ILD Collaborative

A Patient-Physician Collaborative for the Understanding, Management, and Treatment of Interstitial Lung Diseases

Research Designs, Placebo Effects, and Multicomponent Interventions

On Objectivity, Intention, and Complexity

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November 3, 2020

What Is Science?

Science, apart from its results, *is a human attitude.*

Science is the objectivity of accepting reality as it is, and not as one wishes it to be.

The faculty to think objectively is *reason.*

The emotional attitude behind reason is that of *humility.*

Humility and objectivity are indivisible.

Informing Clinical Practice

The purpose of clinical research is to inform clinical practice. Clinical practice includes:

- making a diagnosis,
- prescribing a medicine,
- performing a procedure,
- providing a prognosis.

Risk Versus Cause and Effect

Clinicians need to make decisions about clinical practice.

There are many scientific studies that establish an association between a disease and a risk factor. Nonetheless, one should not readily assume that doing something about the risk for the disease will change the disease outcome.

For example, high blood pressure increases the risk of death. There are drugs that lower blood pressure, but do not lower the risk of death.

Risk Versus Cause and Effect

ScienceDaily®

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Science News

Low vitamin D levels associated with scarring lung disease

Date: June 19, 2018

Source: Johns Hopkins Medicine

Summary: Reviewing medical information gathered on more than 6,000 adults over a 10-year period, researchers have found that lower than normal blood levels of vitamin D were linked to increased risk of early signs of interstitial lung disease (ILD).

Risk Versus Cause and Effect

“In a series of studies, the researchers sought to learn about new, and potentially treatable, factors related to early signs of the disease seen by CT scans — imaging abnormalities that may be present long before symptoms develop — which may help guide future preventive strategies.”

Low vitamin D levels associated with scarring lung disease
https://www.sciencedaily.com/releases/2018/06/180619123008.htm

Risk Versus Cause and Effect

"Results of the most recent data analysis, published in the *Journal of Nutrition* on June 19 [2018] suggest that low vitamin D might be one factor involved in developing interstitial lung disease."

Low vitamin D levels associated with scarring lung disease
https://www.sciencedaily.com/releases/2018/06/180619123008.htm

Risk Versus Cause and Effect

Senior study author: “Our study suggests that adequate levels of vitamin D may be important for lung health. We might now consider adding vitamin D deficiency to the list of factors involved in disease processes, along with the known ILD risk factors. […] However, more research is needed to determine whether optimizing blood vitamin D levels can prevent or slow progression of this lung disease.”

Low vitamin D levels associated with scarring lung disease
https://www.sciencedaily.com/releases/2018/06/180619123008.htm

Risk Versus Cause and Effect

LIVESCIENCE

Does vitamin D protect against COVID-19?

By Ashley P. Taylor - Live Science Contributor 12 hours ago

Recent studies have found a link between low vitamin D levels and an increased risk of COVID-19 infection, but they don't prove that the vitamin is protective.

Does vitamin D protect against COVID-19?
https://www.livescience.com/vitamin-d-covid-19-risk.html

Risk Versus Cause and Effect

“In the absence of a COVID-19 cure or vaccine, scientists are investigating whether vitamin D can reduce the risk of COVID-19 infection or the severity of the disease.”

Does vitamin D protect against COVID-19?
https://www.livescience.com/vitamin-d-covid-19-risk.html

Risk Versus Cause and Effect

"One study, published Sept. 3 in *JAMA Network Open*, found that the risk of COVID-19 infection in people with vitamin D deficiency was nearly two times higher than in people with sufficient levels of the vitamin."

Does vitamin D protect against COVID-19?
https://www.livescience.com/vitamin-d-covid-19-risk.html

Risk Versus Cause and Effect

“In the JAMA Network Open study, the researchers examined the relationship between likely vitamin D levels and COVID-19 risk in 489 people who took a COVID-19 test at the University of Chicago Medicine between March 3 and April 10 and whose vitamin D levels had been measured within the previous year.”

