

## OPINION

# Integrative oncology: really the best of both worlds?

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**Abstract** | Over the past two decades there has been a growing acceptance of 'integrative oncology', also known as complementary and alternative medicine (CAM), in cancer care and research at academic medical centres and medical schools. Proponents of integrative oncology argue that it is based in science and provides the 'best of both worlds' by combining science-based treatments and 'holistic' medicine. However, a close examination of the methodologies indicates that, from a standpoint of basic science, the vast majority of 'integrative' treatments are supported by little, if any, scientific evidence. What are the consequences of this integration? Is there any harm? Are there any potential benefits?

In 1983, Clark Glymour and Douglas Stalker published a scathing editorial in the *New England Journal of Medicine* (NEJM) about 'holistic medicine', which they characterized as a "pabulum of common sense and nonsense offered by cranks and quacks and failed pedants who share an attachment to magic and an animosity toward reason." (REF. 1). Such has been the sea change in attitude over the past three decades that today it is difficult to imagine the publication of an editorial so harshly contemptuous of holistic medicine in a top-tier medical journal. Indeed, in recent years, the NEJM itself has published studies examining the use of placebo acupuncture in asthma<sup>2</sup> and *Tai Chi* for fibromyalgia<sup>3</sup>, as well as a case study in which acupuncture was recommended for chronic back pain<sup>4</sup>. What Glymour and Stalker once dismissed as holistic medicine three decades ago is today increasingly mainstream and known as either complementary and alternative medicine (CAM) or 'integrative medicine'. The latter term, which is rapidly replacing CAM as the preferred term, signifies that alternative therapies are integrated with science-based medicine in order to produce what is often described as the 'best of both worlds' (REFS 5–7).

In the United States, Canada and Europe<sup>8,9</sup>, this phenomenon has progressed in some highly respected cancer centres from scepticism to outright embrace. As described in an NBC News report in 2012 (REF. 10), treatment modalities such as acupuncture<sup>11</sup>, traditional Chinese medicine (TCM), and even reflexology<sup>12</sup> are increasingly offered at institutions as venerable as Memorial Sloan Kettering Cancer Center (MSKCC), New York, USA. In 2014,

the *Wall Street Journal* reported that the Cleveland Clinic, Ohio, USA, had opened a traditional Chinese herbal clinic, complete with a naturopath carrying out 'tongue diagnosis' (REF. 13). Many National Cancer Institute (NCI)-designated Comprehensive Cancer Centers (NCI-CCCs) have established 'integrative oncology' programmes that offer everything from potentially useful modalities, such as nutritional counselling, meditation, and lifestyle alterations, to treatment modalities that can only be described from a strictly scientific viewpoint as pure pseudoscience, such as 'energy medicine' (REFS 14, 15), reflexology<sup>16,17</sup>, acupuncture<sup>11,18,19</sup> and homeopathy<sup>20,21</sup>. Outside of academia, the Cancer Treatment Centers of America, a private hospital chain, has built its business model offering integrative oncology<sup>9</sup> and naturopathic oncology, despite the lack of evidence for naturopathy<sup>22</sup>. With the growing acceptance of CAM, a new oncology subspecialty, dubbed integrative oncology<sup>6,23–27</sup>, has arisen, complete with its own professional societies, such as the Society for Integrative Oncology.

It is therefore not surprising that the use of CAM among cancer patients has been reported to be higher than among patients with other diseases<sup>28</sup>. Spending, both public and private, for CAM has correlated with the growth of integrative medicine in medical academia. There are now at least two US government entities that, combined, spend approximately a one-quarter of a billion dollars per year funding research and education in CAM and integrative medicine<sup>29–31</sup>. The first is the National Center for Complementary and Alternative Medicine (NCCAM), whose budget in the financial

year 2013 was US\$123.8 million<sup>32</sup>. NCCAM is relatively well-known and has been, at times during its two decade history, the subject of rancorous scientific and political debate over its mission and even continued existence<sup>29,33–37</sup>. By contrast, few oncologists and cancer researchers seem to be aware that the NCI spends approximately as much on CAM research and education through its Office of Cancer Complementary and Alternative Medicine (OCCAM)<sup>38</sup>, whose average yearly budget over the past decade has been roughly equal to that of NCCAM<sup>39</sup>. Even fewer oncologists seem to know of the [Consortium of Academic Health Centers for Integrative Medicine](#) (CAHCIM; see Further information), which consists of 50 academic medical centres in North America (46 in the United States, 3 in Canada and one in Mexico). In the United States, 37 of 46 CAHCIM members (80%) are affiliated with either NCI-CCCs or NCI-designated cancer centres, and 26 of 41 NCI-CCCs (63%) are affiliated with academic medical centres that are members of CAHCIM. This estimate does not even include prominent NCI-CCCs, such as MSKCC and Case Comprehensive Cancer Center, Cleveland, Ohio, USA, that are not CAHCIM members but have large integrative medicine programmes. Clearly, the mainstreaming of integrative oncology is well under way. This Opinion article surveys key issues with this integration.

