Original Experimental

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Think twice before starting a new trial; what is the impact of recommendations to stop doing new trials?

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Abstract

Objectives: In evidence-based medicine, we base our conclusions on the effectiveness of interventions on the results of high-quality meta-analysis. If a new randomized controlled trial (RCT) is unlikely to change the pooled effect estimate, conducting the new trial is a waste of resources. We evaluated whether recommendations not to conduct further RCTs reduced the number of trials registered for two scenarios.

Methods: Analysis of registered trials on the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP). We regarded trial protocols relevant if they evaluated the effectiveness of (1) exercise for chronic low back pain (LBP) and (2) cognitive behavioural therapy (CBT) for chronic pain. We calculated absolute and relative numbers and change of registered trials in a pre-set time window before and after publication of the recommendations, both published in 2012.

Results: We found 1,574 trials registered in the WHO trial registry for exercise in LBP (459 before 2012; 1,115 after) and 5,037 trials on chronic pain (1,564 before 2012; 3,473 after). Before 2012, 13 trials on exercise for LBP (out of 459) fit the selection criteria, compared to 42 trials (out of 1,115) after, which represents a relative increase of 33%. Twelve trials (out of 1,564) regarding CBT for chronic pain, fit the selection criteria before 2012 and 18 trials (out of 3,473) after, representing a relative decrease of 32%. We found that visibility, media exposure and strength of the recommendation were related to a decrease in registered trials.

Conclusions: Recommendations not to conduct further RCTs might reduce the number of trials registered if these recommendations are strongly worded and combined with social media attention.

Keywords: chronic pain; cognitive behaviour therapy; exercise; low back pain; trial registry.

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Introduction

In evidence-based medicine the choice of a treatment is based on patient preferences, scientific evidence and clinical expertise. The scientific evidence on the effectiveness of an intervention is determined when a meta-analysis of high-quality trials demonstrates a statistically significant and clinically worthwhile effect [1]. Until such evidence exists, researchers may claim that a new randomized controlled trial (RCT) is justified. Unfortunately, often the decision to justify another trial is made without consideration of how the findings of a new trial would alter the clinical recommendations for an intervention based on the existing evidence [2]. A trial that is unlikely to alter clinical recommendations is unnecessary and constitutes research waste [3]. Therefore, the need for replication of research should be balanced with the avoidance of mere repetition, even if the underlying mechanisms of effect are not (fully) understood [4]. In addition, the GRADE approach states that when there is high-quality evidence of an effect estimate then "further evidence is very unlikely to change our confidence in the estimate of effect" [3, 5].

Recently, recommendations have been made that a new trial is not necessary in situations when we either know the intervention is, or is not, effective, and there is evidence that new data will not change the clinical recommendation for the use of the intervention [6, 7]. These studies concern recommendations of main interventions in the field of physiotherapy and psychology of: (1) Exercise compared to minimal intervention to reduce pain in people with chronic low back pain (LBP) [6]; or (2) Cognitive Behavioural Therapy (CBT) compared to simple alternatives to reduce disability in people with chronic pain [7].

Therefore, the aim of this study is to determine whether recommendations not to conduct further trials changed the number of registered trials intending to evaluate the above-mentioned research questions. Our secondary aim was to assess whether any change in the number of registered trials was related to trial-specific factors (such as country or origin, sample size, participant condition) or publication factors, such as the journal impact factor or strength of the recommendation.

Methods

Design

We analysed the number of trials registered on the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) as this is the most complete trial registry, in 4-years' time windows before and after the recommendation not to conduct further trials.

Selection criteria

We used the same selection criteria as the two papers that recommended not to conduct further trials (Appendix 1) [6, 7]. For the first recommendation registered trial protocols were included if they met the following criteria: (1) RCT comparing at least two interventions; (2) participants with chronic LBP (≥3 months) randomly allocated to either exercise or a control group of no or minimal intervention; and (3) measured pain or disability as an outcome. For the second recommendation, registered trial protocols were included if they met the following criteria: (1) RCT comparing at least two interventions; (2) participants with chronic pain (≥3 months) that were randomly allocated to CBT or a control group of no intervention or a non-psychotherapy alternative intervention; and (3) measured pain or disability as an outcome.

Trials evaluating psychological treatments with a component of CBT were included, e.g. internet-based CBT, acceptance and commitment therapy (ACT) and other modifications of CBT, both individual as group-based. We excluded physiotherapy as a control arm, assuming that this would be an active intervention.

