CellPress

Clinical trials of integrative medicine: testing whether magic works?

David H. Gorski[1,2] and Steven P. Novella[3]

[1] Michael and Marian Ilitch Department of Surgery, Wayne State University School of Medicine, 3990 John R St., Detroit, MI 48201, USA
[2] Molecular Therapeutics Program, Barbara Ann Karmanos Cancer Institute, 4100 John R St., Detroit, MI 48201, USA
[3] Department of Neurology, Yale University, 40 Temple St, Suite 6C, New Haven, CT 06510, USA

Over the past two decades complementary and alternative medicine treatments relying on dubious science have been embraced by medical academia. Despite low to nonexistent prior probability that testing these treatments in randomized clinical trials (RCTs) will be successful, RCTs of these modalities have proliferated, consistent with the principles of evidence-based medicine, which underemphasize prior plausibility rooted in science. We examine this phenomenon and argue that what is needed is science-based medicine rather than evidence-based medicine.

A new phenomenon in clinical trials has arisen over the past 20 years. Complementary and alternative medicine (CAM) or integrative medicine (IM) modalities based on principles that bespeak infinitesimally low prior probability of success or that even violate well-established laws of physics and chemistry are being tested in randomized clinical trials (RCTs). CAM proponents frequently justify such RCTs by arguing that they will finally settle once and for all which CAM or IM modalities do and do not work. Our response is that this is a misguided viewpoint that has led to the infiltration of pseudoscience in academic medicine. We begin with a thought experiment.

Imagine that someone were to describe to you a treatment modality based on two principles. The first principle states that symptoms should be treated with compounds that cause the same symptoms in asymptomatic subjects and the second principle states that serially diluting such a remedy makes the action of that remedy stronger. These remedies are often diluted 10^{60}-fold and beyond, many orders of magnitude beyond Avogadro's constant, meaning that the chance that a single molecule of original compound remains behind is infinitesimal. Would it be reasonable to believe that such remedies have a sufficient chance of being efficacious and that it would be worthwhile and ethical to test them in RCTs?

This is not a made-up example. What is being described is homeopathy, a 200-year-old system of medicine based on vitalism and prescientific ideas invented by Samuel Hahnemann [1] that has been tested in multiple RCTs. Indeed, a recent search of PubMed for 'homeopathy randomized clinical trial' turned up over 400 references. Although many of these were review articles, many were RCTs. Of these, perhaps the most famous (and notorious) are two randomized, double blind, placebo-controlled clinical trials testing homeopathic remedies to treat acute childhood diarrhea in Nicaragua [2] and Honduras [3]. Depending on the trial, the specific homeopathic remedies tested consisted of 10^{60}-fold dilutions of mixtures containing substances including *arsenicum album* (arsenic trioxide), *calcarea carbonica* (carbonate of lime), *chamomilla* (German chamomile), *podophyllum* (Mayapple), and *mercurious vivus* (quicksilver, metallic mercury). One trial reported a questionable benefit [2]; the other, a later more rigorous study, found no benefit at all [3]. Yet both trials were performed even though the ingredients in the homeopathic remedies tested were not known to be effective against childhood diarrhea, two ingredients, arsenic and mercury, are definitely toxic, and the ingredients were diluted away to nonexistence. These two trials serve as examples of this trend of testing CAM and IM treatments that have a very low to nonexistent pre-test probability of producing a true positive RCT. There are many more such clinical trials of homeopathy, to the point where systematic reviews and meta-analyses are becoming common. Not surprisingly, they tend to be inconclusive or negative [4].

More common in the USA is reiki: 'energy medicine' that involves using hand and touch to direct into the patient's 'healing energy' from what reiki masters call the 'universal source'. It is closely related to therapeutic touch (TT), which makes similar claims. For such modalities, the pre-trial likelihood of a positive effect greater than placebo is negligible, if not zero, given that there is no evidence that this healing energy even exists, much less that humans can manipulate it. Nonetheless, numerous hospitals, including prestigious hospitals [5], have reiki programs and carry out RCTs [6], resulting in at least one systematic review [7], which, not surprisingly, concluded that there is no evidence that reiki has specific therapeutic effects for any condition. Yet RCTs to test whether reiki, TT, homeopathy, reflexology, craniosacral therapy, acupuncture, and other modalities equally lacking in preclinical plausibility are ongoing, as is easily verified by a search of www.ClinicalTrials.gov.

