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Reporting of Harm in Randomized Controlled Trials of Therapeutic Exercise for Knee Osteoarthritis: A Systematic Review

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ABSTRACT:

Objective. The Consolidated Standards of Reporting Trials (CONSORT) recommends reporting adverse events (AEs) and dropouts (DOs) with their definitions. The purpose of this study was to identify how AEs and DOs were reported in randomized controlled trials (RCTs) of therapeutic exercise for knee osteoarthritis (OA).

Methods. Data sources were the Cochrane Library, EMBASE, PUBMED, and CINAHL. Databases were searched to identify RCTs of therapeutic exercise for Knee OA published from January 1, 1980, through July 23, 2020. Researchers independently extracted participant and intervention characteristics and determined whether a clear statement of and reasons for AEs and DOs existed. The primary outcome was exercise-related harm. Physiotherapy Evidence Database (PEDro) scoring described study quality and risk of bias. Descriptive and inferential statistics characterized results. Meta-analysis was not performed due to data heterogeneity.

Results. One hundred 13 studies (152 arms) from 25 countries were included with 5909 participants exercising. PEDro scores ranged from 4 to 9. Exercise intensity was not specified in 57.9% of exercise arms. Fifty studies (44.2%) included an AE statement and 24 (21.2%) reported AEs, yielding 297 patients. One hundred three studies (91.2%) had a DO statement. Sixteen studies (15.5%) provided reasons for DOs that could be classified as AEs among 39 patients, yielding a 13.1% increase in AEs. Thus, 336 patients (6.0%) experienced exercise-related harm among studies with a clear statement of AEs and DOs. A significant difference existed in misclassification of DOs pre– and post–CONSORT 2010 (12.2% vs 3.1%; X21=21.2).

Conclusions. In some studies, the reason for DOs could be considered AEs, leading to potential underreporting of harm. Improvements in reporting of harm were found pre– and post–CONSORT 2010. Greater clarity regarding AE and DO definitions and TherEx intensity are needed to determine safe dosing and mode of therapeutic exercise for knee OA.

Impact. More adherence to the CONSORT statement is needed regarding reporting of and defining AEs, DOs, and therapeutic exercise intensity; however, despite this, therapeutic exercise seems to be associated with minimal risk of harm.

Introduction

Therapeutic exercise is a major component of the conservative management of knee osteoarthritis (OA).[1-3] Evidence suggests that the mechanical loading associated with exercise can reduce inflammation and cartilage degradation,[4] improve physical function, muscle strength

and reduce joint pain.[5-7] Therapeutic exercise is the "systematic performance or execution of planned physical movements or activities intended to remediate or prevent impairments of body functions and structures, enhance activities and participation, reduce risk, optimize overall health, and enhance fitness and well-being".[8] Prescription of therapeutic exercise includes information regarding the intensity, frequency, duration, and mode of exercise along with the type of supervision used to ensure proper dosing and technique. Without a complete description of therapeutic exercise interventions in clinical trials, clinicians and patients cannot reliably implement therapeutic exercises shown to be effective, and researchers cannot replicate findings or extend the research in this area.[9]

While therapeutic exercise is perceived as a less risky intervention for managing knee OA symptoms in comparison to invasive interventions such as surgery and NSAIDs, it does require active participation by the patient and substantial time commitment. The potential exists for exercise to lead to increased knee pain or exercise-related injury (eg, falls).[10-12] Thus, it is important for patients to receive detailed instruction in the prescription of therapeutic exercise from physical therapists or other appropriate health professionals. In this process, patients should be informed about exercise-related symptoms (eg, temporary muscle discomfort) that are to be expected and not harmful, and the potential for and the incidence of risk for exercise-related adverse events. Disclosure of harm from therapeutic exercise is also a necessary component of informed consent in clinical trials of therapeutic exercise.

The CONSORT statement for reporting clinical trials[13] is a universally accepted method for enhancing the consistency of reporting components of and problems with clinical trials.[14] Originally published in 1996,[15] the CONSORT statement has been updated three times[13, 15, 16] with the most recent version being published in 2010.[13] In 2004, CONSORT published a

statement specifically addressing the reporting of harm.[17] This statement specifies that adverse events and dropouts should be reported separately along with their corresponding reasons and that adverse events should be classified by severity.