Search strategy

We searched the WHO-ICTRP (http://apps.who.int/trialsearch/) for trial protocols using the selection criteria. The papers that made the recommendations were published in 2012. Therefore, we searched for trials registered in an a priori set period of 4 years between 1st January 2008 and 31st December 2011 and for trials registered between 1st January 2015 and 31st December 2018. The a priori set period after the recommendation was chosen based on the idea that researchers should have been able to read the recommendation prior to planning and conducting a RCT.

We were unable to use "exercise" or "CBT" as search terms to limit the yield (Appendix 2) and therefore the yield in CBT for chronic pain was much larger than in exercise for LBP. To ensure we had comparable numbers we decided to limit the period for CBT to 2-year periods (1st January 2009 and 31st December 2010 and between 1st January 2016 and 31st December 2017).

Screening

Two authors independently screened all titles and abstracts for relevance (IS and LvR), and a third author (AV) resolved the conflicts. We extracted the data from the registry, and in case of uncertainty, we checked the original registration and all available (published) data. In addition, the third assessor performed a 10% random check of all titles and abstracts from the original registration.

Data extraction

Data were extracted on: (1) the number of trials registered that evaluated exercise/CBT compared to no intervention in patients with LBP and chronic pain, and absolute numbers of registered trials on LBP and chronic pain in the trial registry; (2) trial-specific factors (e.g. condition, setting, country, sample size, ethical approval and granting body [last check August 2019]); and (3) factors related to the publication (e.g. journal of publication [impact factor], strength of recommendation, Altmetrics score, keywords used). The Altmetrics score, literally "alternative metrics", measures and monitors the reach and impact of research publications through online interactions, next to the traditional measurements of academic success such as citation counts, impact factor, and author H-index (www.altmetrics.com). While the Almetric score does not measure how many times a particular article is read it does provide an indication of the extent of the readership.

Data synthesis

First, we calculated frequencies of the absolute and relative numbers of included trial protocols before and after 2012 both for exercise in LBP and for CBT in chronic pain. We calculated the relative number by dividing the number of trials that met our selection criteria (included trials) by the total number of trials that evaluated exercise/CBT in patients with LBP/chronic pain in the trial registry during the search

period. Next, the relative risk ratio, absolute change and relative change were calculated. For our primary aim, we decided a priori that we consider a change in the number of trials registered that was a relative positive or negative change, when this change was >10%. If the relative change was between –10 and 10% we would consider this as no change.

Results

Search

There were in total 1,574 trials registered for exercise in LBP: 459 before 2012 and 1,115 after (Figure 1) and 5,037 trials on chronic pain: 1,564 before 2012 and 3,473 after (Figure 2). There was a 90.7% agreement between the two authors in the selection of included trials. We present all trial-specific factors in Appendix 3.

Impact of recommendations

Exercise for LBP

We found an increase in the number of registered trials of exercise for LBP before and after 2012 of 33%; from 13 trials out of 459 (2.83%) to 42 trials out of 1,115 (3.77%) (Table 1).

CBT for chronic pain

We found a decrease in the number of registered trials of CBT for chronic pain before and after 2012 of 32%; from 12 out of the 1,564 (0.77%) trials to 18 out of 3,473 trials (0.52%) (Table 1).

Characteristics of included trials

Exercise for LBP

Out of 1,574 trials we found 13 that evaluated exercise compared to a control condition in the period of 2008–2011 and 42 in the period of 2015–2018 (Appendix 3). Participants in the control condition received treatment as usual (n=11), education (n=10) or no intervention/waiting list (n=20). The majority of the trials (n=35, 63%) recruited participants in a primary care setting with a mean sample size of 94 participants (range 20–600). After 2012, the mean sample size declined, from 115 to 89 participants and trials were less likely to be registered in a first world country (Europe, USA or Australia). More than half of all trials (n=30) mentioned ethical approval, in other cases it was either unclear (n=21) or not obtained (n=4). The government funded most trials, except for seven trials (12.5%). Trials registered before 2012, six out of 13 trials (46.2%)