## CAM: the problem of definition

One of the most vexing problems that complicates any discussion of CAM or integrative medicine (the latter term being preferred now by most practitioners), regardless of specialty, is defining what, exactly, constitutes CAM. This question is not as straightforward as it might seem. In general, definitions<sup>40–42</sup> tend to stress that CAM includes treatments that are 'outside of the mainstream', although they rarely make clear what constitutes mainstream. This definition is particularly problematic for a subset of CAM modalities, such as nutrition and exercise, interventions that are routinely claimed by CAM but, depending on how they are applied, can clearly be mainstream<sup>43–47</sup>, thus bringing into question why a separate CAM category is needed. In addition, although some CAM interventions are so unlikely to cause harm that it is difficult to have too strong an objection to them in general, it is also highly questionable to ascribe anything other than nonspecific effects to them for cancer — or for any other medical condition. For instance, massage can make cancer patients feel better, and yoga can be viewed as a system of exercise

that, properly done, can be as beneficial to general health as many other forms of exercise. The confusion arises when massage becomes ‘massage therapy’, a billable, reimbursable medical treatment, rather than support, and when the religious and mystical underpinnings of some forms of yoga, such as Kundalini energy<sup>48</sup>, are represented as essential for the exercise and thus necessary for its benefits. Taken this way, it is difficult not to sense in CAM and integrative oncology a certain ‘medicalization’ of practices not previously considered to be medical — even spirituality (see below).

This blurring of the lines in CAM, between medicine and nonspecific supportive measures, coupled with the appropriation by CAM of mainstream science-based modalities, such as exercise, results in a bevy of problems in determining which treatments are CAM and which are mainstream, which interventions are actually used with therapeutic intent, and which, like massage, simply help patients to cope with a serious disease. Let us consider a case in ‘conventional’ medicine. For example, is prescribing weight-loss and exercise as the first intervention for preventing the progression from prediabetes to type II diabetes, as most primary care doctors routinely do, mainstream medicine or CAM? What, if anything, is outside of the mainstream about it? It is, after all, a standard of care, according to the American Diabetes Association<sup>49</sup>; however, dietary interventions, particularly probiotics and supplements, are often claimed as ‘integrative’ for a variety of conditions<sup>50–52</sup>.

Unfortunately, official definitions of CAM<sup>40–42</sup> fail to clarify this issue. For example, NCCAM defines alternative medicine

as “using a non-mainstream approach in place of conventional medicine” and complementary medicine as “using a non-mainstream approach together with conventional medicine” (REF. 42). To confuse matters further, in NCCAM parlance, integrative medicine refers to combining “treatments from conventional medicine and CAM for which there is some high-quality evidence of safety and effectiveness” (REF. 40). However, it is seldom clear which, if any, CAM modalities have sufficient high quality evidence supporting their efficacy and safety to justify their integration into mainstream medicine. NCCAM’s original definition divided CAM into five areas, including natural products<sup>41</sup> (TABLE 1). To confuse matters further, the NCCAM 2011–2015 strategic plan<sup>53</sup> redefined ‘mind–body’ interventions as ‘mind and body’ interventions and broadened the category to include virtually any CAM treatment that is not diet or herbal, including energy medicine, acupuncture, meditation, yoga, craniosacral therapy, and even reflexology (TABLE 2). OCCAM goes even further and subdivides CAM into eight areas<sup>39</sup> (TABLE 3), separating out nutritional therapies such as macrobiotic diets<sup>54</sup> and the Gerson protocol<sup>55</sup> for cancer from ‘biologically based’ therapies, such as herbal medicines, and adding categories for exercise therapy and spiritual therapies, such as intercessory prayer, which does not work<sup>56–58</sup>, or energy medicine, such as *reiki* or therapeutic touch, whose purported mechanism rests on manipulating life ‘energy’ fields that have never been shown to exist<sup>15,59</sup>, much less to produce detectable effects on human physiology<sup>59</sup>.

Arguably, there is no scientific reason why biologically based therapies should be considered to be alternative or integrative, making their inclusion as CAM problematic. Nor is there a reason why integrative medicine interventions with some biological plausibility cannot be tested in randomized controlled trials (RCTs), just like any other intervention. But what of alternative whole medical systems, such as homeopathy<sup>60,61</sup> or naturopathy (a hodgepodge of interventions that include homeopathy, TCM and dietary interventions<sup>62</sup>)? It is also difficult not to wonder whether the inclusion of lifestyle interventions, such as dietary interventions, exercise, and relaxation techniques, which arguably have been underutilized in medicine, in the same category as homeopathy, naturopathy, and spiritual interventions, lend by association the appearance of scientific plausibility to interventions that, from a basic science viewpoint, are incredibly implausible at best, while ‘rebranding’ more plausible non-pharmacological and nonsurgical treatments as alternative or integrative.