Adverse events (AEs) are defined as any negative outcome resulting either directly or indirectly from the assigned treatment.[18] More recently the PRISMA Harms checklist provides guidance on how systematic reviews should address the reporting on harms.[19] The PRISMA Harms group created a new term, "adverse effects" which is defined as "an unfavorable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it." Adverse effects become adverse events when the causality of the unfavorable outcome can potentially be attributed to the intervention. Finally, study-related harm is considered to be the totality of adverse consequences occurring during or after an intervention.[19]

Patient withdrawal (or dropout) from studies due to harm-related reasons can occur, but dropouts can also occur and not be associated with harm attributed to the intervention. Understanding why patients decide not to continue in a study is important to determine whether the intervention has any harmful impact, as their reasons for dropping out could indicate their inability to tolerate the intervention.[17] Thus, clear definitions of both dropouts (DOs) and AEs are needed. However, there is little guidance regarding how to define and categorize AEs and DOs in therapeutic exercise trials[20] and this lack of consistency may lead to overlap in reasons for AEs and DOs. As such, it is difficult to ascertain the risk of harm in therapeutic exercise as well as the most effective dosage, intensity, and mode of therapeutic exercise for patients with knee OA.

Exercise-related harm has been investigated in a number of systematic reviews[11, 21-25] but each review operationalized harm differently and assessed exercise-related harm in different

populations. For example, Sherrington examined whether exercise performed by older adults reduced their risk of falls.[12] Neimeijer et al, examined whether exercise therapy among adult patients, regardless of health condition, led to a 1.19 increased risk of non-serious AEs.[11] None of these studies specifically addressed AEs in adults with arthritis. In a review of harm reporting in clinical trials within rheumatic diseases, Ethgen et al (2005) compared pharmacologic trials to nonpharmacologic trials and found pharmacologic trials were 5.2 times more likely to discuss harms than non-pharmacologic trials.[18] Additionally, Quicke et al. performed a systematic review of physical activity interventions in adults aged 45 years and older with knee pain to examine safety-related outcomes and found no serious safety issues in studies which used primarily low intensity physical activity interventions.[22]

This study aimed to identify how AEs and DOs are defined in randomized controlled trials of therapeutic exercise among adults with knee OA and whether statements of AEs and DOs were included in manuscripts, in order to better describe the frequency and severity of therapeutic exercise-related harm, as recommended in the CONSORT Harms statement.[17] Additionally, this study aimed to characterize the attributes of the study populations and therapeutic exercise interventions and to ascertain the incidence rate of therapeutic exercise related harm in these studies. We hypothesized that the classification of AEs and DOs would be inconsistent across studies and that studies published prior to the CONSORT-2010 consensus statement[13] would be less likely to mention AEs and consistently define AEs and DOs than studies published after this statement. Based on our findings, we provide recommendations for documenting exercise intervention details and the use of operational definitions of DOs and AEs along with methods for reporting these in clinical trials of therapeutic exercise. We also discuss

how our recommendations align with or add to the current CONSORT[13] and CONSORT Harms[17] reporting guidelines.

[H1]Methods

[H2] Data Sources and Searches

Four researchers (MDI, JvH, SC, JB) used the American Physical Therapy Association's definition of therapeutic exercise[8] to conduct a systematic review of randomized controlled trials of therapeutic exercise for managing knee OA symptoms. We searched the Cochrane Library, CINAHL, PUBMED, and EMBASE databases for peer reviewed randomized controlled trials conducted in adults diagnosed with knee OA and published in English between January 1, 1980 and July 23, 2020 using the following search terms: (knee osteoarthritis OR knee arthritis) AND (exercise OR exercise therapy OR strengthening OR aerobics OR anaerobic OR dynamic exercise OR isotonic OR isometric OR isokinetic OR physical therapy). These particular search terms were used in an effort to include every relevant type of therapeutic exercise. Studies which compared non-pharmacologic interventions to therapeutic exercise were eligible as long as the therapeutic exercise intervention arm included only therapeutic exercise. As we used the APTA definition of therapeutic exercise,[8] exercise was broadly defined and could include Tai Chi, yoga, strengthening, flexibility, aerobic [on land or in water], balance or agility training etc. We excluded studies which (1) enrolled patients with non-specified knee pain, (2) studies which enrolled patients with other forms of arthritis (hip OA, rheumatoid arthritis, etc.) and which did not separately report patient outcomes by diagnosis (either primary outcomes or for DOs and AEs) and (3) studies of unsupervised exercise or studies where the level of supervision was unspecified. We used the PRISMA harms guidelines[19] for the development and reporting of this

systematic review (Suppl. Appendix 1). This systematic review was registered with and approved by PROSPERO, the international prospective register of systematic reviews.[26]