Does vitamin D protect against COVID-19?
https://www.livescience.com/vitamin-d-covid-19-risk.html

Risk Versus Cause and Effect

“A strength of the University of Chicago study is that vitamin D levels were measured before patients’ COVID-19 tests,” said Adrian Martineau, who studies respiratory infections and immunity at Queen Mary University of London, and who was not involved with the study.

Does vitamin D protect against COVID-19?
https://www.livescience.com/vitamin-d-covid-19-risk.html

Risk Versus Cause and Effect

“Because the University of Chicago study was observational — participants were not randomly assigned to take vitamin D or not — it still doesn't prove that vitamin D deficiency increases COVID risk, Martineau said.”

Does vitamin D protect against COVID-19?
https://www.livescience.com/vitamin-d-covid-19-risk.html

Risk Versus Cause and Effect

“To try to answer the chicken-and-egg question, Martineau is leading a study in which participants are randomized to take differing doses of vitamin D, then followed to see whether taking more vitamin D reduces COVID-19 risk or severity.”

Does vitamin D protect against COVID-19?
https://www.livescience.com/vitamin-d-covid-19-risk.html

Clinically Relevant Questions

In clinical medicine, the most (perhaps only) relevant question is:

Does this medical practice improve the patient's survival, health, or quality of life?

Followup questions if the answer is yes:

What are the side effects/harms of the treatment?

Is the cost of the practice worth the gain?
(Cost to whom? Patient, insurer, hospital, etc.)

Randomized Controlled Trial (RCT)

The RCT is the gold standard for evidence in clinical medicine.

It is designed in three steps.

- Enrollment: participants are enrolled according to selection criteria;

- Randomization: participants are randomized to either the treatment group or a control group — randomization assures that each group is the same, on average;

Generating Medical Evidence

Randomized Controlled Trial (RCT)

- Randomization: participants are randomized to either the treatment group or a control group — randomization assures that each group is the same, on average; the control is something as close as possible to the actual treatment but without the *active ingredient;*

- Analysis of treatment effect on outcome measure/ endpoint: the intervention and control groups are compared with respect to the endpoint of the trial. Differences between the groups in the outcome variable are believed to be result of the treatment.

Randomized Controlled Trial (RCT)

The RCT is a prospective experiment. The study design controls for all factors, other than the planned treatment/intervention, that might lead to different outcomes.

Randomization accounts for known and unknown risk factors.

Ethically, a randomized trial can only be done if there is real uncertainty whether the treatment or placebo (non-treatment) is better. RCTs are done to test treatments with potential benefit.

Generating Medical Evidence

Randomized Controlled Trial (RCT)

Each arm/group of the RCT needs the other for its protection.

Devised in 1940, the RCT does not elucidate mechanism of action, but it can conclusively show whether a treatment is beneficial.

RCTs are expensive to conduct; people need to agree to be placed in either the treatment or control group; sometimes *surrogates* are chosen for clinical outcomes that can lead to misleading conclusions.

Cohort Trial

The cohort trial is not an experiment. It describes natural, unplanned events. It is an *observational trial.*

Two or more groups (cohorts), which differ is some important/interesting way, are identified. These groups are followed to discover what proportion of each cohort reaches the predetermined endpoint.

Cohort trials are great at describing the course of a medical disease, for supporting a claim that risk exists, or that a treatment is associated with a better outcome.

Case-Control Study

A case-control study starts with the outcome and then looks back to the exposure. It is a *retrospective* observational trial.

It starts by identifying people who had a *rare event* (the cases) and similar people who have not (the controls). The study then looks back in time to discover if the cases we more likely to be exposed to something than the controls.

For the validity of the design, there needs to be a reliable way to determine exposure.

RCT Versus Observational Trials

Observational trials cannot prove cause and effect.

The cohorts, or the cases and controls, may differ in regard to things other than the outcome of interest — these differences are called *confounders*.

When confounders are not correctly adjusted for statistically, conclusions of observational trials can be wrong. It is estimated that they are wrong 15%–50% of the time.

RCT Versus Observational Trials

If one wants to verify a claim that a medical practice is beneficial, one has to do a randomized controlled trial.

RCTs are not perfect, but when large and well done, they provide stronger evidence than any other study design. This evidence often becomes more nuanced as subsequent RCTs examine the same question.

