Overview of Registered Clinical Trials on Manual Therapy: Possible Implications of Genetic Testing for Personalized Treatment

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Abstract. *Background/Aim: Manual therapy (MT) is a frequently applied intervention offering individualized treatment in the clinic. In addition to the traditional approaches of MT, measuring molecular response to MT may offer better understanding of MT outcomes in order to provide specific personalized treatment. The aim of this study was to summarize MT-related registered clinical trials, as well as to search for any evidence on MT and genetics. Patients and Methods: A comprehensive search was conducted within the Clinical Trials database with predefined keywords mining for all types of MT-related clinical trials. Results: From the 47 trials, 20 had results and 27 had no results. MT alleviated pain and improved function almost in all trials. One registered clinical trial had investigated molecular outcomes of MT. Conclusion: MT is an effective and individualized treatment offering option in the management of several conditions. Interestingly, a clinical trial was found investigating molecular genetics and MT pinpointing an already existing link between genetics and MT. Therefore, further clinical trials may focus on genetics and MT for providing specific personalized treatment in future.*

Manual therapy (MT) has been defined by the International Federation of Orthopaedic Manipulative Physical Therapist (IFOMPT) as skilled hand movements, which “intend to optimize any or all of the following: improve tissue extensibility; increase range of motion; mobilize or manipulate soft tissues and joints; induce relaxation; change muscle function; stabilize the joint complex; modulate pain; reduce soft tissue swelling, inflammation or movement restriction” (1). Joint-based (including mobilization and manipulation), muscle-based and nerve-based techniques are frequently applied patient interventions that offer individualized treatment in the clinic. As the clinical effects of MT are measurable through several available investigation methods (2-4), the effect of MT has been well documented in the management of a number of different conditions, such as neck pain, shoulder pain or knee osteoarthritis (5-7), resulting in recommendation of MT in a wide range of disorders (8-10). Effectiveness of MT is especially well documented in clinical trials. As registration of these MT-related trials requires thorough, in-depth information, comprehensive investigation of MT clinical trials may provide details regarding the examination area and the personalized treatment effectiveness of MT. However, a systematic evaluation of MT-related clinical trials has not been conducted yet.

Personalized treatment is a key component of successful rehabilitation. As the genomic era of health care is evolving, evidence for using genetic factors for identifying disease risk as well as tailoring preventive and therapeutic regimens is growing (11, 12). Based on the recommendation of the American Physical Therapy Association (APTA), genetics is defined as a high priority area to advance science and improve physical therapy (13). As there is evidence suggesting a genetic influence on the clinical course of patients with osteoarthritis,

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low back pain, and cardiovascular disease, interaction between clinical genetics and physical therapy practice may be beneficial (12). In addition, genetic factors related to exercise response have been recently identified (11). As suggested by Cornwall *et al.*, awareness of physical therapists on gene examination procedures during physical therapy rehabilitation in order to deliver even more personalized treatment might be essential in the future (12). As MT is a crucial part of physical therapy intervention, development and assessment of molecular and clinical genomics and its role in personalized MT may support this future trend.

The objective of this study was to identify and summarize all MT-related clinical trials to recognize the importance of MT in clinical practice. Therefore, interventions and outcomes in MT-related clinical trials were assessed. In addition, special attention was paid to personalized treatment options based on possible application of molecular genetic measurements in MT.

Patients and Methods

Data collection. All data was collected in June 2020. The publicly available Clinical Trials database (www.clinicaltrials.gov) was mined for the registered MT-related clinical trials. The following terms were included in the “other terms” search field: “end-range mobilization”, “joint manual therapy”, “joint mobilization”, “manipulation”, “manual therapy”, “non-thrust manipulation”, “non-thrust mobilization” and “thrust manipulation”.

Search criteria. After initial search, the duplicated trials were excluded. Manual exclusion of trials not referring to the application of MT at peripheral joint or spine marked at the intervention column and/or in the title was also done. Since osteopathy, chiropractic and visceral therapy are not recognized MT interventions based on IFOMPT protocol (1), trials referring to the application of these techniques in the title and at the intervention column were also excluded. When MT was mentioned only at the intervention column, but without precise description of the applied technique, manual search was performed within the trial description to obtain further information. MT technique mentioned as a single intervention or as a complementary technique was accepted as eligible. In cases of more than one follow-up, the result of the last follow-up was investigated.