[H2] Study Selection

Four researchers (MDI, JvH, SC, JB) individually screened 4,649 titles and 386 abstracts for eligibility and eliminated studies which did not meet the inclusion criteria. In instances where article eligibility was unclear, the researchers discussed the rationale for inclusion and after deliberating, came to a consensus about whether or not the study met inclusion/exclusion criteria. Figure 1 provides the flowchart portraying the process of study elimination. Two hundred thirty-four full text articles were screened for eligibility and the article reference lists were examined for eligible studies. Prior to the final data analysis, the search was re-run to determine whether any relevant studies had been missed.

[H2] Data Extraction and Quality Assessment

The research team (JvH, MDI, SC, JB, KJ) extracted data from final 113 studies (Suppl. Appendix 2 and 3) according to predefined criteria, using a standardized form. This form included the following data elements: year of publication, country where study was conducted, total number of subjects in exercise arm(s), program length, exercise intensity and how intensity was assessed (eg, BORG scale, 70% of one repetition max), frequency and mode of exercise, and duration of exercise sessions, the amount of exercise supervision, whether there was a clear statement of AEs, the number and type of AEs (related to therapeutic exercise and not related to therapeutic exercise), whether there was a clear statement of DOs, the number of DOs and reasons for DOs. The results section of each article was thoroughly annotated to ensure that a definition of AEs associated with therapeutic exercise was clearly reported in the narrative

tables, or figures and not overlooked. In instances where a DO could be considered an AE or an adverse effect, we recorded that outcome as harm.

We used the first assessment after the exercise intervention as the primary endpoint for the collection of AEs and DOs. Many studies did not record AEs and DOs at each follow-up assessment, rather, they reported these outcomes at the first assessment period post-exercise intervention and then summarized the outcomes across all evaluation timepoints.

The PEDro scoring method[27] was used to independently rate the internal validity of the studies and identify risk of bias. Specific data elements examined included: eligibility, random allocation, concealed allocation, baseline comparability, subject blinded, therapist blinded to allocation, assessor blinded to allocation, measures of key outcomes, intention to treat, results comparison, and point estimate of variability. One point was given to each item, except for study eligibility criteria, which is not included in the PEDro score. These points were then summed to create a single score for each article ranging from 0 to 10.[27] When disagreements occurred between the raters regarding the PEDro scoring, the researchers discussed and make to a consensus regarding the scoring attributed to the articles (Suppl. Appendix 4).

[H2] Data Synthesis and Analysis

We conducted both a qualitative and quantitative synthesis of the studies. A meta-analysis was not conducted due to study heterogeneity and the focus on counts of outcomes versus intervention effect sizes.[28] To evaluate therapeutic exercise data, data were grouped into categories of exercise modes (strengthening, aerobic etc.), frequency per week, and session durations (eg, unspecified, 1-2x per week, etc.). In cases where a range of values was provided for any of these variables, the average was calculated, or the number was rounded up to the next category. Next, the percent of studies using various modes of exercise, along with exercise

intensity level, and how intensity was assessed, duration, and frequency was calculated. We stratified studies based on the timeframe of the publication of the CONSORT-2010 statement using a cut point of 2011 (eg, by pre-CONSORT-2010 statement and post CONSORT-2010 statement publication).[13]

We calculated the percent of AEs and DOs occurring among the group of individuals exercising within each study or each study arm (when more than one exercise program was being tested). In studies where it was difficult to ascertain the reasons for DOs due to data being reported across intervention groups and during the follow-up periods when no therapeutic exercise was provided, we coded those data as unspecified reasons for DOs. We documented all reasons for DOs and specifically identified when the reason for dropping out of a study was an exercise-related harm (ie, DOs that met the definition of an AE were reclassified as AEs). For example, if exercise-related knee pain was given as a reason for someone refusing to continue in the study, then the DO was reclassified as an AE. Additionally, AEs and newly reclassified DOs were categorized by severity using the following operational definition: severe (fracture, permanent damage, disability or death) and non-serious (muscle strain, soreness, fall not related to exercise program).[29]