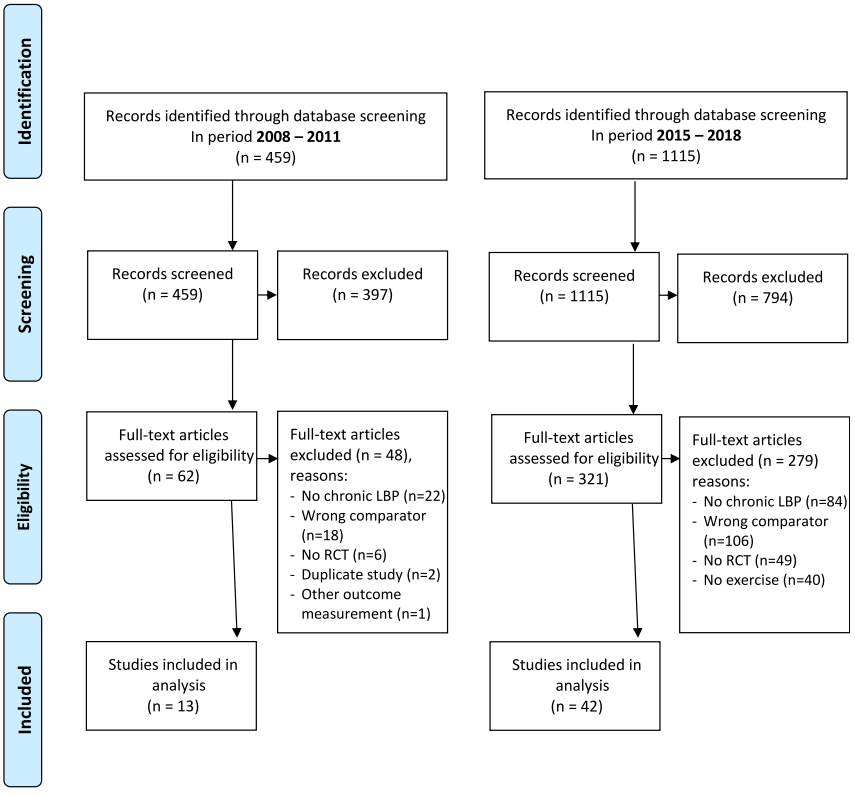

Figure 1: PRISMA flowchart for trials evaluating exercise for low back pain (LBP) in period 2008–2011 (pre-recommendation) and 2015–2018 (post-recommendation).

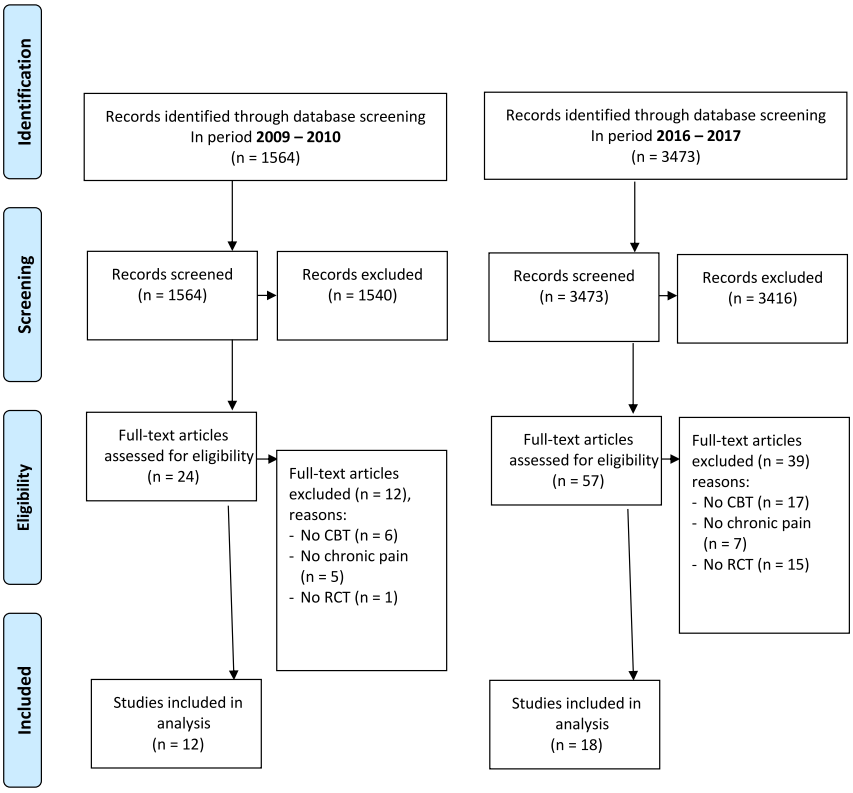

Figure 2: PRISMA flowchart for trials evaluating cognitive behavioural therapy (CBT) for chronic pain in period 2009–2010 (pre-recommendation) and 2016–2017 (post-recommendation).

published their results in a journal (with impact factors ranging from 0.22 up to 19.36 by August 2019).