Structuration of MT-related trials. The identified MT-related clinical trials were divided in 2 groups: trials completed with results (Table I) and not completed before the time of the study, thus without results. In case of trials without results, no result was reported in the database. Regarding trials with results, statistically significant difference was accepted at $p \leq 0.05$. The flow diagram of the search method is displayed in Figure 1.

Results

After an initial search, 454 MT-related clinical trials have been identified. After removing the duplicates and trials not referring to MT application, 47 trials remained for further

investigation. All 47 trials were interventional studies. From these, 20 trials had results, whereas 27 trials had no results. Information of trials with results, including National Clinical Trial Number (NCT number), phase, sponsor, title, condition and interventions are presented in Table I.

Trials with results. From the 20 trials with results, two trials were in phase II, one trial was in phase II/I, while the phase was not applicable for the rest 17 clinical trials (Table I).

The most investigated medical condition was low back pain ($n=6$), referring to its importance and prevalence in the population (14). The next frequently investigated medical condition was neck pain ($n=5$), indicating another frequently occurring musculoskeletal condition amongst the population (15). Other investigated conditions were temporomandibular joint disorder ($n=2$), stroke ($n=1$), cerebral palsy ($n=1$), hemophilia ($n=1$), cervical radiculopathy ($n=1$), impingement syndrome ($n=1$), thoracic spine condition ($n=1$) and lumbar spinal stenosis ($n=1$). Overall, 15 trials examined spine, 2 trials investigated temporomandibular joint, 2 trials measured lower extremity condition and 1 trial investigated upper extremity condition.

The following outcomes have been used in the MT-related clinical trials with results. In low back pain trials ($n=6$), pain including visual analogue scale (VAS) and numerating pain rating scale (NPRS), range of motion (ROM) including flexion, extension, both direction of lateral flexion, biomechanics including lumbar spine stiffness (LSS) and flexion-relaxation ratio, LSS and normalized global stiffness variation, spinal segment load (SSL) alone, rate of loading for force and moment, postural sway, postural sway speed, response to sudden load and response time, muscle response per side, gait analysis, sick leave, questionnaires including Oswestry low back pain disability questionnaire (ODQ), Roland Morris low back pain disability questionnaire (RMDQ), low back leg pain intake questionnaire (LBLPIQ), patient reported outcomes measurement information scale-29 (PROMIS-29) and subjective outcomes including believability of placebo, bothersomeness, expectation for treatment effectiveness and treatment success. In neck pain trials ($n=5$) pain including VAS and NPRS, plasma concentration, ROM including flexion, extension, both direction of lateral flexion and rotation and T1-T3 flexion, extension, both direction of lateral flexion and rotation, pressure pain threshold (PPT), questionnaires including neck disability index questionnaire (NDIQ), self-perceived global rating of change (GROC) and subjective outcome including fear avoidance belief were investigated. In temporomandibular joint disorder trials ($n=2$), the defined outcomes were pain including VAS, ROM including opening of the jaw, PPT, questionnaires including chronic pain scale (CPS), NDIQ, sick leave, subjective outcomes including nonspecific physical symptoms with and without pain,