Objective Versus Subjective Endpoints

Objective Endpoints: life events (deaths, heart attacks, strokes), laboratory values and other measurable variables (blood pressure, oximetry, PFTs, weight).

Subjective Endpoints: certain physiologic experiences (pain, shortness of breath), emotional experiences (fear, hope, quality of life).

Most people go to the doctor to *feel better.* Medical research has not given subjective endpoints the importance that they deserve.

The Placebo Effect

Placebo Effect Is Real

A *placebo* is an intervention with no active ingredient: e.g. sugar pill, sham procedures.

When patients respond to a placebo with an improvement in their condition, this is called a *placebo effect.*

The placebo effect is real and has been supported in many studies. There are efforts to better uncover the mechanisms behind the physiological responses of placebo (e.g. changes in heart rate, blood pressure, pain perception, and chemical activities of the brain).

Feeling Better Versus ‘Doing’ Better

A 2011 (double blind, crossover, randomized) study in the *New England Journal of Medicine* comparing asthma treatments is instructive when considering treatments aimed at improving subjective endpoints.

People in the study were randomized to four different therapies: albuterol inhaler; placebo inhaler; sham acupuncture; and no intervention.

Active albuterol or placebo, sham acupuncture, or no intervention in asthma

Wechsler ME, Kelley JM, Boyd IO, et al.
N Engl J Med. 2011;365(2):119-126.

The Placebo Effect

Feeling Better Versus ‘Doing’ Better

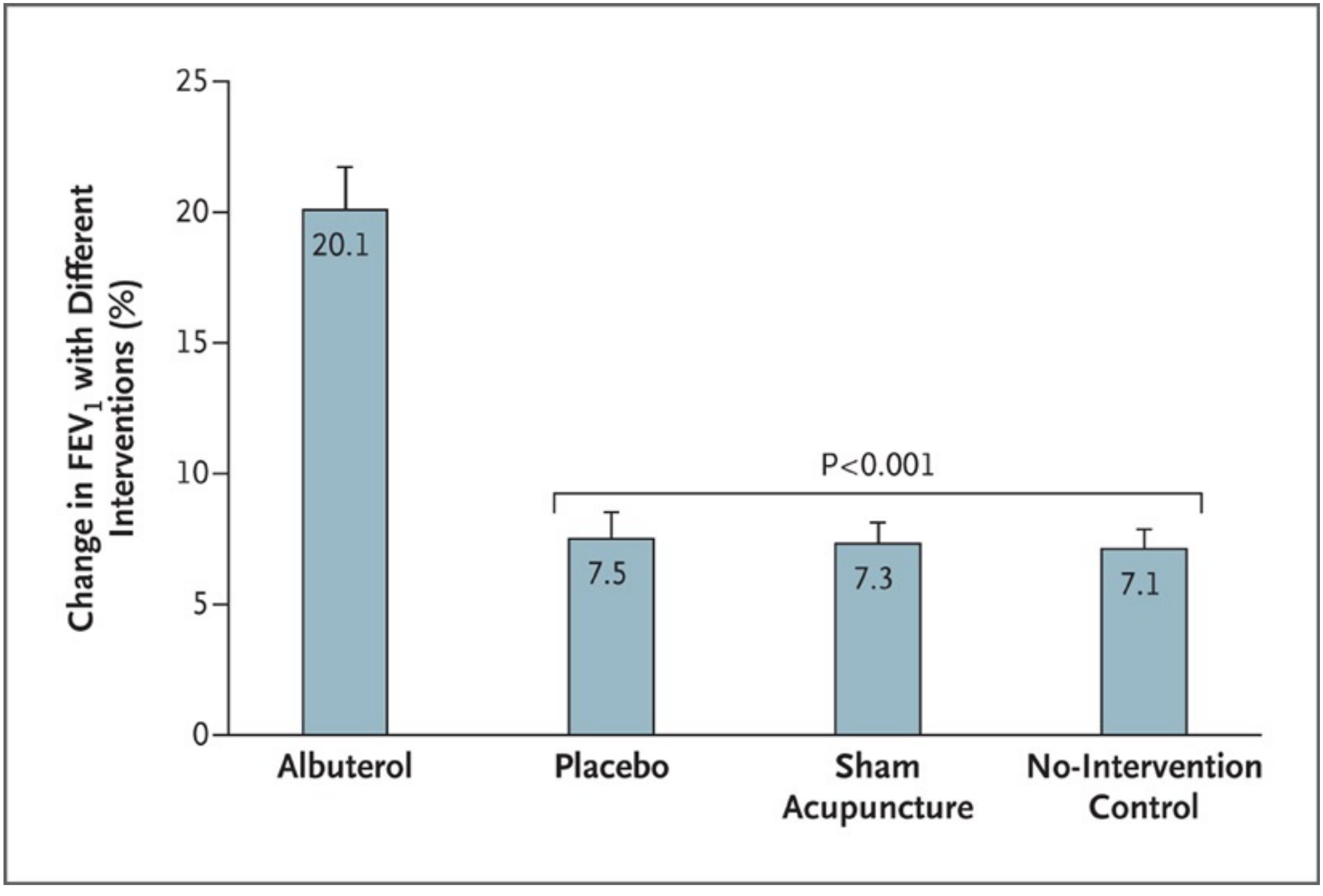
After use of the treatments, FEV_1 (objective endpoint/ measure of lung function) and patients’ own assessment (subjective endpoint) were evaluated.