CBT for chronic pain

Out of 5,037 trials we found 12 that evaluated a modality of CBT in the period of 2009–2010 and 18 in the period of 2016–2017 (Appendix 3). The control arm consisted of education (n=11), a waiting list group (n=10) or treatment as usual (n=9). Most trials were offered in a hospital setting (n=22, 73%) with a mean sample size of 127 participants (range 28–400). After 2012, the mean sample size increased from 101 to 145 participants. Ethical approval was obtained for 14 trials (47%), and unclear for 16 (53%). Trials were primarily funded by the government (n=16), or by a charity or industry. Nine out of 12 trials registered before 2012 (75%) published their results in a journal (with impact factors ranging from 2.01 to 4.52).

Specific factors related to the recommendation

Exercise for LBP

The recommendation was as follows: "…a new trial, even a large trial, would not resolve the uncertainty about whether the effects are large enough to be worthwhile." [6]. We classified this as a weak recommendation. The study was published in the BMJ (impact factor of 27.6) in 2012. This paper has an Altmetrics score of 21, based on 30 citations and media exposure on three different forums (half of the impact is from tweets [last updated March 3rd 2020]).

Table 1: Differences before and after recommendations.

	Total	Pre		Post		Relative risk ratio	Absolute change (%)	Relative change (%)
		Included	Registered	Included	Registered			
Exercise for LBP	1,574	13	459	42	1,115	(3.77–2.83)/(3.77) =0.33	+0.94	+33
CBT for chronic pain	5,037	12	1,564	18	3,473	0.52–0.77)/(0.52) =–0.32	–0.25	–32

In addition, as this paper was a research methods paper, not a 'recommendations on stopping exercise trials' paper, this paper did not use keywords which might have influenced the visibility of this paper in any data source.

CBT for chronic pain

The recommendation was: "We recommend the immediate cessation of new trials of CBT against simple alternatives". [7]. We classified this recommendation as strong. It was published in the Cochrane database of systematic reviews which has an impact factor of 7.75. This paper has an Altmetrics score of 110, based on 586 citations and media exposure on six different forums (last updated March 3rd 2020).

Discussion

Main findings

We found a marked reduction in clinical trials of CBT for chronic pain, but a marked increase in clinical trials of exercise for LBP, following clear recommendations that neither intervention required further investigation. Our data demonstrated that researchers can, but don't always, follow recommendations from other researchers as regards the value of conducting further RCTs.

The increase in the number of LBP trials registered may not have been influenced by the publication of this recommendation. The publication itself did not have a clear statement on exercise in LBP in the title or abstract, and there were no keywords provided [6]. Although it was published in a relatively high impact journal, it did not result in much media exposure (Altmetrics score). Also, an overview of Cochrane reviews on exercise in adults with chronic pain stated that further research is needed [13]. Although this overview was not specifically targeted at LBP, just three out of 21 included reviews were on LBP, and conclusions were not specific for LBP either, it could have influenced the increase in exercise for LBP protocols.

By contrast, the chronic pain recommendation in the Cochrane review (also a high impact journal) had a firmer recommendation, was easier to find due to the inclusion of keywords, and had a higher Altmetrics score [7]. The Altmetrics score could be a more realistic reflection of the attention of research output and its impact on researchers (and their plans to conduct new trials) than journal impact. It shows that research may have more impact, if it is available, accessible and has a clear message. We conclude that the difference in adherence to the recommendation between exercise for LBP and CBT for chronic pain was not related to the impact factor of the journal in which the recommendation was published, but probably more related to the strength of the recommendation, the visibility (i.e. Altmetrics score) of the paper and probably also to the use of keywords.

Strengths and limitations

This study is the first study to investigate the impact of recommendations not to conduct further trials on the registration of new trials. It identifies specific factors related to the impact of the recommendations.

This study nevertheless has some limitations. It was difficult to search the WHO-ICTRP, which might be a result of the format of the search boxes in the trial register. The search parameters were restrictive making it difficult to conduct an extensive search, but this influenced both searches equally.

The wording of the recommendations differs between studies. As for exercise in LBP it was not really a "recommendation", which might explain why it had less impact than a "clear" recommendation stated in the conclusion of a Cochrane systematic review.