Table I. *Manual therapy-related clinical trials with results (n=20).*

NCT Number Phase Sponsor	Title	Condition	Intervention arms	Results
NCT01168999 Phase 1, phase 2 University of Florida	The Mechanisms of Manual Therapy in the Treatment of Low Back Pain	Low back pain	1. SM 2. Sham SM 3. Enhanced sham SM 4. Control	Baseline: believability of placebo and expectation for treatment effectiveness was greater in enhanced sham SM and SM compared to control ($p<0.01$); Postintervention: VAS decreased after sham SM compared to other groups with significant between-group difference ($p=0.05$); 2-week follow-up: NPRS and ODQ decreased in all groups without significant between-group difference ($p>0.05$); Flexion improved more after sham SM compared to other groups without significant between-group difference ($p>0.05$); Extension improved only after enhanced sham SM compared to other groups; Both direction of lateral flexion improved more after SM compared to other groups 2-month follow-up: RMDQ decreased more without significant difference ($p>0.05$) and treatment success improved more after McKenzie exercises compared to SM; 1-year follow-up: LBLPIQ and sick leave decreased more after SM compared to McKenzie exercises
NCT00939107 Phase not applicable Back and Rehabilitation Center, Copenhagen; The Danish Rheumatism Association; The Danish Physiotherapy Organization; Foundation for Chiropractic Research and Post Graduate Education; The Danish Institute for Mechanical Diagnosis and Therapy	The McKenzie Method <i>Versus</i> Manipulation for Patients With Chronic Low Back Pain	Low back pain	1. SM 2. McKenzie exercises	2-month follow-up: RMDQ decreased more without significant difference ($p>0.05$) and treatment success improved more after McKenzie exercises compared to SM; 1-year follow-up: LBLPIQ and sick leave decreased more after SM compared to McKenzie exercises
NCT00285649 Phase not applicable Palmer College of Chiropractic; Department of Health and Human Services	Predicting Patients' Response to Spinal Manipulation	Low back pain	1. HVLA-SM 2. LVVA-SM 3. medical care	3-week follow-up: RMDQ decreased more after HVLA-SM compared to LVVA-SM and medical care
NCT01670292 Phase not applicable Palmer College of Chiropractic; University of Iowa; National Center for Complementary and Integrative Health	Patient Response to Spinal Manipulation	Low back pain	1. HVLA-SM	6-week follow-up: VAS, NPRS, RMDQ and bothersomeness decreased and PROMIS-29 General Health Status Scale improved; LSS and flexion-relaxation ratio decreased, LSS - normalized global stiffness variation remained, SSL alone and rate of loading for force and moment increased
NCT00830596 Phase not applicable Palmer College of Chiropractic; National Center for Complementary and Integrative Health	Effect of Spinal Manipulation on Sensorimotor Functions in Back Pain Patients	Low back pain	1. HVLA-SM 2. LVVA-SM 3. Sham intervention	2-week follow-up: postural sway improved more after HVLA compared to LVVA-SM and sham intervention; Postural sway speed, response to sudden load and response time decreased more after LVVA-SM compared to HVLA-SM and sham intervention; Muscle response per side decreased more after HVLA-SM

Table I. *Continued*

Table I. Continued

NCT Number Phase Sponsor	Title	Condition	Intervention arms	Results
NCT02645123 Phase not applicable University of Ioannina	Gait in Low Back Pain Patients After Spinal Mobilization	Chronic low back pain	1. TENS 2. SM 3. Swedish type massage 4. Static hamstring stretch 5. Sham intervention	5-week follow-up: gait analysis improved more after sham intervention compared to other groups; 6-month follow-up: NPRS, ODQ and RMDQ decreased more after SM compared to other groups
NCT00566930 Phase not applicable Université du Québec à Trois-Rivières, Foundation for Chiropractic Education and Research	Preventive Care of Chronic Cervical Pain and Disabilities	Neck pain	1. SM 2. SM+exercises	10-month follow-up: VAS decreased more after SM compared to SM+exercises
NCT03194490 Phase not applicable Loma Linda University	Benefit of Adding Stretching to Standard Intervention For Patients With Nonspecific Mechanical Neck Pain	Neck pain	1. Combined intervention (cervical passive mobilization, passive stretching and home program: ROM exercises) 2. Standard intervention (cervical passive mobilization and home program: ROM exercises)	8-week follow-up: except left lateral flexion improved more after standard intervention compared to combined intervention, all other direction of ROM improved in both groups; NPRS and NDIQ decreased, GROC and PPT improved more after combined intervention compared to standard intervention 30-day follow-up: VAS decreased more after MT+DN compared to MT+sham DN and Control
NCT02435966 Phase not applicable University European of Madrid	Dry Needling in Patients With Chronic Neck Pain	Neck pain	1. Control 2. MT+sham DN 3. MT+DN	
NCT03176654 Phase not applicable Loma Linda University	The Effect of Manipulation of the Cervical Spine on Pain Biomarkers	Posterior neck pain	1. HVLAT manipulation 2. Sham HVLAT manipulation	Postintervention: plasma concentration improved more after HVLAT manipulation compared to HVLAT manipulation 24-48 h follow-up: all direction of T1-T3 ROM improved more and NPRS decreased more after SM and TheraBand kinesiology tape compared to SM
NCT02691143 Phase not applicable Sport and Spine Rehab Clinical Research Foundation	The Effect of TheraBand Kinesiology Tape on Post-manipulation Pain and Range of Motion	Acute non-complicated postural neck pain	1. SM 2. SM and TheraBand kinesiology tape	
NCT03454581 Phase 2 Federal University of Rio Grande do Sul	Effectiveness of Photobiomodulation and Manual Therapy Alone or Combined in Temporomandibular Dysfunction Patients	Temporomandibular disorder	1. Photobiomodulation 2. MT (mobilization of the jaw, MPRT) 3. Photobiomodulation +MT	90-day follow-up: VAS decreased ($p<0.001$), CPS and all directions of jaw ROM decreased ($p=0.05$), depression decreased ($p<0.05$), nonspecific physical symptoms with pain decreased ($p<0.01$), nonspecific physical symptoms without pain, mandibular function and anxiety increased ($p=0.05$) in all groups 3-month follow-up: VAS and depression decreased in both groups ($p<0.001$); ROM of opening decreased in both groups; PPT, kinesiophobia, catastrophizing, state anxiety, trait anxiety, trait depression decreased more after MPRT compared to sham intervention; NDIQ improved more after MPRT compared to sham intervention
NCT03619889 Phase not applicable Universidad Complutense de Madrid	The Effectiveness of a Physiotherapy Technique in Patients With Chronic Myofascial Temporomandibular Disorder	Temporomandibular disorder	1. MPRT on trigger points 2. Sham intervention	

