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Dose-Response Effects of Tai Chi and Physical Therapy Exercise Interventions in Symptomatic Knee Osteoarthritis

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Abstract

Background: Therapeutic exercise is a currently recommended non-pharmacological treatment for knee osteoarthritis (KOA). The optimal treatment dose (frequency or duration) has not been determined.

Objective: To examine dose-response relationships, minimal effective dose, and baseline factors associated with the timing of response from two exercise interventions in KOA.

Design: Secondary analysis of a single-blind, randomized trial comparing 12-week Tai Chi and Physical Therapy exercise programs (Trial Registry #NCT01258985).

Setting: Urban tertiary care academic hospital

Participants: 182 participants with symptomatic KOA (mean age 61 years; BMI 32kg/m², 70% female; 55% white).

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Methods: We defined dose as cumulative attendance-weeks of intervention, and treatment response as 20% and 50% improvement in pain and function. Using log-rank tests, we compared time-to-response between interventions; and used Cox regression to examine baseline factors associated with timing of response, including physical and psychosocial health, physical performance, outcome expectations, self-efficacy, and biomechanical factors.

Main Outcome Measures: Weekly Western Ontario and McMasters Osteoarthritis Index (WOMAC) pain (0 to 500) and function (0 to 1700) scores.

Results: Both interventions had an approximately linear dose-response effect resulting in a 9 to 11-point reduction in WOMAC pain and a 32 to 41-point improvement in function per attendance-week. There was no significant difference in overall time-to-response for pain and function between treatment groups. Median time-to-response for 20% improvement in pain and function was 2 attendance-weeks and 4 to 5 attendance-weeks for 50% improvement. On multivariable models, outcome expectations were independently associated with incident function response (Hazard Ratio: 1.47; 95% CI: 1.004 to 2.14).

Conclusions: Both interventions have approximately linear dose-dependent effects on pain and function, their minimum effective doses range from 2–5 weeks, and patient perceived benefits of exercise influence the timing of response in KOA. These results may help clinicians optimize patient-centered exercise treatments and better manage patient expectations.

Level of Evidence: Level I

Keywords

Knee Osteoarthritis; Exercise; Dose Response; Tai Chi; Physical Therapy

INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of chronic pain and physical disability[1,2]. Although it affects up to 30% of older adults worldwide, disease-modifying treatments do not yet exist[3]. Currently, major clinical guidelines recommend various exercises for conservative treatment, irrespective of disease stage or symptom severity[4–12]. Recent studies have shown that treatment duration may be the most relevant aspect of exercise dosing[7,12,13]. The optimal duration of treatment required to elicit an initial response remains unclear[7,11,13–16]. The scarcity of this information has contributed to an underutilization of prescriptive exercise by clinicians and poor exercise adherence by patients[10,14,15,17–26].

Measuring outcomes such as pain severity and physical functioning frequently during intervention can be used to ascertain clinically meaningful treatment courses of exercise[7,11,13–16]. Specifically, this information can provide a more nuanced comparison of interventions and a more precise estimate of dose-response effects[7,16]. One prior study used frequently measured pain scores during walking exercise to find that the maximum tolerated dose may be 70 minutes per week among those with severe knee OA, but this study was limited by its brief treatment course (1 week of walking), small sample size (24 participants), and lack of meaningful symptomatic improvements[27]. To date, no study has

comprehensively investigated the dose response effects of Tai Chi and Physical Therapy exercise interventions among this patient population.

The purpose of this study was to examine the dose-response effects of Tai Chi and Physical Therapy exercise interventions on our primary outcome measures of weekly pain and physical function among adults with symptomatic, radiographic knee OA. Specifically, we evaluated the unique course of symptomatic change, the minimum effective dose (i.e. the treatment time required to achieve meaningful response), and baseline factors associated with the timing of response. We hypothesized there would be no significant difference in timing of response between the physical therapy and Tai Chi groups. These results may help clinicians make informed decisions regarding treatment and better manage patient expectations[11,17,27–30].

METHODS

Study design

This was a secondary analysis of a 52-week National Institutes of Health (NIH)-funded, single-blind, randomized trial comparing the effectiveness of 12-week Tai Chi versus Physical Therapy among adults meeting the American College of Rheumatology Criteria for symptomatic knee OA (Trial Registry #NCT01258985). The parent trial demonstrated that Tai Chi produced clinically significant improvements in pain and other secondary outcomes similar to those from physical therapy[31]. The Tai Chi group showed significantly greater improvement in depression and physical quality of life compared with the physical therapy group. A detailed description of the methodology, protocol, and primary study results for this trial has been previously published[31,32]. The *a priori* decision to collect weekly pain and function data during active intervention was made for the purpose of examining dose-response effects of treatment.