In addition, we had trouble extracting data from the trial protocols, as protocols were often incomplete, and provided unclear descriptions of the intervention and control conditions. To make sure we did not miss any relevant protocols, we searched for the full text for final selection. This shows again the importance of a high-quality protocols addressing the study methodology in full, particularly a clear description of the intervention [8]. Studies of published trial reports showed that the poor description of interventions meant that 40–89% were non-replicable and hence increase research waste [9]. Therefore, authors are advised to follow a standardized format (e.g. SPIRIT statement), regularly update the trial protocol, and report all results. Almost half of the studies on LBP before 2012 published their results. This is in line with a recent European study that showed that half of all trials are non-compliant with reporting results to the EU Clinical trials register [10]. This is comparable to another study that found that half of all non-registered studies are not published [11]. In addition, the current study investigated only one domain of science-allied health interventions for chronic pain. We cannot be certain that the same pattern would emerge in other domains of science such as RCTs on medications. We do feel however that the recommendations below are applicable to all domains and research areas.

Recommendations

To reduce research waste and increase research impact, researchers should have a clear message to other researchers. In addition, one may consider a targeted media campaign to address policy makers, funding bodies and society. Researchers should be encouraged to thoroughly research the available, published and unpublished literature before designing a new trial [12]. When a meta-analysis of existing trials does not provide clear findings about whether an intervention has worthwhile effects, extended funnel plots can be used to explore the potential impact of a new trial on the updated meta-analysis and chance of changing clinical recommendations [6]. It is hoped that the use of living systematic reviews will help to inform researchers when a clinical question has been adequately addressed and further deter researchers from planning and conducting RCTS that do add to the overall existing evidence. We acknowledge that the current research landscape encourages and rewards early career researchers, including PhD candidates, who have conducted RCTs. An investigation into the rationale, not only for early career researchers but all researchers, for conducting RCTs would assist in understanding how to ensure only necessary RCTs are conducted. We encourage researchers and policymakers to actively spread and follow recommendations to increase their impact and to reduce research waste. Also funding bodies and ethical committees should take some responsibility for this, especially in a competitive research environment.

Conclusion

We found a marked reduction in protocols of CBT for chronic pain, but a marked increase in protocols of exercise for LBP, following clear recommendations that neither intervention required further investigation. This study shows that strong recommendations, visibility and media exposure may be relevant.

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Informed consent: Not applicable as no patients are involved.
Ethical approval: Not applicable as no patients are involved.

Appendix 1: Definitions of selection criteria for trial protocols

Exercise for LBP:

(1) ***P***atients with chronic nonspecific low back pain, defined as a nonspecific episode of low back pain (with or without leg pain) lasting for 12 weeks or longer.

(2) ***I***ntervention: exercise therapy that included the performance of any physical activity in order to develop the body (or part of the body) and improve health.

(3) ***C***ontrol intervention included no intervention or a waiting list or a minimal (passive) intervention such as laser therapy, education or massage therapy.

(4) ***O***utcome: pain, disability, quality of life

Cognitive Behavioural Therapy for chronic pain:

(1) ***P***atients with chronic pain, defined as more than 3 months of pain irrespective of the cause.

(2) ***I***ntervention: cognitive behavioural therapy (CBT), that included psychological treatments with a component of CBT, e.g. internet-based CBT, acceptance and commitment therapy (ACT) and other modifications of CBT, both individual as group-based.

(3) ***C***ontrol intervention: a simple alternative that included no intervention, waiting list or a minimal (non-psychotherapy) intervention such as exercise, education, or standard care.

(4) ***O***utcome: pain, disability, quality of life (return to work)

Appendix 2: Search strategy

Advanced search of the WHO International Clinical Trials Registry Platform

Search 1:

Box 1: Left black (Search terms entered in Box 1 search the title of the protocol)

Box 1: Condition/Participants (without synonyms boxed left unticked) – "low back pain"*

Box 2: Intervention (without synonyms boxed left unticked) – Left blank

Search for clinical trials in children: Box not ticked

Recruitment status is: "ALL"

Primary Sponsor is: Leave blank

Secondary ID: Leave blank

Countries of Recruitment: Leave blank – all countries searched.

Date of Registration is between: "01/01/2008" and "31/12/2011"

Phases are: "ALL"

With results only: Box not ticked

Search 2:

Box 1: Left black (Search terms entered in Box 1 search the title of the protocol)

Box 1: Condition / Participants (without synonyms boxed left unticked) – "low back pain"*

Box 2: Intervention (without synonyms boxed left unticked) – Left blank

Search for clinical trials in children: Box not ticked

Recruitment status is: "ALL"

Primary Sponsor is: Leave blank

Secondary ID: leave blank

Countries of Recruitment: Leave blank – all countries searched.

Date of Registration is between: "01/01/2015" and "31/12/2018"

Phases are: "ALL"

With results only: Box not ticked

Search 3:

Box 1: Left black (Search terms entered in Box 1 search the title of the protocol).