Table I. Continued

Table I. *Continued*

NCT Number Phase Sponsor	Title	Condition	Intervention arms	Results
NCT02667821 Phase not applicable Canadian Memorial Chiropractic College; National Chiropractic Mutual Insurance Company	Vertebral Artery and Cerebral Hemodynamics After Various Head Positions & Manipulation in Patients With Neck Pain	Vertebral artery dissection, cerebrovascular accident, stroke	1. Neutral neck position 2. Neutral head position 3. SM	Postintervention: blood flow through vertebral artery increased after neutral neck position and SM compared to neutral head position; 1-year follow-up: blood flow through vertebral artery increased after neutral head position compared to SM and neutral neck position; tissue perfusion increased more after SM compared to neutral neck and head position
NCT01207570 Phase 2 The Hong Kong Polytechnic University; Phoelia co. Ltd.	Endermotherapy for Children With Developmental Disabilities	Developmental delay in cerebral palsy	1. Endermotherapy 2. Passive manual stretching	1-day follow-up: passive ankle ROM increased more after passive manual stretching compared to endermotherapy; 4-day follow-up: passive ankle ROM increased more after endermotherapy compared to manual stretching
NCT02198040 Phase not applicable Universidad Católica San Antonio de Murcia	Physiotherapy in the Haemophilic Arthropathy of the Elbow	Patients with hemophilia	1. MT (termo/cryotherapy, mobilization of elbow, passive muscle stretching, proprioceptive neuromuscular function) 2. Education	1-month prior beginning of the trial: frequency of elbow hemarthrosis decreased after education compared to MT; 6-month follow-up: elbow flexion ROM, circumference of arm and biceps strength increased, VAS decreased more after MT compared to education 2-4 days follow-up: NPRS, ULNT and NDIQ decreased and PSFS increased after soft tissue mobilization compared to therapeutic ultrasound 1-year follow-up: SPADI decreased more after MT compared to corticosteroid injection; GROC increased similar in both groups
NCT02081456 Phase not applicable University of Nevada	Soft Tissue Mobilization <i>Versus</i> Therapeutic Ultrasound for Subjects With Neck and Arm Pain	Cervical radiculopathy	1. Soft tissue mobilization 2. Therapeutic ultrasound	
NCT01190891 Phase not applicable Madigan Army Medical Center; University of Puget Sound; Franklin Pierce University	Physical Therapy <i>Versus</i> Steroid Injection for Shoulder Impingement Syndrome	Shoulder impingement syndrome	1. MT (mobilization of the joints around the shoulder and cervical/thoracic spine) 2. Corticosteroid injection	
NCT02550132 Phase not applicable Université du Québec à Trois-Rivières, Fondation Chiropratique du Québec	The Role of the Rate of Force Application in Responses to Spinal Manipulation Therapy	Spinal manipulation	1. SM 2. Apparatus used to deliver SM-s	Postintervention: RMS and vertebral displacement increased after SM performed with the most Newton
NCT01943435 Phase not applicable Patient-Centered Outcomes Research Institute; University of Pittsburgh	Study Comparing 3 Different Treatments for Arthritis of the Lower Back (Lumbar Spinal Stenosis)	Lumbar spinal stenosis	1. Medical care: NSAIDs, adjunctive analgesics, adjunctive anti-depressants; lumbar epidural injection 2. MT+exercise: (mobilization of the spine, sacroiliac and hip joint); individualized exercises in clinical setting 3. Exercise: group exercise in community setting	8-week follow-up: SSS decreased after MT+exercise without significant difference compared to medical care ($p=0.02$) and exercise ($p=0.01$); SPWT increased after MT+exercise without significant difference compared to medical care ($p=0.10$) and exercise ($p=0.61$); SWA decreased after MT+exercise without significant difference compared to medical care ($p=0.16$) and exercise ($p=0.40$)