Study inclusion criteria were: 1) age ≥ 40 years, 2) fulfillment of the American College of Rheumatology criteria for knee OA, and 3) Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score ≥ 40/100 on at least 1 of 5 questions. Exclusion criteria were: 1) prior experience with complementary medicine or Physical Therapy programs for knee OA within the past year, 2) severe medical limitations precluding full participation, 3) intra-articular steroid injections or surgery in the past three months, 4) intra-articular hyaluronic acid injections in the past six months, 5) Mini-Mental Status examination score <24, or 6) inability to walk without an assistive device.

Participants were randomly assigned in a 1:1 ratio to either 12-weeks of Tai Chi or Physical Therapy. The research study nurses and physical function assessors were blinded to the treatment assignments during enrollment, and the blinded assessors did not have access to the data until data collection was complete. All participants signed an informed consent form before enrollment, and the study was approved by the University Institutional Review Board.

Interventions

Tai Chi is a multi-component, lower intensity Chinese mind-body exercise that consists of slow, flowing movements and incorporates muscle strengthening, balance, postural training, meditation, and deep breath training. Accumulating evidence supports the role of Tai Chi as an effective therapeutic exercise option for patients with chronic pain and other chronic conditions such as fibromyalgia, cancer, heart failure, and chronic obstructive pulmonary disease[33–35]. In this study, each Tai Chi class lasted 60 minutes and occurred twice weekly over 12 weeks. One of 3 Tai Chi instructors each with over 20 years of experience administered a standardized 10-form Yang style Tai Chi protocol for knee OA at each class[32]. Classes typically involved 1) 10 minutes of initial warm-up and review of Tai Chi principles, 2) 30 minutes of Tai Chi movement, 3) 10 minutes of breathing technique, and 4) 10 minutes of relaxation.

The Physical Therapy intervention followed national guidelines for knee OA treatment[36] and consisted of joint mobilizations, lower limb stretching, active and passive range-of-motion, and strengthening, aerobic, neuromuscular, and balance exercises. One of 3 licensed Physical Therapists with over 20 combined years of experience taught and supervised two 30-minute one-to-one progressive exercise sessions per week for the first 6 weeks. For the second 6 weeks, participants completed four 30-minute sessions per week at home with weekly telephone monitoring by research staff. Thus, the home program (4 times per week for 30 minutes over the latter 6 weeks) was equivalent in total minutes of treatment duration to the second half of Tai Chi intervention (twice a week for 60 minutes). By structuring it with 6 weeks of one-to-one treatment and 6-weeks of monitored home treatment, the Physical Therapy program was intentionally designed to reflect current standards of practice. After an initial 1-hour musculoskeletal examination, physical therapists individualized the Physical Therapy regimen toward specific participant treatment goals. To standardize the documentation of physical exam results, the lead physical therapist (MI) held training sessions with the other physical therapists. They also reviewed and agreed upon standard methods for assessing posture and conducting and recording results of special musculoskeletal physical examination tests. Throughout both the Tai Chi and physical therapy interventions, participants were asked to practice for at least 20 minutes daily at home[32].

Weekly Measures

WOMAC is a widely-used, validated self-report questionnaire in patients with knee OA; has a 48-hour recall period and consists of pain intensity and physical function visual analog subscales[37]. The pain subscale ranges from 0–500mm and consists of 5 items asking about pain during rest or activity. The physical function ranges from 0–1700mm and consists of 17 items asking about ability to perform daily activities. Higher scores indicate greater pain and poorer physical function, respectively. As recommended by the scoring manual, missing items were imputed according to the mean value of the remaining items on the subscale when no more than 1 item for pain, and 3 items for function were missing[37].

The weekly WOMAC was administered before each in-person session. During the home program portion of the physical therapy intervention, it was administered over the phone at the end of each week.

Baseline Measures

Patient-reported outcomes—The *Patient Global Assessment* is a single, 0–10cm visual analog scale item that measures the patient’s perception of global health by asking “Considering all the ways your knee OA affects you, how are you doing today?” Higher score indicates poorer global health.[38]

A generic measure of health-related quality of life, the *Short Form-36* has well-documented psychometric properties and consists of 36 questions related to eight dimensions of health[39]. In this analysis, the *Mental Health* and *Energy and Vitality* subscales were used to complement domains already measured in other instruments. The questions for each subscale are transformed into a normalized scale ranging from 0 to 100, with higher scores indicating better perceived health status. Scores were also combined according to the standard scoring algorithm to obtain two aggregate scores: the *Physical Component Summary* (including physical function, bodily pain, physical role functioning, and vitality) and the *Mental Component Summary* (including social function, emotional role functioning, mental health, and general health) scores.

The *CHAMPS Physical Activity Questionnaire for Older Adults (CHAMPS)* is a 40-item validated instrument that measures weekly physical activity levels in older adults based on caloric expenditure and frequency of exercises such as swimming or walking[40]. Higher scores indicate greater physical activity.

