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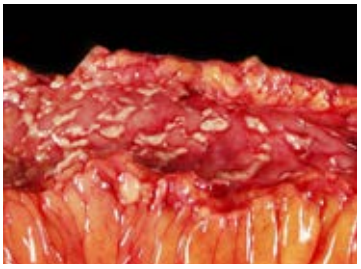

DPP-4 inhibitors associated with an increased risk of inflammatory bowel disease p 479

Practising tai chi mind-body treatment is beneficial in fibromyalgia p 480

Patient's perspective on how to make the most of tai chi to help ease chronic pain p 481

ORIGINAL RESEARCH Population based cohort study

Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes

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Study question Is the use of dipeptidyl peptidase-4 (DPP-4) inhibitors associated with the incidence of inflammatory bowel disease in patients with type 2 diabetes?

Methods This population based cohort study used data from the UK Clinical Practice Research Datalink. A cohort of patients aged 18 years or more starting antidiabetic drug treatment between 1 January 2007 and 31 December 2016 was identified and followed up until 30 June 2017. Use of DPP-4 inhibitors was modelled as a time varying variable and compared with use of other antidiabetic drugs, with exposures lagged by six months to account for latency and diagnostic delays. Hazard ratios with 95% confidence intervals of incident inflammatory bowel disease were estimated for use of DPP-4 inhibitors overall, by cumulative duration of use, and by time since initiation.

Study answer and limitations 141 170 patients generated 552 413 years of follow-up and 208 incident inflammatory bowel disease events (crude incidence rate 37.7 (95% confidence interval 32.7 to 43.1) per 100 000 person years). Overall, use of DPP-4 inhibitors was associated with an increased risk of inflammatory bowel disease (53.4 *v* 34.5 per 100 000 person years; adjusted hazard ratio 1.75, 95% confidence interval 1.22 to 2.49). Hazard ratios gradually increased with longer durations of use, peaking after three to four years (2.90, 1.31 to 6.41) and decreasing thereafter. A similar pattern was observed with time since initiation. Given the observational nature of this study, residual confounding remains possible.

Adjusted hazard ratios for association between use of DPP-4 inhibitors and risk of inflammatory bowel disease

Exposure	Events/ person years	Incidence rate (95% CI)*	Adjusted hazard ratio (95% CI)†
Use of other antidiabetic drugs	159/460 623	34.5 (29.4 to 40.3)	1.00 (reference)
DPP-4 inhibitors	49/91 790	53.4 (39.5 to 70.6)	1.75 (1.22 to 2.49)
Cumulative duration of DPP-4 inhibitor use (years):			
≤1.0	16/36 030	44.4 (25.4 to 72.1)	1.42 (0.84 to 2.41)
1.1-2.0	15/25 491	58.8 (32.9 to 97.1)	1.91 (1.11 to 3.32)
2.1-3.0	S‡	55.8 (24.1 to 110.0)	1.90 (0.91 to 3.96)
3.1-4.0	7/8423	83.1 (33.4 to 171.2)	2.90 (1.31 to 6.41)
>4.0	S‡	39.9 (8.2 to 116.7)	1.45 (0.44 to 4.76)
Time since first DPP-4 inhibitor use (years): prescription (years):			
≤2.0	15/38 608	38.9 (21.7 to 64.1)	1.23 (0.72 to 2.11)
2.1-4.0	24/32 385	74.1 (47.5 to 110.3)	2.50 (1.57 to 3.99)
>4.0	10/20 797	48.1 (23.1 to 88.4)	1.75 (0.86 to 3.58)

*Per 100 000 person years.
†Adjusted for age, sex, year of cohort entry, body mass index, alcohol related disorders (alcoholism, alcoholic cirrhosis of liver, alcoholic hepatitis, and hepatic failure), smoking status, haemoglobin A_{1c}, microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes, duration of treated diabetes, antidiabetic drugs used at cohort entry, aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives, other autoimmune conditions, and total number of unique non-diabetic drugs in year before cohort entry.
‡Numbers <5 are not shown, as per confidentiality policies of Clinical Practice Research Datalink.

What this study adds Use of DPP-4 inhibitors was associated with an increase in the risk of inflammatory bowel disease. This association was elevated between three and four years of use and between two and four years after the start of treatment.