CPS: Chronic pain scale; DN: dry needling; FRR: flexion-relaxation ratio; GROC: global rating of change; HVLAT, HVLA: high-velocity low-amplitude; HVLA-SM: high-velocity low-amplitude spinal manipulation; LBLPIQ: low back leg pain intake questionnaire; LVVA-SM: low-velocity, variable amplitude spinal manipulation; LSS: lumbar spine stiffness; MPRT: manual pressure release technique; MT: manual therapy; NCT number: national clinical trial number; NDIQ: neck disability index questionnaire; NPRS: numerating pain rating scale; NSAID: non-steroidal anti-inflammatory drug; ODQ: Oswestry low back pain disability questionnaire; PPT: pressure pain threshold; PSFS: patient specific functional scale; PROMIS-29: patient-reported outcomes measurement information system; QOL: quality of life; RMDQ: Roland Morris low back pain disability questionnaire; RMS: root mean square; ROM: range of motion; Sham intervention: placebo intervention; SM: spinal manipulation; SPADI: shoulder pain and disability index; SPWT: self-paced walking test; SSL: spinal segment load; SSS: swiss spinal stenosis; SWA: sense wear armband; TENS: transcutan electro neuro stimulation; ULNT: upper limb neural tension test; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster universities arthritis index.

Figure 1. Flow diagram of search strategy for clinical trials in manual therapy.

mandibular function, depression, kinesiophobia, state anxiety, trait anxiety, trait depression, catastrophizing, anxiety, cost effectiveness and bothersomeness. In the stroke trial, blood flow and tissue perfusion; in the cerebral palsy trial passive ankle ROM were assessed. The hemophilia trial investigated pain including VAS, extremity circumference, elbow flexion ROM, MS including musculus biceps brachii and frequency

of hemarthrosis as outcome. The cervical radiculopathy trial inspected pain including VAS, neurodynamics including upper limb neural tension test (ULNT), questionnaires including NDIQ and patient specific functional scale (PSFS). In the impingement trial, two scales were used including the shoulder pain and disability index (SPADI) and GROC. In the thoracic spine trial, biomechanics including root mean square

(RMS) and vertebral displacement were explored. Finally, in the lumbar spinal stenosis trial, the self-paced walking test (SPWT) as well as the sense wear armband (SWA) and a questionnaire including Swiss spinal stenosis (SSS) were used as outcomes.

The results of MT effectiveness can be summarized as follows: in low back pain trials, VAS decreased immediately, NPRS, ROM and ODQ decreased at 2-week follow-up, RMDQ decreased and treatment success improved at 2-month follow-up, LBLPIQ and sick leave decreased at 1-year follow-up, RMDQ decreased at 3-week follow-up, VAS, NPRS, RMDQ and bothersomeness decreased, PROMIS-29 and biomechanics enhanced at 6-week follow-up, biomechanics augmented at 2-week follow-up, gait improved at 5-week follow-up, NPRS, ODQ and RMDQ decreased at 6-month follow-up. In neck pain trials, VAS decreased at 10-month follow-up, ROM including all directions, PPT and GROC improved and NPRS and NDIQ decreased at 8-week follow-up, VAS decreased at 30-day follow-up, plasma concentration developed immediately, ROM including all directions improved and NPRS decreased at 24-48 h follow-up. In temporomandibular joint disorder trials VAS, CPS, ROM, depression, nonspecific physical symptoms with and without pain and anxiety decreased at 90-day follow-up, VAS, depression, PPT, kinesiphobia, catastrophizing, state anxiety, trait anxiety, trait depression decreased, ROM including opening and NDIQ improved at 3-month follow-up. Blood flow developed immediately, and blood flow and tissue perfusion increased at 1-year follow-up in the stroke trial. Passive ankle ROM was better at 1-day follow-up according to the cerebral palsy trial. In the hemophilia trial, the frequency of elbow hemarthrosis decreased at 1-month prior beginning of the trial, flexion ROM, circumference of arm and biceps strength increased and VAS decreased at 6-month follow-up. NPRS, ULNT and NDIQ decreased and PSFS increased at 2-4-day follow-up reported by the cervical radiculopathy trial. In the impingement trial, SPADI decreased and GROC improved at 1-year follow-up; in the thoracic spine trial, the biomechanics developed immediately. SPWT, SWA and SSS enhanced at 8-week follow-up according to the lumbar spinal stenosis trial. In summary, MT improved almost all subjective and objective outcomes both short-term and long-term in several investigated conditions.