The Patient-Reported Outcomes Measurement Information Systems *Sleep Disturbance Short Form (v.8a)* measures perceptions of sleep quality, sleep depth, and sleep restoration[41]. Scores are converted to a T-score normalized to the general population with a mean of 50 and standard deviation (SD) of 10. This short form has a total T-score range from 28.9 to 76.5.

The *Beck Depression Inventory, second edition*, is a 21-item validated instrument that measures the severity of depressive symptoms[42]. Total scores range from 0–63, and higher scores reflect greater depressive symptoms.

The validated *Perceived Stress Scale* (10-items; higher scores reflect a greater stress) measures the degree to which situations over the past month are appraised as uncontrollable/overwhelming[43].

The *Five Facet Mindfulness Questionnaire* is a self-reported instrument measuring total mindfulness and its five facets. It consists of 39 five-point Likert scale questions and the total score sums all responses (39–195); higher scores reflect greater mindfulness. Validated among both meditating and non-meditating participants, this scale was the highest rated mindfulness patient-report outcome instrument for construct validity and internal consistency[44].

The validated *Arthritis Self-Efficacy Scale-8* (10-point Likert scale; higher scores indicate higher self-efficacy) measures self-efficacy, the belief that one can successfully take action to produce a desired outcome[45].

The *Outcome Expectations for Exercise Scale* is a validated instrument that measures the perceived benefits of exercise among older adults[46]. The concept of expectancy refers to the belief that performing a particular behavior will lead to a desired outcome. This scale consists of 9 questions, each rated from 1 to 5, and higher scores represent greater exercise outcome expectations.

The *Medical Outcomes Study Social Support Survey* is a 19-item, Likert-scale measure of functional social support in community dwelling chronically ill persons[47]. Higher scores indicate greater social support.

Physical performance measures—The *Six-minute Walk Test* measures functional exercise capacity[48] by having participants walk as far as possible within a six-minute period, and the resulting distance is noted and recorded.

The *20-Meter Walk Test* measures gait speed,[49] in seconds, over a 20 meter distance. Longer times indicate slower gait speed. Gait speed is commonly used as an objective measure of lower extremity strength and mobility in OA[49]. Both walking tests were performed in quiet hallways and were administered by trained investigators following a standard script.

The *Berg Balance Scale* is a performance-based test of dynamic balance, including the performance of 14 functional tasks such as standing from a seated position, standing unsupported for two minutes, turning 360°, and standing on one foot[50]. Berg scores range from 0 to 56 with higher scores indicating better balance.

Leg extensor muscle strength (measured in newtons) was assessed according to a computer-interfaced bilateral leg press apparatus (Leg Press A420; Keiser) using the one-repetition maximum technique and defined as the maximum load that the subject could move through their full range of motion (ROM) while maintaining proper form[51]. *Leg extensor peak muscle power and peak contraction velocities* were subsequently measured following a 5-minute rest period after the muscle strength test. Briefly, each participant was instructed to complete a total of 5 repetitions, each separated by 30 seconds, as quickly as possible through their full ROM at 40% and then at 70% of the one-repetition maximum. The highest measured power output (measured in watts) and corresponding contraction velocity (meters/second) were recorded. Further details about these methodological procedures have been previously published[52].

Biomechanical outcomes—The *Kellgren and Lawrence (K/L) grade* for global tibiofemoral radiographic severity was also used to score weight-bearing knee radiographs[53]. K/L scores are reported for the more severely affected knee based on osteophyte formation, joint space width, and subchondral bone sclerosis of each knee compartment.

Baseline radiographic knee alignment of participants was measured using anatomic axis on weight-bearing semi-flexed antero-posterior knee radiographs according to previously validated methods[54]. We adjusted anatomic axis measures by sex (female, -3.5° ; male, -6.4°) to better reflect mechanical axis and categorized them using standard definitions: valgus ($>182^{\circ}$), normal (178 to 182°), or varus ($<178^{\circ}$).

Knee genu recurvatum is hyperextension of the knee joint greater than 0° and was assessed by one of the physical therapists as a part of the initial standardized physical examination for the Physical Therapy intervention. In addition, the physical therapist assessed ankle-foot alignment, pes planus or cavus. Because this assessment was only part of the Physical Therapy program, participants from the Tai Chi group did not have this data.

Procedure—At the beginning of the first attended class for each week, participants were required to sign-in and complete self-report measures of pain and physical function (i.e. WOMAC). During the home-exercise portion of the Physical Therapy intervention, WOMAC data were collected during weekly monitoring phone calls by study staff. Baseline measurements were collected at the screening visit, prior to randomization. To mitigate the influence of self-inclusion bias and regression to the mean, we only included participants with post-randomization WOMAC data (collected at the first scheduled class) in this analysis. We defined exercise ‘dose’ according to treatment duration, measured as the cumulative number of weeks attended (i.e. attendanceweeks). If participants attended at least 1 session in a given week, this was considered an attended week in this analysis. This approach for exercise dosage is concordant with those used in related Cochrane Reviews because it provided a quantitative outcome for the number of potential progressions through the exercise programs[7,13].