Funding, competing interests, data sharing Funded by the Canadian Institutes of Health Research. No additional data available.

Effect of tai chi versus aerobic exercise for fibromyalgia

Wang C, Schmid CH, Fielding RA, et al

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Study question How effective is tai chi compared with aerobic exercise—the current most commonly prescribed non-drug treatment—in patients with fibromyalgia?

Methods The authors carried out a comparative effectiveness randomised trial in an urban tertiary care academic hospital in the US. 226 participants with fibromyalgia were randomly assigned to either supervised aerobic exercise (24 weeks, twice weekly) or one of four classic Yang-style supervised tai chi interventions (12 or 24 weeks, once or twice weekly). Participants were followed for 52 weeks. The primary outcome was change in scores on the revised fibromyalgia impact questionnaire (FIQR), which measures participant rated overall severity of fibromyalgia. Secondary outcomes included changes of scores in patient's global assessment, anxiety, depression, self efficacy, coping strategies, physical functional performance, functional limitation, sleep, and health related quality of life.

Study answer and limitations FIQR scores improved in all five treatment groups, but the combined tai chi groups improved statistically significantly more than the aerobic exercise group at 24 weeks (difference between groups 5.5 points, 95% confidence interval 0.6 to 10.4, P=0.03). Tai chi treatment compared with aerobic exercise administered with the same intensity and duration (24 weeks, twice weekly) had greater benefit (between group difference in FIQR scores 16.2 points, 8.7 to 23.6, P<0.001). The tai chi groups also improved more in secondary outcomes: patient's global assessment (0.9 points, 0.3 to 1.4, P=0.005), anxiety (1.2 points, 0.3 to 2.1, P=0.006), self efficacy (1.0 points, 0.5 to 1.6, P=0.0004), and coping strategies (2.6 points, 0.8 to 4.3, P=0.005). The groups who received tai chi for 24 weeks showed greater improvements than those who received it for 12 weeks (difference in FIQR scores 9.6 points, 2.6 to 16.6, P=0.007). A key limitation is that patients were aware of their treatment group assignment.

What this study adds This study suggests that tai chi mind-body treatment for fibromyalgia has similar or greater benefits than standard care treatment. A longer duration of tai chi had more benefit than a shorter duration. The therapeutic benefits were consistent among three instructors in a large sample of diverse patients, which provides more support for generalisability to other settings and fibromyalgia patient populations. This mind-body approach may be considered a therapeutic option in the multidisciplinary management of fibromyalgia.

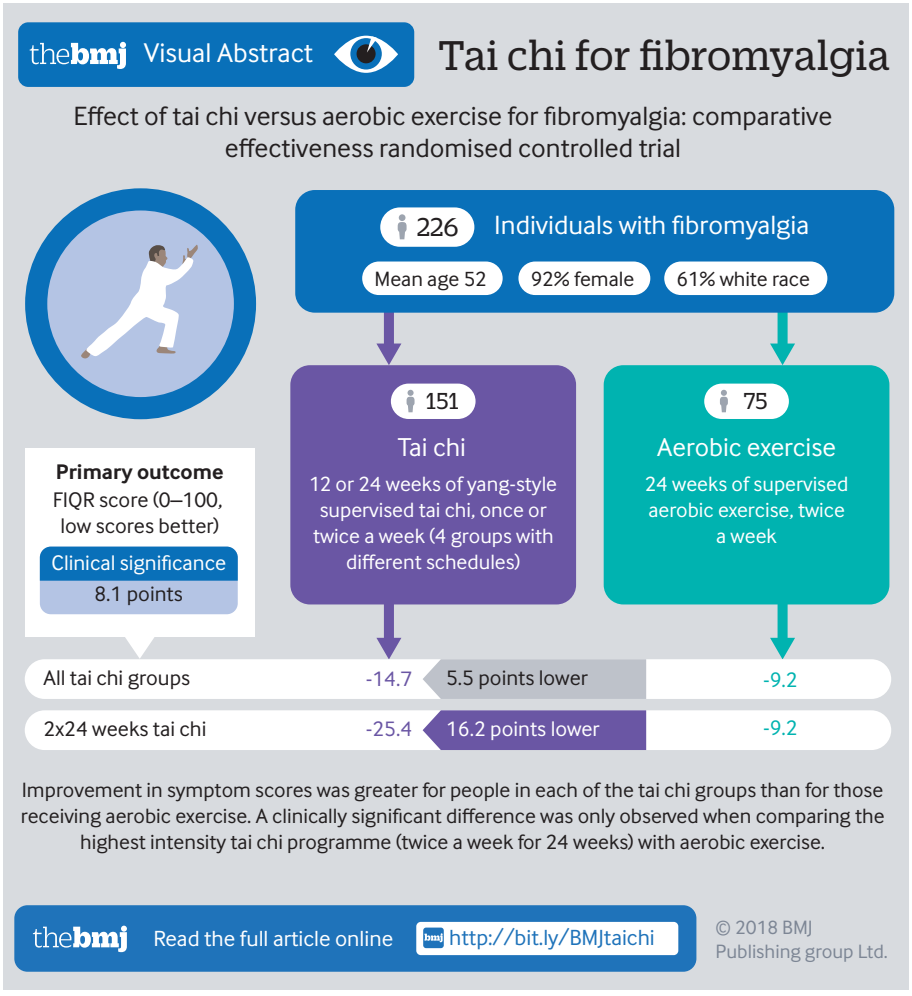
Funding, competing interests, data sharing
Supported by the US National Institutes of Health. There are no competing interests. The investigators will share data on request to the corresponding author (cwang2@tuftsmedicalcenter.org).