MT was used as single intervention in the majority of trials (n=18), while only 2 trials combined MT with another intervention. From the 18 trials, 11 trials applied spinal manipulation underlining the importance of using manipulation. From the remaining 7 trials, 2 applied mobilization, 3 applied muscle-based MT and 2 trials applied both mobilization and muscle-based technique. Two trials investigated MT in combination with exercise therapy and both trials presented superior outcomes.

The MT-related clinical trials were completed at 8 locations around the world including United States (n=11), Canada (n=3), Spain (n=3), Brazil (n=1), China (n=1) and Denmark (n=1). The main sponsors or collaborators in the trials with results were Palmer College of Chiropractic (n=4), National Center for Complementary and Integrative Health (n=3), University of Iowa (n=2) and Loma Linda University (n=2).

Trials without results. From the 27 trials without results, 2 trials were in phase III, 1 trial was in phase III and II, 3 trials were in phase II, 1 trial was in phase II and I and 1 trial was in phase I. In 19 trials, the phase was not applicable.

The most investigated condition was neck pain (n=7). The next frequently investigated condition was knee osteoarthritis (n=4). Further investigated conditions in decreasing order were cervicogen headache (n=3), low back pain (n=3), shoulder pain (n=2), ankle sprain (n=2), fibromyalgia and chronic fatigue syndrome (n=1), adhesive capsulitis (n=1), hip osteoarthritis (n=1), sacroiliac joint pain (n=1), hamstring injury (n=1) and knee pain (n=1). Overall, 11 trials examined spine, 9 trials measured lower extremity condition, 3 trials investigated cervicogenic headache, 3 trials investigated upper extremity condition and 1 trial examined the whole body.

The following outcomes have been used in the MT-related clinical trials without results. In neck pain trials, pain including VAS and NPRS, ROM including all directions and upper cervical flexion and extension, MS including deep cervical flexor endurance test (DCFET), blood oxygen level (BOL), questionnaires including NDIQ, self-perceived GROC, headache impact test (HIT), patient acceptable symptom state (PASS), PSFS and subjective outcome including percent recovery have been assessed. Outcomes of knee osteoarthritis trials were pain including VAS and NPRS, ROM including flexion and extension, MS including musculus quadriceps femoris and hamstring muscles, functional tests including timed up and go test (TUG), six-minute walking test (6MWT), PPT, passive tension (PT) of knee, questionnaires including Western Ontario and McMaster Universities arthritis index (WOMAC) and Leeds assessment of neuropathic symptoms and signs (LANSS). Cervicogen headache trials estimated pain including NPRS, ROM including all directions, questionnaires including NDIQ, HIT, PASS, GROC and subjective outcomes, as headache duration (HAD), headache frequency (HAF), headache intensity (HAI), medication intake and analgesic use. Outcomes of low back pain trials were pain including NPRS, muscle thickness including musculus transversus abdominis, questionnaires ODQ, fear-avoidance beliefs questionnaire (FABQ) and GROC and subjective outcome including overall treatment success. Shoulder pain trials evaluated pain including

NPRS, pain-free ROM, questionnaires including shoulder pain and disability index (SPADI), disability of arm, shoulder and hand index (QuickDASH) and modified FABQ and GROC. Outcomes of ankle sprain trials included ROM dorsiflexion, corticospinal motor excitability, muscle activation and functional tests including Single leg squat reach test (SLSRT) and ankle flexibility test (AFT) performed in standing against a wall and lying down (on stomach) and star excursion balance test (SEBT). In fibromyalgia (FM) and chronic fatigue syndrome (CFS) trial, pain including VAS and fibromyalgia impact questionnaire (FIQ), fatigue including multidimensional fatigue inventory (MFI), gene expression including ribonucleic-acid sequence (RNAseq), autonomic nervous system dysfunction including plantar pressure maps (PPM), questionnaire including 36-item short form survey (SF-36) and Likert scale and an anonymized satisfaction questionnaire have been used as outcomes. Adhesive capsulitis trial assessed SPADI, subjective outcomes including percent of normal functional capacity, activity limitations and medication use. Hip osteoarthritis trial estimated pain including VAS, passive ROM, functional tests including TUG, fast paced walking test (FPWT), stair climb test (SCT), 30-second chair stand test (30SCST) and questionnaire including WOMAC. Sacroiliac joint pain trial allowed NPRS, questionnaire including ODQ and subjective outcome including medication intake. In hamstring injury trial lumbar and hamstring ROM and biomechanics including electromyography (EMG); in knee pain trial pain including NPRS and MS were evaluated.