Only albuterol improved FEV_1, yet patients reported that all three interventions (albuterol, placebo inhaler, sham acupuncture) were better than doing nothing, and all three were equally effective.

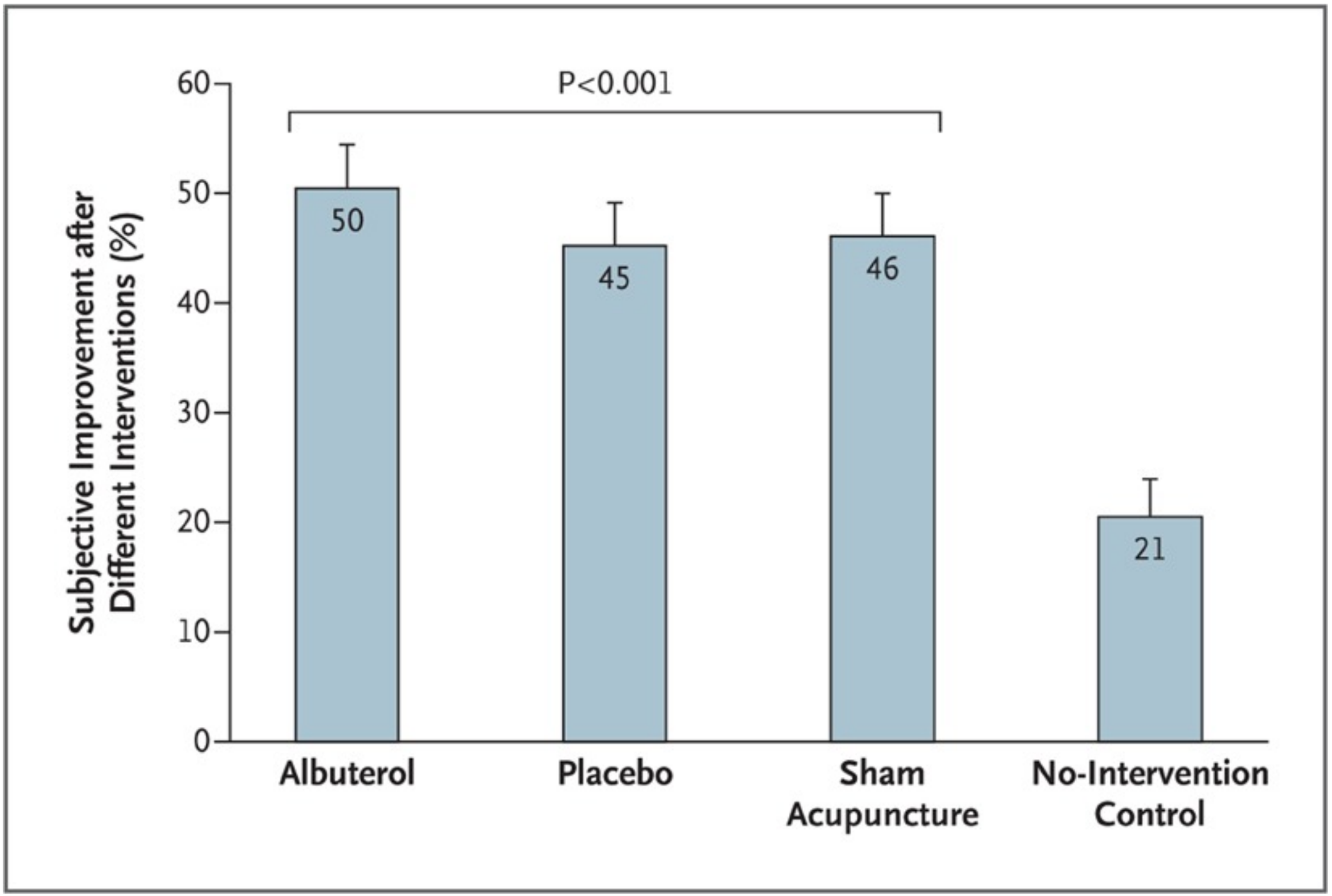
Active albuterol or placebo, sham acupuncture, or no intervention in asthma