Statistical Analysis

Descriptive statistics were computed for baseline variables and presented as mean $\pm$ SD unless otherwise stated. To evaluate the presence of dose-dependent relationships, we used model-fit tests to examine polynomial regressions of linear, quadratic, or cubic shapes of symptom change in relation to dose of exercise.

To evaluate the minimum effective dose, we used time-to-event methods (Kaplan-Meier) to determine the median number of attendance-weeks (time) required to achieve treatment response (event). Two different clinically-meaningful response thresholds were used: 1) 20% improvement; and 2) 50% improvement for both pain and function. 20% improvement is an established threshold of minimal clinically important improvement for WOMAC pain and function scores[55]. 50% improvement is concordant with established thresholds of treatment response from Outcome Measures in Rheumatology and Osteoarthritis Research Society International[56]. We also used log-rank tests to compare time-to-response between Tai Chi and Physical Therapy. Participants who did not respond to treatment were censored at week 12 or, if applicable, the week at which they were lost to follow-up.

Prior to analyses, we selected a list of baseline variables to investigate their respective association with the timing of response. These variables were selected from among

commonly-researched general domains that predicted exercise treatment outcomes in OA literature. We also considered variables that could conceptually or biologically influence treatment response from exercise. Using the 50% improvement response threshold, we examined these associations using Cox proportional hazards regression. Where no significant difference was found for time-to-response between Tai Chi and Physical Therapy, the participants from either group were combined for the corresponding Cox regression models. Baseline factors found significant (at $p \leq .05$) on unadjusted models were subsequently included in multivariable models. Model appropriateness and assumptions for the final multivariable models were checked both graphically and analytically using deviance residuals and Schoenfeld residuals-based tests. Threshold for statistical significance was $p \leq .05$ for all tests. All data were analyzed using SAS statistical software (Version 9.4).

RESULTS

Of the 204 participants from the parent trial, 182 attended their first week of class and were included in this analysis. Table 1 summarizes the baseline characteristics of all participants and by treatment assignment: 96 were randomized to Tai Chi and 86 to Physical Therapy. The 182 participants were predominantly female (70%), white (55%), had some post-secondary education (84%) and radiographic tibiofemoral severity grade 2 (93%). Mean age was 61 ± 10 years and body mass index (BMI) was $32 \pm 7 \text{ kg/m}^2$. The two groups were similar in baseline characteristics, only differing significantly in the 20-Meter Walk Test ($p = 0.048$).

Dose-Dependent Symptomatic Change

Figure 1 displays the dose-response effects of Tai Chi and Physical Therapy interventions on pain (**Panel A**) and physical function (**Panel B**) absolute effects by attendance-weeks. The polynomial regressions showed that linear relationships best fit the trajectory of symptom change with increasing attendance-weeks for pain and function during either intervention. On average, one week of Tai Chi resulted in an 11.4 point improvement (95% CI: 9.4 to 13.4; $p < .0001$) in WOMAC pain and a 40.6 point improvement (95% CI: 33.8 to 47.3; $p < .0001$) in function. Similarly, one week of Physical Therapy resulted in a 9.3 point improvement (95% CI: 6.8 to 11.7; $p < .0001$) in pain and a 32.4 point improvement (95% CI: 23.3 to 41.4; $p < .0001$) in function. **Panel C** and **Panel D** display dose-response effects using percent change from baseline.

Minimum Effective Dose Estimates

Figure 2 shows the Kaplan-Meier curves that model the estimated probability of non-response by attendance-weeks to either Tai Chi or Physical Therapy interventions utilizing the 20% improvement in pain (**Panel A**) or function (**Panel B**) response threshold; and the 50% improvement threshold for pain (**Panel C**) or function (**Panel D**). There was no significant difference between Tai Chi and Physical Therapy in time-to-response according to either 20% or 50% response thresholds for pain or function ($p = .10$ to $.36$). The median time-to-response for 20% improvement in pain and function was 2 attendance-weeks of Tai Chi or Physical Therapy, and a preliminary estimate for cumulative response up to 11

attendance-weeks was $\approx 90\%$ for pain and $\approx 85\%$ for function. Similarly, around half of the participants had 50% improvement after attending 4 weeks of Physical Therapy or 5 weeks of Tai Chi. Furthermore, a preliminary estimate for cumulative response up to 11 attendance-weeks was $\approx 75\%$ for pain and $\approx 71\%$ for function.