MT was used as single intervention in the majority of trials (n=22), 10 of which used mobilization and 1 used manipulation. Seven clinical trials compared the effectiveness of manipulation over mobilization and 1 trial compared the effectiveness of joint mobilization compared to spinal mobilization. MT technique was combined with other, non-MT-related intervention in 5 trials, 4 of which used manipulation, and only 1 trial used mobilization. Only 1 trial investigated the effect of manipulation over mobilization in combination with non-MT-related intervention.

Reflecting on our additional goal to investigate the possible application of genetic measurements in personalized MT treatment, one registered clinical trial evaluating molecular response of MT in FM and CFS was identified (NCT04174300). This is the first MT-related, registered clinical trial involving molecular genetic measurements. Female patients fulfilling Canadian and international CFS criteria, presenting comorbid FM assessed by the American College of Rheumatology 2010, aged between 45-55 and body mass index (BMI) <35 (n=40) were subjected to 8 sessions of MT including pressure maneuvers of about 4.5 N performed twice weekly for 25 min. Blood samples were obtained before and after the first,

the fourth and last treatment to determine molecular blood changes. Peripheral blood molecular cells (PBMC) transcriptome was studied before and after MT to identify treatment-associated differential expression of genes. Patient pain was monitored by VAS and FIQ, MFI, gene expression by RNAseq, autonomic nervous system dysfunction by PPM, health status by SF-36 and Likert Scale and an anonymized satisfaction questionnaire to register potential undesired secondary effects.

These MT-related clinical studies were completed at 6 locations around the world including United States (n=16), Spain (n=4), Hungary (n=3), Great Britain (n=2), India (n=1) and Saudi Arabia (n=1). The main sponsors or collaborators in the trials without results were University of Pecs (n=3), Universidad Rey Juan Carlos (n=3), Alabama Physical Therapy & Acupuncture (n=3), Universidad de Zaragoza (n=2) and University of Colorado (n=2).

Discussion

To the best of our knowledge, this is the first comprehensive study to summarize and interpret MT-related, registered clinical trials and to investigate the possibility of specific personalized treatment based on genetics in MT. According to the results of the present study, MT may lead to effective management of a wide range of common pathological conditions. Furthermore, a clinical trial was found investigating the molecular response after MT, thus specific personalized treatment could be forthcoming. Since not all MT-related clinical trials had results, findings of trials with and without results were discussed separately, while only objective outcomes were evaluated. The only one clinical trial investigating genetic factors is discussed more thoroughly.

From the 20 MT-related trials with results, the two most frequently investigated medical conditions were low back pain and neck pain, both frequent morbidities in the population and significant causes of sick leave (16). MT was effective in the management of these conditions, as it has also been stated in previous systematic reviews (17, 18). Interestingly, the next most investigated condition was temporomandibular joint disorder, in consistence with its emerging prevalence in adults (19). MT was presented as an appropriate technique in the management of this disorder in the studied clinical trials, in agreement with the findings of a previous systematic review (20). Furthermore, several other disorders were also investigated in trials with results and MT has been shown effective in the management of pain and physical function; however, previous findings already presented MT effective in these conditions (10, 21-25). All these investigated conditions were frequent disorders in practice, except congenital hemophilia and cerebral palsy. Therefore, the effect of MT was explored in

common and serious diseases. Application of MT was found as an effective approach in a wide range of conditions. However, further investigation of MT would clarify its efficacy in a broader spectrum of clinical conditions.

Interestingly, many objective outcomes examined in the MT-related trials with results could be recognized as routinely used in clinical trials. These outcomes included evaluation of the measured condition including assessment of pain intensity, functional measurement of the impaired joint, functional tests, biomechanics and neurodynamic. On the other hand, blood flow and tissue perfusion are not routinely assessed; therefore, future MT clinical trials could investigate also blood circulation-associated outcomes.