Wechsler ME, Kelley JM, Boyd IO, et al.
N Engl J Med. 2011;365(2):119-126.

The Placebo Effect



The Placebo Effect



The Placebo Effect

Feeling Better Versus ‘Doing’ Better

The patients’ *subjective* responses directly contradicted their own *objective* physical measures.

What this study also shows is that the ritual of medicine/care makes people more comfortable.

This prompts the question: *could a long-term positive subjective experience with a therapeutic ritual ultimately affect the course of a chronic illness?*

The Placebo Effect

Increasing the Placebo Effect

Instead of only focusing on increasing the treatment/ drug effect, could the placebo effect be increased?

Adults with irritable bowel syndrome (IBS) were randomized to three groups: no intervention; sham acupuncture; sham acupuncture with a patient-practitioner relationship augmented by warmth, attention, and confidence.

Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome

Kaptchuk TJ, Kelley JM, Conboy LA, et al.
BMJ. 2008;336(7651):999-1003.

The Placebo Effect

Increasing the Placebo Effect

The study showed that the patients who experienced the greatest relief were those who received the most care. Moreover, it was the first study to demonstrate that the more care people got — even if it was through sham intervention — the better they tended to fare, i.e. there is a “dose-dependent” response for the placebo effect.

Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome

Kaptchuk TJ, Kelley JM, Conboy LA, et al.
BMJ. 2008;336(7651):999-1003.

The Placebo Effect

Placebo Without Deception

Is deception integral to achieving the placebo effect?

Adults with IBS were randomized to two groups: no intervention; a sugar pill (delivered in bottles labeled “placebo pills”), and patients in this group were told that placebos often have healing effects.

The results were startling.

Placebos without deception: a randomized controlled trial in irritable bowel syndrome

Kaptchuk TJ, Friedlander E, Kelley JM, et al.
PLoS One. 2010;5(12):e15591.

Placebo Without Deception

Patients who knew that they were taking placebo reported twice as much symptom relief as the non-intervention group. This is a significant difference comparable to the improvements seen in clinical trials for the best IBS drugs.

Placebos without deception: a randomized controlled trial in irritable bowel syndrome

Kaptchuk TJ, Friedlander E, Kelley JM, et al.
PLoS One. 2010;5(12):e15591.

The Placebo Effect

Intentions and Perceptions Matter

The placebo effect is many effects woven together. Also the methods of placebo administration are as important as the administration itself.

Patients' perceptions matter, and the way physicians/ practitioners frame perceptions can have significant effects on the patients' health.

Ted J. Kaptchuk, Director of the Harvard Program in Placebo Studies & Therapeutic Encounter (PiPS)

https://www.tedkaptchuk.com

Choosing the Right Placebo

The placebo effect is established most strongly for subjective endpoints.