Evidence-based medicine (EBM) assumes that treatments do not reach the stage of RCTs without having amassed sufficient preclinical evidence to justify the effort, time, and expense of RCTs, as well as the use of human subjects. The EBM paradigm resembles the illustration in Figure 1, with observations and discoveries in basic science

Corresponding author: Gorski, D.H. (gorskid@med.wayne.edu).
Keywords: Evidence-based medicine; science-based medicine; clinical trials; complementary and alternative medicine; integrative medicine.

1471-4914/
© 2014 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.molmed.2014.06.007

CrossMark

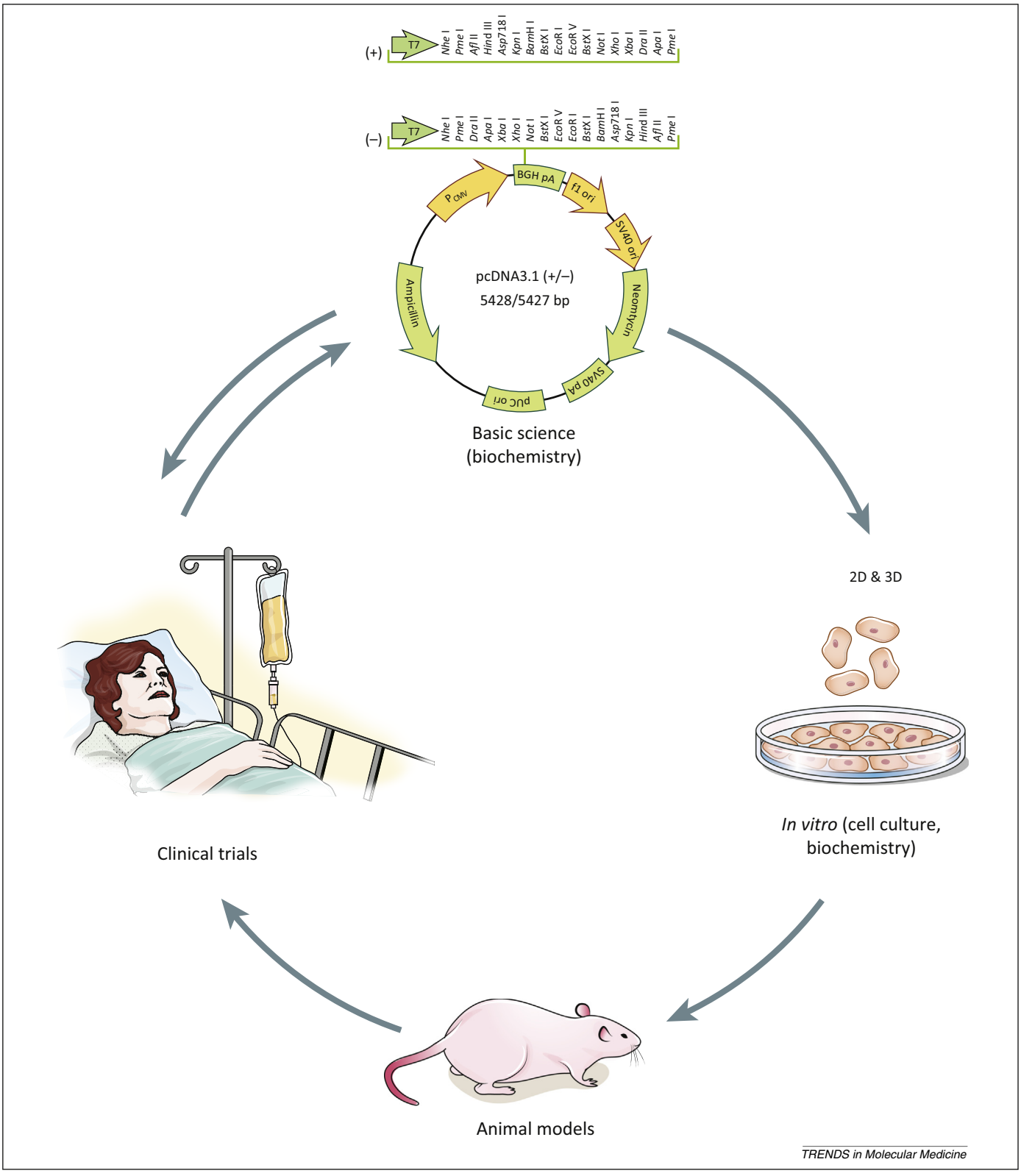

Figure 1. A commonly assumed paradigm in evidence-based medicine: Bench to bedside: findings in basic science progress through cell culture and *in vitro* studies, then to animal models, then to clinical trials. Clinical trials in turn consist of preliminary Phase I/II trials, followed by larger randomized Phase III trials. Although it is true that each stage can 'cross-pollinate' other stages, it is generally assumed that treatments do not reach the clinical trial stage without having passed through the first three stages and demonstrated promise, and thus prior plausibility, in preclinical experiments. Clinical trials of complementary and alternative medicine (CAM) upend this paradigm, with treatments that have little or no prior plausibility based on preclinical experimentation being tested prematurely in clinical trials.

leading to *in vitro* work in cell culture, which leads to *in vivo* experiments and observations in animal models, which, if promising, ultimately lead to clinical trials. Of course, this is a grossly simplified model. Observations from each step frequently cross-pollinate other steps, and the progression is rarely as neat as illustrated. Even so, the major assumption underlying EBM is that by the time an investigational treatment is ready for RCTs it has passed

all preclinical tests and has thus demonstrated biological plausibility. Before, CAM or IM, treatments without biological plausibility and compelling evidence from preclinical studies and pilot clinical trials usually did not reach the stage of RCTs. Indeed, so integral to this process is biological plausibility based on preclinical data that the Declaration of Helsinki [8] states, 'medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation'.

