CellPress

Clinical trials of integrative medicine: testing whether magic works?

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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

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Keywords: Evidence-based medicine; science-based medicine; clinical trials; complementary and alternative medicine; integrative medicine.

1471-4914/
 http://dx.doi.org/10.1016/j.molmed.2014.06.007

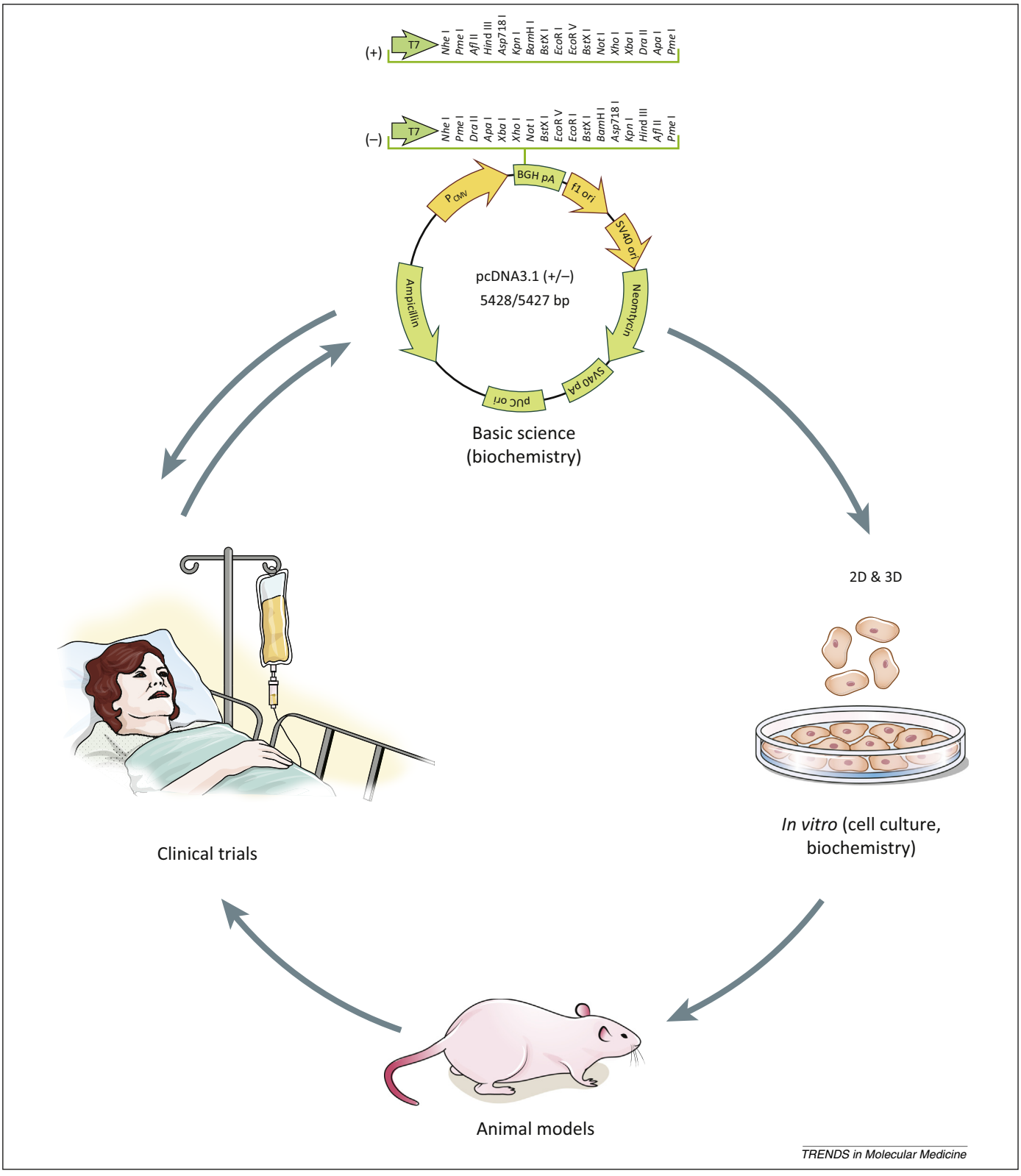

Figure 1. A commonly assumed paradigm in evidence-based medicine: Bench to bedside: findings in basic science progress through cell culture and *in vitro* studies, then to animal models, then to clinical trials. Clinical trials in turn consist of preliminary Phase I/II trials, followed by larger randomized 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