To test the efficacy of a treatment with respect to a subjective endpoint, ideally those in the control/non-treatment group need to receive an intervention that is as close as possible to the actual treatment.

For example, comparing surgery to exercise would not be a good study. By comparing surgery to sham surgery, both groups attain an equivalent placebo effect.

Multicomponent Interventions

Tai Chi, a Rich and Complex Intervention

“An exercise based on slow intentional movements, often coordinated with breathing and imagery, which aims to strengthen and relax the body and mind, enhance the natural flow of (vital) energy (Qi), and improve health, personal development, and self-defense.”

Challenges inherent to T'ai Chi research: part I—T’ai Chi as a complex multicomponent intervention

Wayne PM, Kaptchuk TJ.

J Altern Complement Med. 2008;14(1):95-102..

Multicomponent Interventions

Tai Chi's Therapeutic Components

"Tai Chi is an inherently complex intervention, composed of multiple components each of which have potentially independent and synergetic therapeutic value," particularly for chronic diseases involving many systems throughout the body.

Challenges inherent to T'ai Chi research: part I—T'ai Chi as a complex multicomponent intervention

Wayne PM, Kaptchuk TJ.

J Altern Complement Med. 2008;14(1):95-102.

Multicomponent Interventions

Eight Active Ingredients of Tai Chi

“Tai Chi’s potential therapeutic effects on its practitioners can be summarized into eight broad classes. ”

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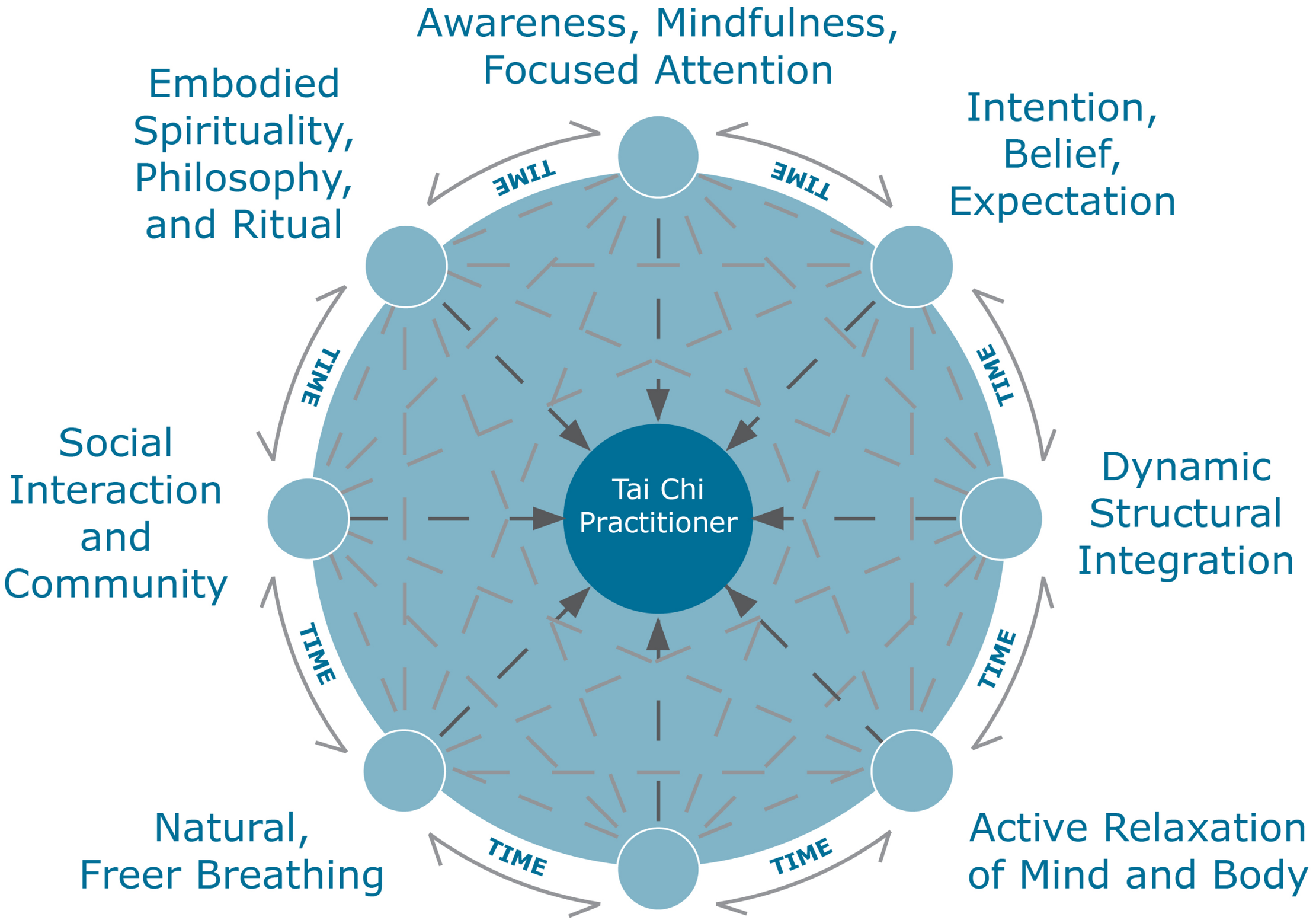
J Altern Complement Med. 2008;14(1):95-102.