Trial registration ClinicalTrials.gov NCT01420640

Mean change (95% CI) in scores on revised fibromyalgia impact questionnaire* from baseline

Follow-up week	Tai chi (n=151) 1×12 weeks (n=39)	2×12 weeks (n=37)	1×24 weeks (n=39)	2×24 weeks (n=36)	Aerobic exercise 2×24 weeks (n=75)
12	−16.5 (−23.4 to −9.6)	−12.3 (−19.0 to −5.6)	−6.6 (−12.8 to −0.3)	−17.2 (−24.0 to −10.3)	−6.2 (−11.0 to −1.4)
24	−11.4 (−18.7 to −4.1)	−11.4 (−18.4 to −4.4)	−16.7 (−23.4 to −10.1)	−25.4 (−32.3 to −18.4)	−9.2 (−14.3 to −4.1)
52	−14.3 (−21.7 to −7.0)	−10.2 (−17.3 to −3.1)	−13.6 (−20.4 to −6.8)	−22.7 (−30.0 to −15.4)	−11.7 (−16.7 to −6.6)

*Range 0-100; higher scores reflect more severe symptoms.



AUTHOR'S PERSPECTIVE Chenchen Wang

Time to rethink exercise for fibromyalgia care

In 2010, the *New York Times* published a story about Mary, a participant in a randomised trial my team conducted, which investigated the efficacy of tai chi for fibromyalgia. Mary is just one of the many patients with chronic musculoskeletal pain who we see in our rheumatology and primary care clinics every day. As with those patients, Mary mentioned that it "hurt so much just to put my arms over my head," "sleeping was difficult," "I couldn't walk half a mile," and said that she felt no motivation or pleasure in life any more. Patients like Mary have often tried different drugs for pain, antidepressants, physiotherapy, and other approaches, and find that nothing works for them. Given the large and growing global burden of chronic pain, finding safe, effective approaches for its management is a priority.

Chronic widespread pain is a complex biopsychosocial medical condition that is associated with substantial mental health comorbidities. Tai chi integrates physical, psychosocial, and behavioural elements, and may be especially suited to tackling the psychological and somatic symptoms associated with chronic pain. A series of studies on tai chi for chronic rheumatic conditions from our team[1-8] found that the practice has short term benefits for pain relief and wellbeing. In our most recent study, published in *The BMJ*, we compared the effectiveness of tai chi with aerobic exercise, which is a standard care, non-drug treatment for fibromyalgia. The study showed that tai chi is as or more effective than aerobic exercise, and that longer duration of treatment provides greater effect. We also found that these therapeutic benefits were consistent across a diverse group of patients, regardless of the instructor. This suggests that the intervention can be delivered in a standardised manner by appropriately trained instructors.