Chi squared tests were used to determine whether differences existed regarding a clear statement of AEs (Y/N) and DOs (Y/N) and regarding the misclassification of dropouts, pre- and post-publication of the CONSORT-2010 statement.[13] Finally, we examined the incidence rate (IR) of non-serious and severe AEs plus exercise-related DOs, along with their 95% confidence intervals (95% CIs). To accomplish this, we calculated exposure time (n = 224,480 person hours of exercise) as the duration of exercise sessions (minutes) x frequency of sessions per week x length of exercise program (number of weeks) among studies which included these data. Forty-

seven (30.9%) study arms with unspecified total weeks of exercise training or/and unspecified frequency per week or/and unspecified duration of individual exercise sessions were excluded from the incidence rate calculation. The statistical significance level for all tests was defined as a *p* value of 0.05. Data analysis were conducted using SPSS for Mac 25.0 (SPSS Inc., Chicago, IL).

[H2] Role of the funding source

The funders played no role in the design, conduct, or reporting of this study.

[H1] Results

[H2] Study Characteristics and Study Quality

Of the included 113 studies conducted in 25 countries, 54 (47.8%) were published from countries in North America and Western Europe. These studies included 152 exercise arms, yielding 5,909 subjects exercising. The median number of patients per therapeutic exercise arm was 28 (range 8 - 209) (Suppl. Appendix 2). The PEDro scores of these studies ranged from 4 to 9. There were two studies[30, 31] that had a PEDro score of 4. With respect to risk of bias, subject blinding was performed in 15 (13.3%) of studies and assessors were blinded in 79 studies (69.9%) (Suppl. Appendix 4).

[H2] Attributes of Therapeutic Exercise

Thirty-eight studies included more than one exercise arm within the study (Suppl. Appendix 3). Most exercise interventions were prescribed for a period of six and up to twelve weeks (32.9%) and the most common frequency examined was three times per week (52.6%). In 61.2% of exercise arms, the duration of each exercise session was 30 minutes up to and including

60 minutes. Of the 152 supervised exercise arms, 112 were supervised throughout the program. Strengthening exercise, whether progressive strengthening or not, was the most common mode of exercise (30.3%), followed by various combinations of exercise modes. The assessment of exercise intensity was not specified in 57.9% of the study arms. As there were too few studies which specified exercise intensity and had reported AEs, we were not able to determine whether exercise intensity was a causative factor for AEs (Tab. 1).

[H2] *Reporting of Adverse Events*

Fifty studies (44.2%) included a statement of AEs, and 24 studies (21.2%) reported exercise-related AEs, for a total of 297 AEs (Tab. 2). While the proportion of studies which included a statement of AEs increased pre- and post-CONSORT-2010[13] (37.2% versus 48.6%), this difference was not statistically significant ($X^2_1 = 1.4$; $p = .24$). We found no established definition of the severity of AEs nor classification of AEs by severity in many of these randomized controlled trials of therapeutic exercise. The following symptoms were recorded as AEs within the 113 studies: dizziness, back pain, hip pain, knee pain, falls/fractures, and "unspecified" injury during strength training. Among the 50 studies with a statement of AEs, 14 (28.0%) studies classified AEs by severity. To determine the total number of nonserious and severe AEs across all studies, we used a modified operational definition of severity of AEs by Vincent et al,[29] and found 286 (96.3%) nonserious AEs and 11 (3.7%) serious AEs reported in these studies (Suppl. Appendix 3).

[H2] *Reporting of Dropouts*

One hundred three studies (91.2%) included a clear statement regarding DOs. There was no significant difference in the inclusion of a statement regarding DOs, pre- and post-

CONSORT-2010 [13] (88.4% vs 92.9%; X_2^1 =0.66; p=0.42). Eighty studies (77.7%) reported DOs occurring during the exercise intervention (Tab. 2). Sixty-one studies (54.0%) reported using an intention-to-treat approach to analysis (Suppl. Appendix 4). The reasons for subject DOs during the intervention period included: heart problems, neck and back pain, leg and knee pain, patient did not like the exercise intervention, time commitment required, and chlorine sensitivity. The most common reason for dropping out was a musculoskeletal pain. Sixteen studies (15.5%) gave reasons for DOs that were similar to types of AEs reported in other studies of therapeutic exercise (Tab. 3).