It should also be noted that 'biologically plausible' does not mean 'knowing the exact mechanism'. What it does mean is that the mechanism should not be so scientifically implausible as to be reasonably considered impossible. In other words, the mechanism should not violate laws and theories in science that rest on far sturdier and longer-established foundations than imperfect, bias-prone clinical trials. For example, homeopathy violates multiple laws of physics with its claims that dilution can make a homeopathic remedy stronger and that water can retain the 'memory' of substances with which it has been in contact before [9]. Thus, treatments like homeopathy should be dismissed as ineffective on basic scientific grounds alone. That is why we propose the term science-based medicine (SBM) as opposed to evidence-based medicine (EBM). SBM restores basic science considerations to EBM and is what EBM should be.

Unfortunately, EBM was blindsided by CAM and IM. RCTs of highly improbable modalities continue to be funded and performed, not because of any compelling scientific rationale or prescientific evidence but rather because they are popular. Indeed, another key argument used by proponents of CAM and IM clinical trials is that they should be carried out because these treatments are used by a lot of people, which is not an argument for subjecting human subjects to pseudoscience. These trials degrade the scientific basis of medicine by treating modalities where the basis rests in prescientific thinking as though they were well-supported science- and evidence-based modalities, while clinical investigators labor under a seemingly reasonable delusion that negative RCT results will lead to the abandonment of CAM and IM modalities that fail to perform above placebo in RCTs. Unfortunately, this abandonment never seems to occur. Acupuncture and reiki remain widely practiced and even embraced at academic institutions, and even homeopathy continues to be practiced, despite clinical trials and meta-analyses [4] that demonstrate effects indistinguishable from placebo.