Baseline Factors Associated with the Timing of Response

Table 2 summarizes the unadjusted hazard ratios (HR) of baseline characteristics for 50% symptom improvement. We found a general pattern wherein physical health factors, self-efficacy, and outcome expectations tended to be significantly associated with treatment response rather than psychosocial or biomechanical factors.

Five baseline factors had significant associations with pain response, and 9 with function response. Poorer patient global assessment was associated with a reduced likelihood of pain (HR: 0.87; 95% confidence intervals [CI]: 0.80 to 0.94) and function response (HR: 0.88; 95% CI: 0.81 to 0.96). Conversely, greater physical activity, walking distance, physical quality of life, and self-efficacy were associated with a greater likelihood of both pain and function response. For only function response, pain, sleep disturbance, and black race (in reference to white race) were associated with a reduced likelihood of response; while increased outcome expectations were associated with a greater likelihood of response.

None of the 5 baseline factors that were significant on unadjusted models remained significantly associated with pain response on multivariable models (data not shown). For function response, outcome expectations (HR: 1.47; 95% CI: 1.004 to 2.14; $p=.05$) were significantly associated with response, independent of the 8 other factors found significant on unadjusted models. In other words, there was a 47% greater likelihood of physical function response for each additional point in outcome expectations at any given point of the 12-week interventions. The 8 other baseline factors did not remain significant on multivariable models (data not shown).

DISCUSSION

In this study, we examined the dose-response effects of 12-week Tai Chi and Physical Therapy exercise interventions on pain and physical function among adults with symptomatic, radiographic knee OA. We found that, up to 12 weeks, both Tai Chi and Physical Therapy have approximately linear dose-response effects on pain reduction and functional improvement. Furthermore, we found initial estimates of their minimum effective doses: 2 weeks for at least 20% improvement, and 4 to 5 weeks for at least 50% improvement in pain and function. Time-to-response did not significantly differ between treatments. Importantly, participants with greater baseline outcome expectations for exercise had physical function response faster. Overall, this study shows the utility of examining weekly-measured symptoms to better understand how improvements occur during exercise treatment. This knowledge may assist the decision making process for clinicians and advance the progress of better patient-centered care.

Our results are consistent with prior studies that found greater exercise exposure caused greater symptom improvements among those with knee OA[27,57]. Ettinger *et al.* found a

dose-response relationship between greater treatment attendance and pain/function improvements from aerobic or strength training exercise programs[57]. In addition, Wallis *et al.* recently found a similar relationship between walking time and improved WOMAC scores during a phase I dose-escalation trial[27]. By frequently measuring symptoms during treatment, our findings expand upon this body of research by providing the shape of meaningful symptomatic change over time and by estimating the minimum effective dose for both interventions. Furthermore, this investigation extends the primary results of the parent trial by finding that Physical Therapy and Tai Chi were similarly potent in their rate of response and shape of symptomatic improvement, up to 12 weeks[31]. While our results are concordant with existing evidence that shows baseline physical health, self-efficacy, and outcome expectations influence exercise treatment response[58], they augment this evidence by showing that these factors may also influence the timing of response.

This finding is discordant with the notion that outcome expectations primarily influence treatment response via improved exercise adherence[10,25,59]. Because outcome expectations were associated with response at any given attendance-week, our results indicate that pathways unrelated to adherence may also explain this association. Indeed, this association might be mediated through reduced pain-related anxiety or greater in-class exercise engagement[60]. In addition, while our list of baseline factors was extensive, it was not exhaustive. Though a definitive conclusion is beyond the scope of this investigation, this knowledge can inform the design of future studies to disentangle the heterogeneity and timing of exercise treatment response in this patient population.

Our findings provide insightful information for clinicians. For example, empirical knowledge of the shape of symptomatic change may help clinicians better discriminate between exercise regimens or combinations of treatments. In addition, clinicians can utilize minimum effective dose estimates to guide more concrete expectations of treatment and enhance patient compliance; which is often diminished due to transient discomforts from participation and the lack of immediate symptom relief[10,24–26]. Long-term adherence is crucial to the efficacy of exercise and is a major barrier to treating knee OA [10]. Health professionals should identify and address individual barriers to exercise adherence when prescribing exercise for OA[10]. Furthermore, because higher perceived benefits of exercise were associated with the timing of response, we speculate that clinicians can improve the effectiveness of exercise among older adults through frequent encouragement, specific guidance, and regular utilization of exercise prescriptions. Although clinician recommendation is the single most important determinant for exercise engagement in OA[61], less than one third of U.S. physicians provide any exercise advice for these patients[62]. Thus, physicians may play an important role to impact better exercise outcomes in knee OA.