On a subject-level, 39 out of 644 (6.1%) individuals who dropped out, dropped out for reasons that could be considered exercise-related AEs, yielding 336 patients (6.0%) experiencing exercise-related AEs. None of the 39 reclassified DOs could be considered severe AEs. There was a significant difference in misclassification of DOs pre- and post-CONSORT-2010[13] (12.2% vs. 3.1%; X^2_1=21.2; p<.00001), wherein studies published prior to the statement had more misclassification of DOs than those published after the statement.

[H2] *Association between Therapeutic Exercise and Severity of Adverse Events*

Due to study heterogeneity with respect to exercise program attributes or lack of specificity of exercise program data, it was not possible to conduct a meta-analysis. However, among the 105 exercise arms with complete information regarding exposure time there were 248 episodes of exercise-related harm. The incidence rate (IR) and 95% confidence interval (95% CIs) per 100,000 exercise hours for non-serious AEs/DOs (n = 237) was 105.6 (101.1-110.3). For severe AEs/DOs (n = 11), the incidence rate was 4.9 (4.0 – 6.0) per 100,000 exercise hours.

Regardless of severity, the incidence rate for all AEs/DOs was 110.5 (105.9-115.3) per 100,000 exercise hours.

[H1] Discussion

We found 44.2% of the 113 randomized controlled trials across the 40-year period included a statement regarding AEs. This result is similar to data in another systematic review by Quicke et al. examining 49 studies of physical activity interventions among adults 45 and older with knee pain, and reported 45% of studies included information about AEs.[22] Ethgen et al examined harm reporting in pharmacologic and non-pharmacologic studies for the management of rheumatic disease including exercise for OA, and found 47.3% of nonpharmacologic studies included a statement of AEs.[18] These data are concerning and suggest adherence to CONSORT reporting guidelines is poor in studies of exercise for OA. There is a possibility that researchers examining therapeutic exercise for OA management believe that it is safe and focus less on the of reporting intervention-related harm compared to researchers engaged in drug trials studies[18,32,33] or spinal manipulation[34] where transient discomfort can be experienced immediately following the procedure, though serious AEs associated with its use have not been identified. Additionally, unlike pharmacologic interventions which have strict regulatory guidelines for testing, therapeutic exercise is not held to that same level of scrutiny.[18, 32, 33] This low prevalence of AE statements suggests that harm reporting in clinical trials of therapeutic exercise may receive less attention than issues related to internal consistency and study efficacy. While some transient musculoskeletal sequelae can be expected beginning an exercise program, it is important to inform patients that transient discomfort may be expected to reduce their fears and decrease the impact of fear avoidance behaviors. But, if musculoskeletal pain is significant

enough to lead patients to discontinue exercise and drop out of the study, then we propose that reason for dropping out should also be considered an AE.

The CONSORT harm statement requires researchers to classify the severity of AEs.[17] We found 14 of the 50 studies which included a statement about AEs, classified AEs by severity. This low rate of adherence to the CONSORT harm statement is similar to rates reported in other studies of nonpharmacologic interventions in arthritis.[18, 22] For example, Ethgen et al. found 16.2% of nonpharmacologic studies classified AEs by severity, a rate 5 times lower than the rate for pharmacologic interventions in arthritis.[18] In this review, we classified all AEs and found 11 (3.7%) serious AEs. Thus, specific attention to reporting severity of AEs in clinical trials of therapeutic exercise in knee OA is warranted.