Despite the well established benefits of aerobic exercise as a core standard treatment for fibromyalgia, patients in our trial had difficulty adhering to the programme. Despite encouragement, many participants missed classes, and attendance was lower than in the tai chi group. By contrast, people from the tai chi group continue to call our office looking for opportunities for tai chi training now the study has ended. What we found suggests that patients may be more likely to enjoy, manage, and continue to practise tai chi, perhaps because it involves gentle, low impact movements with minimal side effects.

> We found patients may be more likely to enjoy, manage, and continue to practise tai chi

It might be time to rethink what type of exercise is most effective for patients with fibromyalgia. More importantly, what types or combinations of exercise would patients embrace in the long term? The public health problem of chronic pain calls for an "all hands on deck" approach to give patients feasible therapeutic options for the management of fibromyalgia. It is time for doctors to explore new approaches and rethink their strategies in order to provide the best care for patients with chronic pain conditions.

Chenchen Wang is a professor of medicine at Tufts University School of Medicine and director of the Center for Complementary and Integrative Medicine in the Division of Rheumatology at Tufts Medical Center

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PATIENT'S PERSPECTIVE Amy Price

The unintended consequences of tai chi for fibromyalgia

I could only see the depressing future of being a patient with chronic pain. I didn't expect tai chi to work, but thought I'd give it a chance

I am a trauma survivor with chronic pain. My options for surgical relief and pain management have been exhausted as I refuse to have an internal pain pump, and the Food and Drug Administration has denied my compassionate use request for dangerous neck and spinal surgery, because of the high risk and a less than 5% chance of any benefit. Someone decided I might have fibromyalgia, but no one could explain what it was. The doctor mumbled something about maybe tai chi helping, and for me it did.

I later learnt that fibromyalgia is a complex and confusing diagnosis, thought to come from an overly aroused nervous system. This dysfunction can result in chronic, intermittent pain, sleep deprivation, and fatigue. These symptoms can trigger mental distress as well as cognitive and memory problems. There is no "one size fits all" approach. This makes finding useful treatment difficult.

The uncertainty and variation between patients that make symptoms hard to treat also make them challenging to research. Research can be enriched by patient and public involvement, and this is one way in which patients can show support for medical research. In addition, interventions or treatments that show benefit are more likely to be reimbursed, and this is good for patients.

Tai chi is an ancient martial art that uses slow and gentle exercises to improve balance and mental calm in order to neutralise force and increase self regulation. My balance was poor from brain and spinal damage, and I could only see the depressing future of being a patient with chronic pain. I didn't expect tai chi to work, but thought I'd give it a chance.

The typical regimen is an hour long class a day. This was the intervention used in a trial by Wang et al. Initially, I could only do 10 minutes, three times a week, with constant supervision, because of memory and balance problems. Gradually, over about six weeks, my balance improved, my anxiety decreased, and my strength increased. The philosophy of tai chi is to leverage force rather than resist it.

Would I recommend tai chi for other patients with a fibromyalgia diagnosis? My answer is a qualified yes. These are some of the things you need to consider:

- discuss with your doctor first
- many instructors offer a free introductory class—use this to ensure it is a good match for you
- if the exercise hurts, stop and speak up—the instructor can show you how to adapt and if this does not help, it is best not to continue
- quality matters—the instructor should be trained and certified to teach people recovering from injury
- the investment of resources—the hour in class, transportation, costs—and balance these against benefit
- ask before you start how long it usually takes before students see a benefit
- some physiotherapy groups offer tai chi with other services, ask if this can be bundled for you as a reimbursed intervention if a doctor prescribes it.

Helpful, cost effective interventions such as tai chi can be empowering as long as they are not used to deny other effective, but more costly, care. Tai chi has been reported as a safe form of exercise that improves functional capacity without making it hard to breathe or move for those with COPD, arthritis, and heart failure. A recent systematic review showed that tai chi can reduce the incidence of falls in elderly people. A systematic overview recommended tai chi as useful for older people for its various physical and psychological benefits.

Tai chi does not work for everyone with fibromyalgia. The advantage of the intervention is that it is low risk and minimally invasive, unlike surgery, and it will not harm your organs, like long term drug use.

Amy Price is *The BMJ* Patient Editor for Research and Evaluation, serves on the BMJ Patient Panel, and is reading for a DPhil in evidence based healthcare at the University of Oxford

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