Another pernicious effect of performing RCTs on CAM and IM modalities is that it leads to clinical trials of highly implausible treatments that may have a significant potential to cause active harm, as opposed to harm from substituting ineffective for effective treatment. One example is the Trial To Assess Chelation Therapy (TACT), in which chelation therapy was tested as a treatment in patients with heart disease: a US$30 million multicenter clinical trial initially funded by the National Center for Complementary and Alternative Medicine (NCCAM) with virtually no preclinical scientific basis, study sites at 'alternative' clinics where reliability was seriously questioned, and the potential for complications due to chelation of critical minerals [10]. A decade and tens of millions of dollars later, after failure to reach accrual goals, TACT results were reported [11,12] and were negative except for one subgroup (diabetics), for which there was ample reason to question the validity of the results [13]. Another example is the trial to test an 'alternative' treatment regimen for pancreatic cancer that involves extreme dietary modifications, juices, large quantities of supplements, and coffee enemas. After several years, abandonment of the RCT format for an unblinded 'patient's choice' design, and considerable controversy over delays in publication, the results, when finally reported [14], were disturbing. One year survival of subjects undergoing this protocol was nearly fourfold worse than subjects receiving standard-of-care chemotherapy and worse than expected based on historical controls, all associated with poorer quality of life.

In RCTs testing modalities with low pre-test probability (i.e., low plausibility), confounding effects are vastly magnified, easily producing false-positives [15]. In these days of extreme scarcity of research funding, it is difficult to justify spending precious research dollars carrying out RCTs of treatments where the likelihood of producing a true positive trial is so low and that have real risks that can lead to outcomes like the TACT or pancreatic cancer trials. All clinical trials, not just RCTs, should be based on scientifically well-supported preclinical observations that justify them, preferably with biomarkers to guide patient selection and follow-up. Until specific CAM and IM modalities achieve that level of preclinical evidence, RCTs testing them cannot be scientifically or ethically justified. That is science-based, rather than evidence-based, medicine.

Disclaimer statement

Neither of the authors have any competing financial interest in the topic of this commentary. D.H.G. is the managing editor and S.P.N. is the founding editor of Science-Based Medicine (http://www.sciencebasedmedicine.org/), a weblog devoted to the analysis of the scientific basis of medical practice and to winnowing out bad science and outright pseudoscience from medicine.

References

1 Ernst, E. (2008) The truth about homeopathy. *Br. J. Clin. Pharmacol.* 65, 163–164
2 Jacobs, J. *et al.* (1994) Treatment of acute childhood diarrhea with homeopathic medicine: a randomized clinical trial in Nicaragua. *Pediatrics* 93, 719–725
3 Jacobs, J. *et al.* (2006) Homeopathic combination remedy in the treatment of acute childhood diarrhea in Honduras. *J. Altern. Complement. Med.* 12, 723–732
4 Shang, A. *et al.* (2005) Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. *Lancet* 366, 726–732
5 Vitale, A. (2011) Introduction for "Reiki at University Medical Center, Tucson, Arizona, a magnet hospital": Mega R. Mease is interviewed by William Lee Rand. *Holist. Nurs. Pract.* 25, 231–232
6 Assefi, N. *et al.* (2008) Reiki for the treatment of fibromyalgia: a randomized controlled trial. *J. Altern. Complement. Med.* 14, 1115–1122
7 vanderVaart, S. *et al.* (2009) A systematic review of the therapeutic effects of Reiki. *J. Altern. Complement. Med.* 15, 1157–1169
8 World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 310, 2191–2194

9 Smith, K. (2012) Homeopathy is unscientific and unethical. *Bioethics* 26, 508–512
10 Atwood, K.C. *et al.* (2008) Why the NIH Trial to Assess Chelation Therapy (TACT) should be abandoned. *Medscape J. Med.* 10, 115
11 Escolar, E. *et al.* (2013) The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). *Circulation Cardiovascular Quality Outcomes* http://dx.doi.org/10.1161/CIRCOUTCOMES.113.000663
12 Lamas, G.A. *et al.* (2013) Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. *JAMA* 309, 1241–1250
13 Nissen, S.E. (2013) Concerns about reliability in the Trial to Assess Chelation Therapy (TACT). *JAMA* 309, 1293–1294
14 Chabot, J.A. *et al.* (2010) Pancreatic proteolytic enzyme therapy compared with gemcitabine-based chemotherapy for the treatment of pancreatic cancer. *J. Clin. Oncol.* 28, 2058–2063
15 Goodman, S.N. (1999) Toward evidence-based medical statistics. 2: The Bayes factor. *Ann. Intern. Med.* 130, 1005–1013