Given that exercise requires active participation of patients over an extended period of time and adherence rates are known to be low, researchers often utilize intention-to-treat analysis to account for DOs. Thus, we found a much higher rate (91.2%) of DO statements, and there was no statistically significant difference in these statements pre-and post-CONSORT-2010.[13] However, among the 16 studies that reported DOs, the intervention-related reasons for dropping out were reported as AEs in other studies. These data support the hypothesis that there is no consistency regarding DO classification across studies of therapeutic exercise, leading to a potential for greater exercise-related harm than currently reported. To enhance the credibility of studies of therapeutic exercise in KOA, it is important for authors to report operational definitions of AEs and DOs within their methods. Additionally, many studies did not report the exact timing of DOs across the study timeframe. We agree the CONSORT Harms Statement[17] is the gold standard for reporting of harms in randomized controlled trials. Based on the results of this systematic review, we provide additional recommendations for documenting exercise

interventions and reporting the number of DOs and AEs at each time point. We emphasize that it is important to clarify whether an AE led to a patient dropping out of the study. Finally, as knee pain is a symptom of KOA, it is important be able to determine whether knee pain experienced during a study intervention reaches a threshold that qualifies it for being defined a "harm" (Fig. 2).

We also aimed to determine whether AEs and DOs were classified differently in studies published prior to versus after the CONSORT-2010 statement.[13] We were able support our hypothesis that reporting of AEs was affected by the CONORT statement, as there was a statistically significant difference in inclusion of statements regarding AEs pre- and post its publication. Thus, CONSORT has improved the manner in which RCTs are reported and these positive impacts can only help to improve our ability to evaluate the evidence for therapeutic exercise in the management of knee OA.

There is agreement across health professionals that therapeutic exercise, while providing benefits, presents greater than minimal risk (eg, may cause fatigue or musculoskeletal pain beyond what would normally be experienced by the subjects in daily activities).[35] Therapeutic exercise should be prescribed to patients in the same manner as medications and along with clear instructions to ensure therapeutic exercises are performed in the correct manner (ie, dose, frequency, intensity, mode, and supervision).[21] Within these studies, therapeutic exercise interventions were not fully described. Researchers consistently reported the frequency of exercise per week and total length of the exercise program. Not surprisingly, the most common frequency utilized was three times per week, as this is often considered the minimal frequency for obtaining benefits from exercise.[20, 21] However, the duration of individual sessions was difficult to discern in many cases, especially when exercises were prescribed as a number of

repetitions for a series of exercises. This limited our ability to synthesize the data from these studies with other studies that provided the duration of the exercise session. There were also many different modes of exercise and combinations of modes of exercise, making it difficult to discern what types of exercise may be less harmful in specific subgroups of patients. Interestingly, we found assessment of exercise intensity was not reported in 57.9% of the exercise programs used in these clinical trials, despite the fact it is common knowledge that intensity of exercise has been associated with risk of harm.[36] It is important to include all dimensions of therapeutic exercise and identify which subgroups of patients benefit the most from various therapeutic exercise prescriptions.[37] It was beyond the scope of this article to try to determine which type of therapeutic exercise is less harmful for these patients. We did attempt to ascertain the incidence rate of severe and non-serious AEs among these studies of therapeutic exercise programs and found the rate was low.

[H1] Limitations and Strengths

There exists a risk for misclassification bias of study-reported AEs reported, as each research team used their own AEs definition. Additionally, our reclassification of DOs as AEs may be at risk for misclassification bias as the details regarding DOs were vague. However, we used a standardized approach to categorize the reasons for DOs and a published definition of AEs.[29] While we did not assess inter-rater reliability for coding of study elements, the research team *a priori* developed and used a standardized protocol for data extraction and conducted data extraction separately before coming to a consensus regarding coding. As we included only studies published in English, we may not be including all relevant studies. To examine AEs and DOs by exercise dose, we calculated incidence ratios, combining modes of exercise and calculating the summative exposure. However, data were limited regarding exercise attributes

and many studies used mixed modes of exercise, which prevented subgroup analysis of AEs and DOs by mode of exercise.

With respect to study strengths, only randomized controlled trials of therapeutic exercise without concurrent inclusion of modalities or medications were included to ensure harm, when it occurred, was attributed only to therapeutic exercise. We also used a universally accepted method, PEDro,[27] for scoring study quality. The search was repeated a second time prior to data extraction to confirm the accuracy of the included studies. Data were extracted regarding all aspects of the therapeutic exercise interventions in order to determine the association between exercise attributes and potential harm. However, the level of missing data regarding interventions prohibited an evaluation of exercise dose and potential harm. Finally, due to the heterogeneity of the studies a meta-analysis could not be performed.