MT was applied in many trials alone or in combination to another non-MT-related intervention. It has been suggested that application of MT additionally with physical therapy may lead to greater improvement in alleviation of pain and development of physical function, compared to MT alone (33); however, most MT-related trials with results compared MT to another type of MT in contrast to exercise therapy. Based on the trials results, MT applied alone or in combination with exercise therapy may be effective in the management of low back pain and neck pain, temporomandibular disorder, cerebral palsy, hemophilia, cervical radiculopathy, shoulder impingement syndrome and lumbar spine stenosis. Furthermore, spinal manipulation was implemented more frequently compared to mobilization in the investigated spine condition trials. This can be of interest, because manipulation is restricted to medical doctors in some countries and education of manipulation requires more time compared to mobilization. A recently published meta-analysis (34) suggested the effectiveness of both manipulation and mobilization in the management of chronic lumbar back pain; however, manipulation appeared to produce a greater effect regarding alleviation of pain and disability compared to mobilization. Therefore, further systematic reviews and meta-analyses may focus on the possible benefit of these techniques in different medical conditions.

In the 27 trials without results, the most investigated condition was neck pain. Interestingly, knee osteoarthritis was the next frequently explored condition underlining its frequent occurrence in the elderly population (35). MT has been applied in wide range of conditions in clinical trials without results but beyond mentioning the efficacy of MT; however, the positive effects of MT in these conditions have already been presented (10, 17-18, 33, 36-44). Interestingly, treatment of painful areas may also contribute to alleviation of pain in adjacent joints (6, 45). Therefore, examination of the adjacent joints or spinal segments after MT could be useful for manual therapists in practice.

The link between MT and genetics has not been well established yet. The APTA defines genetics as a high priority area in order to advance science and improve exercise

therapy. According to APTA, the possible results of the different gene expressions planned to be measured in trials are highly innovative and may give insight into the genes involved in response to exercise therapy (13). Based on Curtis *et al.*, “exercise genomics” may lead to more individualized prescriptions aiming to improve the effectiveness of exercise therapy (11). Therefore, investigating the role of genetics in exercise therapy practice has been already started in clinic. Genetic influence on the clinical course as well as internal and external factors of patients with different conditions has been previously documented (12). In addition, individual responsiveness to interventions has been shown for many conditions based on recommendation of clinical guidelines (12). Thus, the connection between genetics and exercise therapy has been well underlined by now. As a consequence, prevention of chronic conditions could also be feasible (11). As MT can be individualized for each patient, genetic information in addition to MT could improve personalized treatment in practice. Interestingly, one clinical trial was already performed investigating the link between MT and genetics. The clinical trial involved female patients with carpal tunnel syndrome receiving either 3 sessions of MT or decompression surgery, where pain and function outcomes were assessed in connection with Val158Met polymorphism. Nevertheless, no significant difference was observed at 1-year follow-up in alleviation of pain or improvement of physical function after MT intervention (46). Therefore, it would be advisable to perform further MT-related clinical trials focusing on the investigation of MT and genetic outcomes.

Regarding the location of the trials, the majority of MT trials with or without results were conducted in United States and Spain, followed by Canada, Hungary and Great Britain. Although MT is widely used to treat patients worldwide, research interest on the efficacy of MT seems to differ among countries.

Database of Clinical Trials contains probably the highest number of registered clinical trials worldwide. Thus, the targeted database of our comprehensive search was Clinical Trials, but no other database got involved. However, we cannot leave out of consideration that other MT-related clinical trials and clinical trials regarding MT and genetics may exist. Moreover, not all registered trials had results and not every MT technique was applied in the investigated registered trials contributing to a non-clear picture regarding MT. Besides, MT techniques applied in the investigated trials are not precisely standardized and defined. Furthermore, comprehensive summary cannot be provided regarding the different MT interventions due to absence of statistical analysis.

Conclusion

Based on the results of the present comprehensive search, MT is a frequently applied and successful intervention in the

management of different medical conditions offering personalized treatment. Furthermore, one registered MT-related clinical trial investigated genetic outcomes after MT, pinpointing the potential link between MT and genetics. Future clinical trials may focus on genetics after MT for enlarging the already existing connection.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

Pozsgai M: acquisition and analysis of data, drafting the article. Szabo I: acquisition and analysis of data. Nusser N: acquisition and analysis of data, final approval. Varnai R: analysis of data, drafting the article, final approval. Sipeky C: design of the study, drafting the article, final approval.

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