Awareness, Mindfulness, Focused Attention
Embodied Spirituality, Philosophy, and Ritual
Intention, Belief, Expectation
Social Interaction and Community
Dynamic Structural Integration
Tai Chi Practitioner
Natural, Freer Breathing
Active Relaxation of Mind and Body
Aerobic Exercise, Musculoskeletal Strengthening and Flexibility
TIME

Multicomponent Interventions

Implications to Tai Chi's Assessment

Tai Chi integrates physical, cognitive and ritualistic synergetic components. It is hardly possible to attribute observed outcomes to a single, independent component.

It is also not possible to find/construct a credible sham control/placebo that mimics the array of therapeutic components of Tai Chi.

Challenges inherent to T'ai Chi research: part I—T'ai Chi as a complex multicomponent intervention

Wayne PM, Kaptchuk TJ.

J Altern Complement Med. 2008;14(1):95-102.

Multicomponent Interventions

Implications to Tai Chi's Assessment

"One cannot perform valid Tai Chi without the intention or belief that there will be a positive outcome."

Thus "randomization, during which patients not interested or invested in "doing" Tai Chi might be assigned to a Tai Chi intervention, could compromise study validity and create bias."

Challenges inherent to T'ai Chi research: part I—T'ai Chi as a complex multicomponent intervention

Wayne PM, Kaptchuk TJ.

J Altern Complement Med. 2008;14(1):95-102.

Multicomponent Interventions

Study Designs for Tai Chi Interventions

In this paradigm paper, Wayne and Kaptchuk proposed a “pluralistic methodological approach that includes randomized controlled [preference] trials that evaluate pragmatic and fixed protocol interventions, alongside community-based observational studies, cross-sectional studies of long-term practitioners, and studies that integrate qualitative methods to capture the richness of participants’ experiences.”