[H1] Conclusions

While evidence suggests that therapeutic exercise is a safe treatment option for managing knee OA symptoms,[1-3] there is room for improvement in the reporting of AEs and DOs in trials of therapeutic exercise. AEs and DOs may be underreported and not sufficiently represent the risk associated with therapeutic exercise for knee OA. Greater clarity regarding AE definitions and adherence to the CONSORT harm statement[17] is needed to best determine safe dosing of therapeutic exercise for knee OA. Exercise intensity is frequently not specified in randomized controlled trials of therapeutic exercise and the duration of the individual exercise sessions is often missing. Greater details regarding the interventions must be included in published papers to ensure proper implementation of exercises for the treatment of knee OA. We recommend establishing an operational definition of AEs and DOs for therapeutic exercise trials and that researchers use the TIDier,[9] CONSORT statements,[13, 17] and CERT[38] to describe their

interventions details and record AEs and DOs. Results of this paper can be used to inform the design and reporting of trials of therapeutic exercise.

Author Contributions

Concept/idea/research design: M.D. Iversen

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Systematic Review Registration

The protocol for this systematic review was registered on PROSPERO 2019 (CRD42019136191) and is available in full on the National Institute for Health Research Health Technology Assessment (NIHR HTA) program website at (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019136191).

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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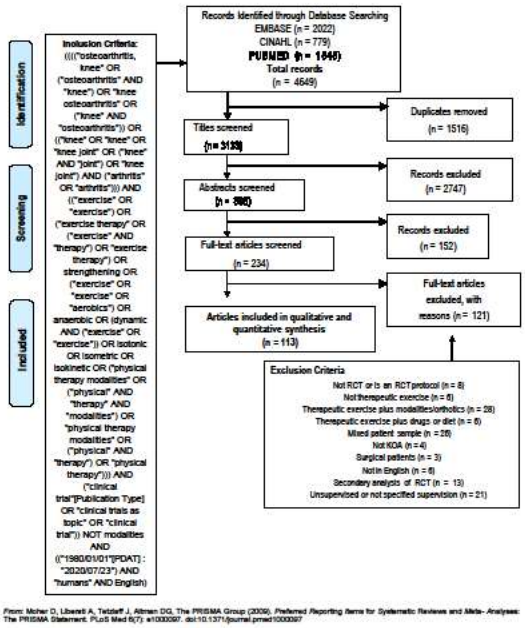

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Figure 1: PRISMA flow diagram of randomized studies of therapeutic exercise for KOA.

- Create operational definitions of adverse events and dropouts that are mutually exclusive and report these definitions within the methodology of the study
- At each evaluation point, record the dropouts and adverse events with corresponding reasons instead of reporting aggregated data
- As knee pain is a symptom of KOA, it is important to determine whether knee pain experienced during an exercise intervention reaches a threshold that qualifies it for being defined a "harm".
- All aspects of the exercise intervention should be detailed even when exercise is individually tailored to patients, a clear statement of the level of exercise intensity and how exercise intensity was measured (eg, BORG scale rating or % max heart rate or % of one repetition max)
- When an exercise intervention is prescribed as a series of exercises (eg, 10 reps of 12 lower extremity exercises), an estimate of the time needed to complete the exercises should be included to allow for comparisons across studies and can provide insight into the intensity of the exercise (ie, greater number of sets and reps over a shorter period of time = less rest = more intense), if not clearly identified by the authors

Figure 2: Additional recommendations for reporting of harm in clinical trials of therapeutic exercise for knee osteoarthritis to complement the CONSORT harms statement. KOA = Knee osteoarthritis

Table 1: Attributes of Therapeutic Exercise Interventions (N = 152) in Randomized Controlled Trials of Exercise for Adults (N = 5909) With Knee Osteoarthritis[a]

Category	No. of Study Arms (%)	No. of Exercisers (%)
Total Weeks of Exercise Training		