Box 1: Condition/ Participants (without synonyms boxed left unticked) – chronic pain

Box 2: Intervention (without synonyms boxed left unticked) – Left blank

Search for clinical trials in children: Box not ticked

Recruitment status is: "ALL"

Primary Sponsor is: Leave blank

Secondary ID: leave blank

Countries of Recruitment: Leave blank – all countries searched.

Date of Registration is between: "01/01/2009" and "31/12/2010"

Phases are: "ALL"

With results only: Box not ticked

Search 4:

Box 1: Left black (Search terms entered in Box 1 search the title of the protocol)

Box 1: Condition/Participants (without synonyms boxed left unticked) – chronic pain

Box 2: Intervention (without synonyms boxed left unticked) – Left blank

"Search for clinical trials in children": Box not ticked

Recruitment status is: "ALL"

Primary Sponsor is: Leave blank

Secondary ID: leave blank

Countries of Recruitment: Leave blank- all countries searched.

Date of Registration is between: "01/01/2016" and "31/12/2017"

Phases are: "ALL"

With results only: Box not ticked

*The WHO International Clinical Trials Registry Platform automatically searches synonyms generated using the UMLS Metathesaurus.

The following terms for low back pain will also therefore be included:

Low back pain synonyms:

"- ACHE, LOW BACK, ACHES, LOW BACK, BACK ACHE, LOW, BACK ACHES, LOW, BACK PAIN, BACK PAIN LOWER BACK, BACK PAIN LUMBAR, BACK PAIN, LOW, BACK PAIN, LOWER, BACK PAINS, LOW, BACK PAINS, LOWER, BACK; PAIN, LOW, BACKACHE, LOW, BACKACHE; LOW, BACKACHES, LOW, LBP, LOW BACK ACHE, LOW BACK ACHES, LOW BACK DERANGEMENT SYNDROME, LOW BACK SYNDROME, LOW BACK; PAIN, LOW BACKACHE, LOW BACKACHES, LOW; BACKACHE, LOWER BACK PAIN, LOWER BACK PAINS, LOWER BACKACHE, LOWER BACKACHE (DIAGNOSIS), LUMBAGO, LUMBAGO (DIAGNOSIS), LUMBAGO NOS, LUMBALGIA, LUMBAR BACK PAIN, LUMBAR PAIN, NONSPECIFIC PAIN LUMBAR REGION, PAIN, LOW BACK, PAIN, LOWER BACK, PAIN; BACK, LOW, PAIN; LOW BACK, PAIN;BACK LOW, PAIN; BACK; LUMBAR, PAINS, LOW BACK, PAINS, LOWER BACK, SPONDYLOSIS; INTERVERTEBRAL DISC DISORDERS; OTHER BACK PROBLEMS, SYNDROME; LOW BACK, low back pain".

Chronic Pain Synonyms:

–CHRONIC; PAIN, PAIN, PAIN CHRONIC, PAIN, CHRONIC, PAIN; CHRONIC, PAIN; CHRONIC, PAINS, CHRONIC, chronic pain

Appendix 3a:

Trials registered (n=13) between 2008 and 2011 on the effectiveness of exercise vs. no or minimal intervention in chronic low back pain patients.

Year	Setting (sample size)	Intervention	Control	Ethical approval	Granting body*	Published results	Impact factor#
2008	Primary care, Australia (160)	Tai chi, twice weekly for 8 weeks	No treatment	Yes	Gov	Yes	4.149
2008	Primary care, Brazil (119)	Back school (incl. exercises)	Weekly lectures	Unclear	Gov	No	

(continued)

Year	Setting (sample size)	Intervention	Control	Ethical approval	Granting body*	Published results	Impact factor#
2009	Hospital, UK (50)	Pedometer driven walking program given by a physiotherapist	Single education session + back book	Yes	Other (physio foundation)	Yes	2.454
2009	Primary care, USA (30)	Hatha yoga	Treatment as usual	Unclear	Gov	No	
2009	Unclear, Spain (60)	Progressive whole-body vibration	Treatment as usual	Yes	Gov	No	
2010	Primary care, USA (72)	Total body resistance exercise program	Standard care	Yes	Gov	Yes	0.22
2011	Unclear, Brazil (44)	Physiotherapy exercises	Exercise booklet	Unclear	Gov	No	
2010	Primary care, Germany (299)	IRENA (intensive rehabilitation program incl. exercises)	Educational booklet	Unclear	Gov	No	
2010	Primary care, Japan (150)	Water-exercise group and booklet	No treatment	Unclear	Gov	No	
2010	Primary care, Iran (36)	Core stability exercises	Waiting list	Yes	Gov	Yes	0.82
2011	Primary care, USA (320)	Physical therapy	Back pain help book	Yes	Gov	Yes	19.384
2011	Hospital, Germany (176)	Yoga	No intervention**	Yes	Gov	Yes	4.519
2011	Primary care Germany (40)	Whole vibration training	No treatment	Yes	Other (pension insurance)	No	