This study responds to the call for further research on the dose-response effects of exercise[7,14,15]. Although dose-ranging studies are optimally conducted in a traditional phase II design, this is rarely utilized due to well-documented methodological challenges and resource limitations associated with conducting exercise trials[7,14,16,63]. Hence, by frequently-measuring symptom data throughout a large comparative-effectiveness trial, our approach may demonstrate a more pragmatic means for researchers to understand the dose-

response effects of exercise. We recommend consideration of this approach as a part of standard investigative practice for emerging consensus guidelines, including the Consensus on Exercise Reporting Template[64]. Second, the nearly linear shape of symptomatic improvement indicates that the average participant may continue to improve from these interventions beyond 12 weeks. This finding is of particular interest given that exercise therapy is only covered by insurance for 6–8 weeks in the United States. At minimum, our findings indicate that additional study on the superiority of 12-week (or greater) treatment durations versus 6–8 week durations is warranted.

Limitations

First, in order to reduce response burden, WOMAC data were only collected once per week rather than at each treatment session. Second, without a control group in the parent trial, this study was unable to fully disentangle placebo or other non-specific effects that may occur in any therapeutic trial[59,64,65]. We also acknowledge that a completer analysis may slightly overestimate treatment effect. However, we utilized 50% improvement as a response threshold as indicated by the Outcome Measures in Rheumatology and Osteoarthritis Research Society International responder criteria for clinically meaningful treatment response [56]. Furthermore, the decision to collect weekly symptom data for the purpose of this analysis was made *a priori*, and we utilized several other methods to reduce bias, including a robust treatment randomization scheme, blinded assessors of physical performance, both radiographic and symptomatic verification of diagnosis, and our use of post-randomization WOMAC pain/function data as the baseline measure, which likely reduced the influence of self-selection bias and regression to the mean. Despite these limitations, our time-sensitive evaluation of these interventions provides insights that can help advance the science of exercise prescription for those with knee OA.

Further study is required to confirm our findings using different treatment durations, frequencies, modalities, and intensities. A larger body of high quality evidence can be used to generate conclusive guidelines through large-scale network meta-analyses. Additional study on the dose effects of exercise treatment on psychosocial symptoms, cost-effectiveness, adverse events and injury, and surgical outcomes is also warranted. Furthermore, a better understanding of the physiological mechanisms underlying these dose-response effects would complement these findings. Finally, future research to identify subgroup patterns among response trajectories may help to further disentangle the heterogeneity of exercise response among these patients.

In conclusion, this study supports the utility of weekly-measured symptoms to better understand the dose-response effects of exercise interventions among adults with symptomatic knee OA. We found an initial indication that 12-week Tai Chi and Physical Therapy treatments resulted in approximately linear improvements in pain and function; minimally important benefits after 2 weeks and substantial benefits after 4 to 5 weeks. Importantly, greater outcome expectations for exercise were associated with the timing of functional recovery. Our investigation may demonstrate a more pragmatic means of analyzing the dose-response effects of exercise, inform treatment-making decisions for clinicians, and facilitate better patient-centered care among this large patient population.

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Figure 1 (A-B). Dose-dependent Symptomatic Changes from Tai Chi and Physical Therapy Interventions in Knee OA:

PT= Physical Therapy; TC= Tai Chi; WOMAC=Western Ontario and McMasters Osteoarthritis Index. WOMAC pain score range: 0–500; WOMAC function score range: 0–1700. Greater scores indicate greater pain and worse physical function, respectively. Approximately linear improvements in pain (Panel A) and physical function (Panel B) occurred with increasing attendance–weeks to either intervention in a dose-dependent manner. Note: Participant sample sizes are listed at each cumulative attendance week by treatment group.

Figure 2 (A-D). Time-to-Response from Tai Chi and Physical Therapy Interventions in Knee OA: PT= Physical Therapy; TC= Tai Chi. Kaplan-Meier curves for 20% improvement in pain (Panel A) and physical function (Panel B); and for 50% improvement in pain (Panel C) and physical function (Panel D) by attendance-week. P -values refer to log-rank tests comparing overall time-to-response between interventions. The number “at risk” (i.e. participants not responded) is listed at each cumulative attendance-week by treatment group.

Table 1.