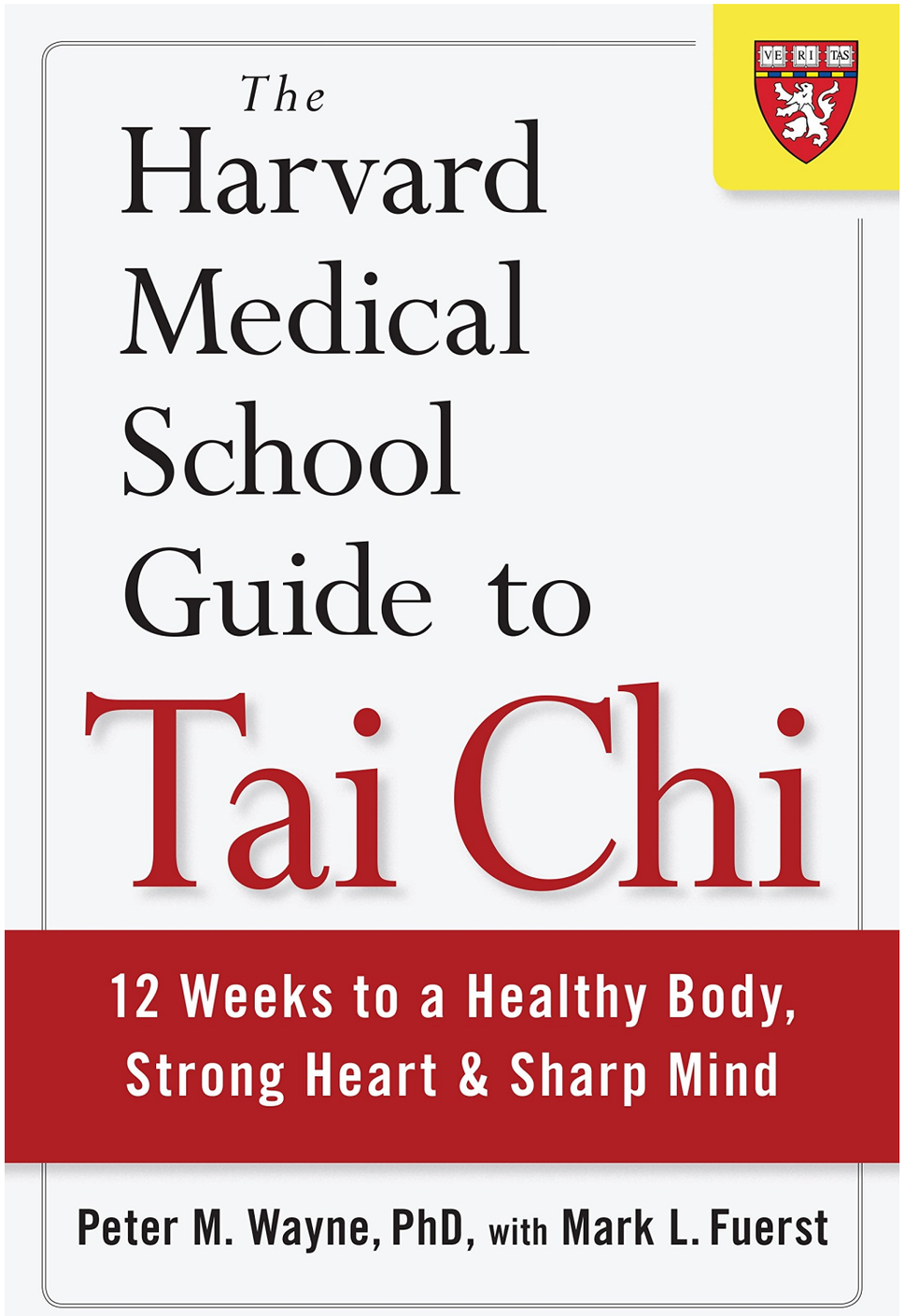
Challenges inherent to T'ai Chi research: part II-defining the intervention and optimal study design

Wayne PM, Kaptchuk TJ.

J Altern Complement Med. 2008 Mar;14(2):191-7.

Multicomponent Interventions

Putting Principles Into Practice



Multicomponent Interventions

“Teaching From the Inside Out”

A simplified 12-week Tai Chi program that includes traditional exercises, and is further shaped and informed by Wayne’s medical research experience.

The exercises deliver and maximize the “dose” of the Eight Active Ingredients of Tai Chi. Participants are taught in a way that helps them understand how the practice impacts their health.

The Harvard Medical School Guide to Tai Chi: 12 Weeks to a Healthy Body, Strong Heart, and Sharp Mind

Wayne, PM, Fuerst, ML.
Harvard Health Publications. 2013

Multicomponent Interventions

ILD Collaborative Tai Chi Pilot Study

Single-arm pre/post study to evaluate the effects of Tai Chi in ILD patients.

Outcome measures: semi-structured interviews with participants before, during and after a 12-week adapted Tai Chi protocol intervention; self-reported quantitative assessments.

The study will seek IRB approval, and prior informed research consent will be obtained form all participants.