*Industry, governmental (Gov), other.
**5-year impact factor, if not available impact factor of 2018.
#In trial register there is only 1 control group (Qigong), in the publication there is also a no intervention group.

Appendix 3b:

Trials registered (n=12) between 2009 and 2010 on the effectiveness of CBT vs. no or minimal treatment in chronic pain patients.

Year	Setting (sample size)	Intervention	Control	Ethical approval	Granting body*	Published results	Impact factor
2009	Hospital, Netherlands (50)	Internet CBT	Waiting list	Yes	Other (health insurance)	Yes	4.519
2009	Hospital, USA (86)	Patient-controlled CBT	Waiting list	Yes	Gov	Yes	3.249
2009	Hospital, Norway (234)	CBT	Waiting list	Yes	Gov	Yes, part of the trial	2.699
2009	Hospital, USA (48)	Internet CBT (also for headache)	Waiting list	Yes	Gov	Yes	3.189
2009	Hospital, USA (47)	CBT	Education	Unclear	Other (VA Connecticut healthcare system)	No	
2009	Hospital, Germany (28)	CBT-PMP	Waiting list	Yes	Gov	Yes	2.012
2009	Hospital, Switserland (120)	CBT	Physiotherapy	Yes	Other (rehabilitation foundation)	Yes	2.012
2010	Primary care, USA (41)	Telephone CBT	Telephone pain education	Unclear	Gov	No	
2010	Hospital, Canada (48)	CBT self-help manual / approach for insomnia	Sleep diary	Unclear	Gov	No	
2010		CBT for pain		Yes	Gov	Yes	4.519

(continued)

Year	Setting (sample size)	Intervention	Control	Ethical approval	Granting body*	Published results	Impact factor
	Primary care, USA (367)		Osteoarthritis education				
2010	Hospital, Ireland (50)	CBT-PMP	Waiting list	Yes	Industry	Yes	2.454
2010	Hospital, UK (92)	Contextual CBT	Back to fitness class	Yes	Other (charity)	Yes	2.012

*Industry, governmental (Gov), other.

Appendix 3c:

Trials registered (n=42) between 2015 and 2018 on the effectiveness of exercise vs. no or minimal treatment in chronic low back pain patients.

Year	Setting (sample size)	Intervention	Control	Ethical approval	Granting body*
2015	Primary care, USA (40)	Yoga	Back pain helpbook	Unclear	Governmental
2015	Primary care, USA (152)	Yoga	Treatment as usual	Unclear	Governmental
2015	Primary care, Brazil (40)	Physical therapy	Osteopathic manipulation	Yes	Governmental
2015	Primary care, Iran (60)	Exercise	Education	Yes	Governmental
2015	Hospital, Australia (92)	Mind-body exercises	Treatment as usual	Yes	Governmental
2015	Hospital, Australia (60)	Exercise program wii	Treatment as usual	Yes	Governmental
2015	Primary care, Italy (96)	Exercise rehabilitation program	Waiting list	No	Other (self-funded)
2016	Hospital care, Thailand (72)	Qigong	Waiting list	Unclear	Governmental
2016	Unclear, Brazil (30)	Pilates	No intervention	Unclear	Governmental
2016	Unclear, Japan (46)	Exercise	Thermotherapy	Yes	Other(Self-funded)
2016	Primary care, Iran (20)	Exercises	No treatment	Yes	Governmental
2016	Hospital, China (108)	Taijiquan exercise	NSAIDs	No	Governmental
2017	Unclear, Brazil (26)	Pilates	No treatment	Yes	Governmental
2017	Primary care, USA (57)	Tai chi	Education	Unclear	Other (NGO)
2017	Primary care, Spain/Denmark (85)	Strength training	Treatment as usual	Unclear	Governmental
2017	Primary care, Spain (38)	Physiotherapy	Treatment as usual by GP	Unclear	Governmental
2017	Unclear, Brazil (90)	Exercise	Electroanalgesia	Unclear	Governmental
2017	Primary care, Nigeria (120)	Motor control exercise	Education	Unclear	Governmental
2017	Primary care, Brazil (84)	Exercise	Analgesia	Unclear	Governmental
2017	Hospital, USA (42)	Exercise & meditation	Listen to audio book	Unclear	Governmental
2017	Primary care, USA (40)	Exercise program	Waiting list	Unclear	Governmental
2017	Primary care, Sweden (600)	Physiotherapy	Booklet	Yes	Governmental
2017	Primary care, Iran (45)	Suspension exercises	No treatment	Yes	Governmental
2017	Primary care, Iran (64)	Back school program, including information establishing and maintaining correct posture and exercises for stability	No treatment	Yes	Governmental
2017	Hospital, China (178)	Baduanjin qigong	Treatment as usual	Yes	Governmental
2017	Hospital, China (136)	Rehabilitation exercise training	No treatment	No	Governmental
2017	Hospital, Australia (346)	Physiotherapy and coaching	Treatment as usual	Yes	Governmental
2018	Primary care, Japan (20)	Exercise	Waiting list	Unclear	Governmental
2018	Primary care, Brazil (60)	Pilates	No treatment	Yes	Governmental
2018	Primary care, Brazil (30)	Aerobic exercise	Shockwave	Unclear	Governmental
2018	Primary care, USA (70)	Exercise	Waiting list	Unclear	Governmental
2018	Primary care, Nigeria (30)	Motor control exercise	Education	Unclear	Governmental
2018	Primary care, Australia (80)	Green exercise	No treatment	Yes	Governmental (EU)
2018	Primary care, Iran (75)	Exercise	Education	Yes	Governmental