Unspecified	1 (0.7)	30 (0.5)
< 6 weeks	20 (13.2)	682 (11.5)
≥ 6 weeks and <12 weeks	50 (32.9)	1406 (23.8)
12 weeks	48 (31.6)	2110 (35.7)
> 12 weeks to < 52 weeks	27 (17.8)	1145 (19.4)
≥ 52 weeks	6 (3.9)	536 (9.1)
Frequency per week		
Unspecified	6 (3.9)	147 (2.5)
1-2x/week	52 (34.2)	1899 (32.1)
3x/week	80 (52.6)	3255 (55.1)
4-5x/week	11 (7.2)	511 (8.7)
> 5x/week	3 (2.0)	97 (1.6)
Duration of individual exercise sessions		
Unspecified	43 (28.3)	1393 (23.6)
< 30 minutes	14 (9.2)	695 (11.8)
≥ 30 minutes to ≤45 minutes	41 (27.0)	1430 (24.2)
> 45 to ≤ 60 minutes	52 (34.2)	2098 (35.5)
> 60 minutes	2 (1.3)	293 (4.9)
Supervised sessions		
Yes, partial	40 (26.3)	1796 (30.4)
Yes	112 (73.7)	4113 (69.6)
Modes of exercise		
Unspecified	2 (1.3)	116 (1.9)
Strengthening (progressive or not)	46 (30.3)	1534 (26.0)
Aerobic (including walking)	7 (4.6)	148 (2.5)

Balance and neuromuscular training	9 (5.9)	260 (4.4)
Tai chi, yoga and other non-traditional exercise	18 (11.8)	551 (9.3)
Any combined aerobic, flexibility, ROM, strengthening	26 (17.1)	1342 (22.7)
Aquatic or aquatic and land exercises	15 (9.9)	539 (9.1)
Combined balance, ROM, flexibility, strengthening	27 (17.8)	1249 (21.1)
Physical therapy plus all modes of exercise	2 (1.3)	170 (2.9)
Assessment of Exercise Intensity		
Unspecified	88 (57.9)	3816 (64.6)
Perceived exertion scale	21 (13.8)	597 (10.1)
% heart rate reserve or maximal heart rate	16 (10.5)	651 (11.0)
% strength performance test	24 (15.8)	680 (11.5)
Not well described	3 (2.0)	165 (2.8)

[a]Some studies had more than one exercise program being tested. ROM = Range of motion

Table 2: Summary of Adverse Events and Dropouts Reporting in Clinical Trials of Therapeutic Exercise (n = 113)[a]

Category	**Number (%)**
Total number of subjects in exercise arm	*5909*
Studies with a clear statement of AEs	50 (44)
Studies which reported exercise-related AEs occurring among those subjects who were	24 (21.2)

allocated to exercise	
Studies which reported exercisers experiencing an AE NOT related to exercise (among those with statement about AEs)	5 (12.5)
Total number of exercisers in studies which had a clear statement of AEs	*2856*
Number of exercisers who had an exercise-related AE in exercise study arms that had a clear statement about AEs	297 (10.4)
Number of exercisers who had an AE NOT related to exercise in studies that had a clear statement about AEs	58 (2.0)
Studies with a clear statement of DOs	103 (91.2)
Studies which reported DOs among studies which had a clear statement of DOs	76 (73.9)
Studies in which reasons for DOs could be considered AEs (eg, back pain, knee pain, neck pain, leg pain, wrist pain) among all studies which had a statement of DOs	16 (15.5)
Total number of exercisers in studies which had a clear statement of DOs	*5562*
Number of exercisers who DO out where DO reason could be considered an AE among all exercisers in studies which reported DOs	39 (0.7)
Number of exercisers who DO out where DO reason was not considered harm	605 (10.9)
Total number of exercisers in studies that had a statement of AEs or a statement about DOs	*5579*
Number of exercisers who DO out where reasons for DO could be interpreted as an exercise-related AE plus total number of exercise-related AEs reported	336 (6.0)

[a]AE = Adverse Event; DO = Dropout.

Table 3: Comparison Between Types of Adverse Events and Reasons for Dropping Out of Studies Among Patients Who Exercised

Types of Adverse Events Reported	Reasons for Dropping Out of Study That Are Similar to Reported Adverse Events	Reasons for Dropout Which Are Not Similar to Adverse Events
Back pain	Back pain	Did not like type of exercise
Hip pain	Knee pain	Bad general health
Leg pain	Neck pain	Required joint injection
Falls/Fractures	Leg pain	Chlorine sensitivity
Knee pain	Wrist pain	Unable to attend sessions
Muscle strain/soreness		NSAID taken after allocation
Swollen knees		Heart problems
Varices		Discontinued intervention- no reason
Dizziness		
Osteoarthritis flare/pain		
Injury during strength training		