Baseline Characteristics of Participants

Characteristic	Tai Chi n= 96	Physical Therapy n= 86
Demographic		
Age, years	60.8±10.1	60.4±10.6
Female Sex, n (%)	68 (70.8)	59 (68.6)
Race, n (%)		
White	50 (52.1)	50 (58.1)
Black	35 (36.5)	24 (27.9)
Asian/Other	11 (11.5)	12 (14.0)
Body Mass Index, kg/m ²	32.5±6.8	32.3±7.0
Duration of knee pain, years	8.3±10.7	8.5±10.3
Kellgren-Lawrence grade, n (%) *		
0–1	7 (7.5)	6 (7.0)
2	35 (37.6)	34 (39.5)
3	37 (39.8)	27 (31.4)
4	14 (15.1)	19 (22.1)
Highest Level of Education, n (%)		
High school Graduate or Less	17 (17.7)	13 (15.1)
Some College or more	79 (82.3)	73 (84.9)
Self-reported comorbidities, n (%)		
Heart Disease	7 (7.3)	8 (9.3)
Hypertension	52 (54.2)	40 (46.5)
Diabetes	19 (19.8)	12 (14.0)
Opioid Use, n (%)	11 (11.7)	9.0 (10.7)
NSAID Use, n (%)	58 (60.4)	51 (60.0)
Patient-Reported Physical Health		
WOMAC Pain (Range: 0–500)	248.8±95.2	253.7±101.4
WOMAC Physical Function (Range: 0–1700)	897.9±344.7	872.9±371.3
Patient Global Assessment (Range: 0.0–10.0cm)	5.2±2.1	5.0±2.3
SF-36 Physical Component Summary (Range: 0–100) #	36.7±8.4	36.9±9.8
PROMIS Sleep Disturbance Short Form (Range; T-score: 28.9–76.5)	50.6±9.3	50.2±9.8
SF-36 Energy and Vitality (Range: 0–100) #	56.7±18.5	56.6±20.0
CHAMPS Physical Activity mod-high calories/week #	1499.5±1906.2	1456.5±1669.4
Physical Performance		
6-Minute Walk Test meters (Reference Range: 400–700) * #	393.7±92.9	402.9±81.6
20-Meter Walk Test seconds	19.5±6.4	18.0±3.5

Characteristic	Tai Chi n= 96	Physical Therapy n= 86
Leg Extensor Muscle Strength** newtons[#]; 1RM	948.2±384.7	1025.1±416.3
Muscle Contraction Velocity** meters/second (40% of 1RM)[#]	0.4±0.2	0.5±0.2
Muscle Contraction Velocity** meters/second (70% of 1RM)[#]	0.4±0.1	0.3±0.1
Muscle Power** watts (40% of 1RM)[#]	251.8±137.1	290.0±196.0
Muscle Power** watts (70% of 1RM)[#]	305.6±168.7	314.2±184.5
Berg Balance Score (Range: 0–56)[#]	51.9±5.5	52.4±4.4
Psychosocial Health		
SF-36 Mental Component Summary (Range: 0–100)[#]	52.7±9.4	52.1±9.4
SF-Mental Health (Range: 0–100)[#]	74.7±16.0	73.6±16.3
Beck II Depression Inventory (Range: 0–63)	7.5±8.3	7.7±8.6
Perceived Stress (Range: 0–40)	13.4±6.9	13.5±7.0
Total Mindfulness (FFMQ)[†] (Range: 39–195)[#]	142.6±17.1	14.9±17.0
MOS Social Support (Range: 19–95)[#]	65.6±21.9	70.5±23.2
Patient Cognitions/Beliefs		
Arthritis Self-Efficacy Scale-8 (Range: 0–10)[#]	6.2±2.1	6.3±2.2
Outcome Expectations (Range: 1.0–5.0)[#]	3.9±0.5	3.9±0.6
Biomechanical Factors		
Radiographic Leg Alignment[‡], n (%)		
Normal	30.0 (48.4)	28.0 (47.5)
Varus	14.0 (23.7)	14.0 (23.7)
Valgus	20.0 (32.3)	17.0 (28.8)
Knee Recurvatum[¶], n (%)		
Presence	n/a	4.0 (4.8)
Absence	n/a	80.0 (95.2)
Foot-Ankle alignment[¶], n (%)		
Normal	n/a	35.0 (41.7)
Planus	n/a	47.0 (56.0)
Cavus	n/a	2.0 (2.4)

1RM= one-repetition maximum; CHAMPS= Community Healthy Activities Model Program for Seniors; FFMQ= Five Facet Mindfulness Questionnaire; MOS= Medical Outcomes Survey; PROMIS= Patient-Reported Outcomes Measurement Information Systems; SF-36= Short Form-36; WOMAC= Western Ontario and McMaster Osteoarthritis Index. All values are mean ± standard deviation, unless otherwise specified.

* Normal range reported for the general population.

** For muscle strength, power, and velocity, total n= 165 to 168: 86 to 88 for Tai Chi and 78 to 80 for Physical Therapy.

[†] For FFMQ, total n = 74: 41 for Tai Chi and 33 for Physical Therapy.

[‡]For radiographic leg alignment, total n= 121: 62 for Tai Chi and 59 for Physical Therapy.

[¶]Recurvatum and foot-ankle alignment examinations were distinctly performed as a part of the Physical Therapy program.

[#]Higher score indicates greater health.

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Table 2.

