to be 3.0 points, as described previously [31]. Using this value, we observed an MCID after 12 and 26 weeks, but we have to consider that slightly older publications report a larger range of MCID for the NDI, varying between 3.5 and 9.5 points (scores ranging from 0 to 50) [60, 61]. On the basis of these references, we would not have observed an MCID in CNP. The same is true for the MCID of the low back pain rating scale, which we considered to have an MCID of 1.2 points [40], although another paper reported the overall MCID to be 6 points [62]. Furthermore, we considered the MCID for the DASH total score (range 0–100) to be 8 points [43]. This MCID was calculated [43] using data from a prospective cohort study conducted by a multicenter collaborative study group, the Surgery of the Ulnar Nerve group, including 38 patients (mean age 49.3 years, range 23–70 years), in the USA. However, a more recent publication reported the MCID to be 25.41 points on the same scale in a convenience sample of 200 younger patients (mean age 39.4 ± 12.6) recruited from 3 outpatient physiotherapy clinics located in Iran [63]. However, the patient characteristics, especially the age of the population,

in the first mentioned study [43] more closely resemble those of our study population.

In our study, no adverse events were reported in the 40 patients. However, the study population was too small to draw conclusions for treatment safety. In the United Kingdom, in private OM practices, a total of 1,630 complete datasets were collected [19]. Osteopaths performed OM treatments in addition to other treatments, including counselling, acupuncture and electrotherapy. In $n = 969$ (54%) patients, no adverse events after first treatment were experienced; in $n = 1,260$ (77%), no adverse events were observed after subsequent treatments. The authors stated that the treatment provided was safe and did not yield severe or moderately severe adverse events. A recent OM study in the USA [64] that recorded adverse events at 1,847 office visits in 884 patients (75% female, mean age 51.8 ± 15.8 years) found the incidence rate for adverse events to be 2.5% (95% CI 1.3–4.7%). The most common adverse event was pain/discomfort, with an incidence of 0.9% (0.5–1.6%). Within our study population ($n = 40$), this incidence suggests that one patient may have experienced an adverse event. An explanation for no adverse events being reported in this study might be that although the study physician asked patients about adverse events at each treatment session (as performed in routine care) and patients were encouraged to contact the study center if they experience adverse events, we did not provide a diary for the documentation of adverse events. For future research, patients should be provided with diaries to document adverse events in a timely manner. Adverse events, especially severe adverse events, might seldom occur in patients treated with OM. Therefore, to further investigate adverse events related to OM, we advise designing larger and multicenter studies.

The main strength of this trial is that we conducted the study in a university research environment. To the best of our knowledge, this is the first European OM study in patients with CMPDs conducted in a university research environment following the quality standards of the Declaration of Helsinki [65] and the ICH-GCP guidelines, including prospective trial registration and ethics approval. Another strength is the long follow-up of 52 weeks during which long-term changes in patients with CMPDs were observed. OM treatment was performed by a well-trained provider, an osteopath who was also an orthopedic physician, with the individualized diagnosis-related osteopathic treatment method that is typically used.

However, the study has various limitations. First, the study observed only a small number of patients in total and per diagnosis group. Furthermore, this study was a single-center study recruiting at one university and involving only one provider with good but very specific training, clearly limiting the generalizability of our results. In addition, it applied only subjective outcome pa-

rameters. However, we used a variety of standardized and validated patient-reported outcome measures. Another limitation is the study design. The absence of a control group follows the empirical approach of health care providers in routine care but limits the interpretation of the observed changes. The reported improvements may have been caused by known study effects, including observer effects [66, 67] and regression to the mean. Such study effects impact the results less in studies including a control group, and interventional trials like RCTs. However, this study was designed to observe changes along and after the OM treatment in addition to routine care. Furthermore, prior to the study, we empirically observed that patients seeking OM in addition to routine care often have a strong desire to undergo the desired treatment within a reasonable timeframe. By omitting an observed control group, we could immediately include all interested patients and provide them with OM treatment. Overall, the observed changes have to be interpreted with caution, and the results reported here have to be validated in RCTs.

The effectiveness of OM in the treatment of CMPDs should be further investigated in studies such as larger high-quality RCTs because it might be an effective and safe nonpharmacological treatment option. This is especially important because adverse events in analgesics include gastrointestinal bleeding, drug-induced headache [14, 15], and other severe adverse events caused by opioids [16].

The results presented here provide data for sample size calculations for future OM RCTs. Future studies should investigate the effectiveness and efficacy of OM in RCTs by investigating specific therapeutic effects of OM in comparison with a sham procedure and other effective therapeutic methods. Sham procedures should simulate OM diagnostics and therapies [68], or include single sham techniques that are compared with verum techniques [69]. However, a systematic review [70] comparing sham procedures with OM showed that 43 studies used very heterogeneously different types of manual sham procedures and provided little information about their application. The authors emphasized the need for guidelines to design sham procedures [70]. In our opinion, sham OM should simulate OM diagnostic and therapeutic procedures in studies investigating the specific therapeutic effects of OM. Regarding the comparison of OM with other effective therapy methods, these therapies could include single therapies, such as physiotherapy and analgesic intake, or could include multimodal therapeutic approaches. The blinding of study participants, outcome assessors, and statisticians should be considered in future trials, although blinding might not be necessary, as recently discussed [71]. Future trials conducted on OM should include multiple centers to investigate the external validity and transferability of our results. Adverse events should be reported by patients in diaries.

Conclusion

We observed beneficial changes along and after the OM treatment in addition to routine care in patients with four CMPDs. Moreover, the observational study was straightforward to conduct. Given the high rate of use of OM in CMPD patients, high-quality multicenter clinical RCTs are urgently needed. The data provided in this study are sufficient for sample size calculations.

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Statement of Ethics

The study was approved by the Ethics Committee, Charité – Universitätsmedizin Berlin (approval number EA1/068/15, no addendums, the study was performed without any changes during the trial). All patients gave oral and written informed consent before inclusion in the study. This study (German Clinical Trials Register DRKS00008319, Universal Trial Number, UTN: U1111-

1169-9945) followed the standards of the Declaration of Helsinki [65] and the ICH-GCP guidelines. The study was an investigator-initiated trial with no external funding sources.

Conflict of Interest Statement

Gabriele Rotter receives irregular lecture fees for teaching osteopathic medicine and musicians' medicine. She is a board member of the European Register for Osteopathic Physicians (EROP). The other authors do not have any conflicts of interest regarding this study.

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Author Contributions

G.R. conceived, coordinated, and carried out the study, interpreted the data, and drafted the manuscript. S.B. managed the data, carried out the statistical analyses, interpreted the data, and revised the manuscript. T.T.-D. revised and carried out the statistical analyses and revised the manuscript. M.O. helped design the study and revised the manuscript. B.B. helped design the study and methodology, contributed to the interpretation of the data, and revised the manuscript. All authors have read and approved the final version of the manuscript and agree with the order in which the authors are listed.

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