(continued)

Year	Setting (sample size)	Intervention	Control	Ethical approval	Granting body*
2018	Hospital, Iran (72)	Exercise	No treatment	Yes	Governmental
2018	Primary care, Iran (30)	Pilates	No treatment	Yes	Governmental
2018	Primary care, India (96)	Yoga	Treatment as usual	Yes	Governmental
2018	Primary care, India (90)	Exercises	Education	Yes	Governmental
2018	Primary care, India (20)	Physiotherapy	Ayurvedic classical herbal formulation	Yes	Other (private)
2018	Hospital, China (100)	Aquatic exercise	Physical agents	Yes	Governmental
2018	Hospital. China (76)	Hip bone balance exercise	Massage	No	Other (self-funded)
2018	Hospital, Australia (32)	Resistance exercise program	Treatment as usual	Yes	Governmental

*Industry, governmental, other.

Appendix 3d:

Trials registered (n=18) between 2016 and 2017 on the effectiveness of CBT vs. no or minimal treatment in chronic pain patients.

Year	Setting	Intervention	Control	Ethical approval	Granting body*
2016	Hospital, Germany (54)	CBT	Treatment as usual	Yes	Other (PRANA foundation)
2016	Hospital, Sweden (91)	CBT	Waiting list	Unclear	Governmental
2016	Hospital, USA (60)	Online self-management program based on cognitive behavioural principles	Treatment as usual	Unclear	Governmental
2016	Hospital, Norway (120)	ACT	Treatment by GP	Yes	Governmental
2016	Primary care, Iran (30)	CBT	No treatment	Yes	Governmental
2016	Primary care, China (150)	CBT	Education	Yes	Other (charity)
2017	Hospital, USA (420)	CBT	Coping skills training and physical exercise program	Unclear	Governmental
2017	Primary care, Ireland (70)	CBT	Treatment as usual	Unclear	Other (person, charity)
2017	Hospital, USA (139)	CBT	Treatment as usual	Unclear	Governmental
2017	Unclear, Nigeria (37)	CBT	Exercise	Yes	Governmental
2017	Unclear, Cyprus (150)	ACT	Psycho-education	Unclear	Governmental
2017	Primary care, Sweden (400)	ACT	No treatment	Unclear	Governmental
2017	Hospital, Sweden (200)	Internet CBT	Waiting list	Unclear	Governmental
2017	Hospital, USA (231)	CBT	Health education	Unclear	Governmental
2017	Hospital, Sweden (113)	Internet ACT	Waiting list	Unclear	Other (AFA insurance)
2017	Hospital, Ireland (160)	ACT + exercise	Exercise	Unclear	Governmental
2017	Hospital, USA (40)	CBT	Education	Unclear	Governmental
2017	Hospital, USA (143)	Internet CBT	Treatment as usual	Unclear	Governmental

*Industry, governmental, other.

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