Hazard Ratios of Treatment Response (50% improvement) in Pain and Physical Function by Baseline Factors (n=182)

Characteristic	Hazard Ratio (95% Confidence Interval)			
	Pain		Function	
Demographic				
Age, years	1.01	(0.99, 1.03)	1.02	(1.00, 1.04)
Female Sex, n (%)	1.32	(0.87, 2.01)	1.29	(0.85, 1.96)
Race, n (%)				
White	reference		reference	
Black	0.71	(0.47, 1.07)	0.59	(0.39, 0.91)
Asian/Other	0.94	(0.53, 1.67)	0.91	(0.52, 1.58)
Body Mass Index, kg/m ²	0.98	(0.96, 1.01)	0.98	(0.95, 1.00)
Duration of knee pain, years	1.01	(1.00, 1.03)	1.01	(1.00, 1.03)
Highest Level of Education, n (%)				
High school graduate or less	reference		reference	
Some college or more	1.69	(0.97, 2.94)	1.85	(1.02, 3.36)
Self-reported comorbidities, n (%)				
Heart Disease	0.66	(0.31, 1.41)	0.93	(0.45, 1.90)
Hypertension	1.14	(0.80, 1.63)	0.88	(0.61, 1.27)
Diabetes	1.01	(0.62, 1.65)	1.04	(0.63, 1.72)
Opioid Use, n (%)	1.12	(0.60, 2.09)	1.05	(0.56, 1.96)
NSAID Use, n (%)	1.16	(0.80, 1.68)	1.08	(0.74, 1.57)
Patient-Reported Physical Health				
WOMAC Pain (Range: 0–500); (50-point units)	n/a		0.86	(0.78, 0.95)
WOMAC Physical Function (Range: 0–1700); (100-point units)	0.96	(0.91, 1.004)	n/a	
Patient Global Assessment (Range: 0–10cm)	0.87	(0.80, 0.94)	0.88	(0.81, 0.96)
SF-36 Physical Component Summary (Range: 0–100) [#] ; (10-point units)	1.35	(1.10, 1.65)	1.46	(1.18, 1.81)
PROMIS Sleep disturbance (Range, T-Score: 28.9–76.5); (10-point units)	0.88	(0.74, 1.05)	0.83	(0.69, 1.00)
SF-36 Energy and Vitality (Range: 0–100) [#] ; (10-point units)	1.06	(0.96, 1.17)	1.08	(0.97, 1.19)
CHAMPS Physical Activity moderate-high calories/week [#] (500-calories/week units)	1.05	(1.003, 1.10)	1.06	(1.009, 1.11)
Physical Performance				
6-Minute Walk Test meters [#] (50-meter units)	1.12	(1.01, 1.25)	1.14	(1.03, 1.27)
20-Meter Walk Test seconds	0.96	(0.92, 1.01)	0.97	(0.92, 1.01)
Leg Extensor Muscle Strength [*] newtons; 1RM [#] (100-newton units)	0.98	(0.93, 1.03)	1.01	(0.96, 1.06)
Leg Extensor Muscle Contraction Velocity [*] meters/second (40% of 1RM) [#]	1.47	(0.52, 4.17)	1.62	(0.57, 4.67)
Leg Extensor Muscle Contraction Velocity [*] meters/second (70% of 1RM) [#]	1.40	(0.32, 6.13)	1.95	(0.44, 8.79)

Characteristic	Hazard Ratio (95% Confidence Interval)			
	Pain		Function	
Leg Extensor Muscle Power* watts (40% of 1RM) # (100-watt units)	1.02	(0.91, 1.15)	1.04	(0.93, 1.17)
Leg Extensor Muscle Power* watts (70% of 1RM) # (100-watt units)	1.00	(0.90, 1.12)	1.05	(0.95, 1.17)
Berg Balance Score (Range: 0–56)#	1.02	(0.98, 1.06)	1.03	(0.99, 1.07)
Patient Cognitions/Beliefs				
Arthritis Self-Efficacy Scale-8 (Range: 0–10)#	1.11	(1.01, 1.21)	1.14	(1.04, 1.25)
Outcome Expectations (Range: 1.0–5.0)#	1.14	(0.82, 1.57)	1.43	(1.03, 1.97)

1RM= one-repetition maximum; CHAMPS= Community Healthy Activities Model Program for Seniors; SF-36= Short Form-36; PCS= Physical Component Summary; PROMIS= Patient-Reported Outcomes Measurement Information Systems; WOMAC= Western Ontario and McMaster Osteoarthritis Index. Exercise interventions were 12 weeks of Physical Therapy or Tai Chi. Hazard ratios were from unadjusted Cox regression models.

* For muscle strength, power, and velocity, total n= 165 to 168: 86 to 88 for Tai Chi and 78 to 80 for Physical Therapy.

Higher score indicates greater health. Note: For brevity, hazard ratios for Psychosocial and Biomechanical factors are not shown as all variables were not significantly associated with pain or function response at $p \leq .05$. Bold text indicates statistical significance, $p \leq .05$.