Contrary to laudable efforts by its champions<sup>63</sup> to distinguish it from blatant cancer quackery (for example, Cantron (also known as CanCell, Protocol and Entelev)<sup>63,64</sup>, laetrile<sup>65–67</sup>, and German New Medicine<sup>63,68</sup>), integrative oncology still has a problem. Specifically, the rationales for many of the treatments falling under the rubric of ‘respectable’ integrative oncology are based on concepts rooted in the very same pre-scientific vitalism as a lot of disreputable cancer quackery. How is a patient to distinguish between the two? Therein lies a key problem with integrative oncology. The less ‘alternative’ the intervention, the more it resembles conventional oncology; the more ‘alternative’ the intervention, the more it resembles the quackery from which integrative oncologists rightly distance themselves<sup>63</sup>.

### The problem with integrative oncology

Integrative oncology is often touted as being useful for relieving symptoms, rather than as a primary treatment for the actual cancer<sup>6,69,70</sup>. Unfortunately, a closer examination of many CAM modalities indicates that the vast majority of them rest on principles that, from a strictly basic science standpoint, range from highly implausible to virtually impossible — some rest on principles whose precepts violate well-established laws of physics and chemistry and/or are rooted in pre-scientific vitalism<sup>71,72</sup> (such as homeopathy and energy medicine)<sup>60,61,73</sup>. For example, some CAM modalities postulate anatomical structures

Table 1 | CAM subtypes as defined by NCCAM prior to 2011\*

CAM subtype	Definition	Examples
Alternative medical systems or whole medical systems	Complete medical systems outside of mainstream medicine based on concepts that vary widely depending on the whole medical system	Homeopathy, traditional Chinese medicine, Ayurvedic medicine, Native American medicine, and naturopathy
Biologically based therapies	Practices involving the use of substances found in nature, including diet	Herbal medicines, dietary supplements, probiotics, nutrition and diet manipulation
Energy medicine	Practices involving manipulation of ‘life energy’ fields, sometimes called ‘biofields’	Therapeutic touch, reflexology, rolfing, <i>reiki</i> , acupuncture and <i>Qi Gong</i>
Manipulative and body-based practices	Practices based on manipulation of musculoskeletal structures to affect physiology	Osteopathy, chiropractic, craniosacral therapy and massage therapy
Mind–body medicine	Practices based on influencing physiology through influencing the mind	Meditation, yoga, guided imagery, deep breathing exercises, progressive relaxation, and <i>Tai Chi</i>

CAM, complementary and alternative medicine; NCCAM, National Center for Complementary and Alternative Medicine. \*Using data from REF. 41.

or abnormalities that do not exist, such as acupuncture ‘meridians’ (REFS 11,74) or chiropractic ‘subluxations’ (REF. 75). Other CAM modalities postulate nonexistent physiological functions, such as craniosacral therapy, which seeks to correct the ‘craniosacral rhythms’ of the cerebrospinal fluid by manipulating joints in the skull<sup>76,77</sup>, and reflexology, which claims a nonexistent connection between organs and specific points on the soles of the feet, or palms of the hands<sup>17,78</sup>. One of the most popular whole medical systems, TCM, postulates similar links between specific organs and locations on the tongue<sup>79</sup> and ascribes illness to six pernicious influences, which include wind, cold, heat, dampness, dryness and summer heat<sup>80,81</sup>, strongly reminiscent of European medicine dating back to Hippocrates, who postulated imbalances in the four ‘humors’ as the cause of disease<sup>82</sup>, particularly cancer<sup>83</sup>. More popular in Europe than in the United States, homeopathy rests on two laws, the ‘law of similars’, which states that relief from a symptom requires the use of a substance that causes that symptom in healthy individuals, and the ‘law of infinitesimals’, which states that serial dilution of a remedy, with vigorous shaking between dilutions, ‘potentizes’ it, thereby making it stronger. Neither law has any scientific basis. Indeed, most homeopathic dilutions surpass 10<sup>60</sup>-fold; that is, more than 10<sup>36</sup>-fold greater than Avogadro’s number<sup>20,21,60,84</sup>, meaning that it is incredibly unlikely that there is a single molecule of original substance left.

Advocates of integrative medicine respond to such criticisms by arguing that science changes all the time based on evidence and that the development of medical treatments has, for a long time, mostly been empirical. A few even argue that alternative medicine cannot be science-based<sup>85,86</sup> and/or accuse evidence-based medicine (EBM) of ‘scientism’ (REF. 87). On the surface, this appeal to empiricism<sup>88</sup> seems compelling, given that EBM is a relatively recent development in the history of medicine and that, even now, EBM remains mostly empirical, as evidenced by its ranking of aggregated results of high-quality RCTs as the highest form of evidence<sup>89,90</sup>, far above basic science considerations. For instance, the history of chemotherapy<sup>91</sup> is sometimes cited as an example of empirical development of effective therapies. However, this history of empiricism is irrelevant to scientific criticisms of highly implausible CAM claims. We know, empirically, that chemotherapy works<sup>92</sup>. We do not

Table 2 | CAM subtypes as defined by NCCAM after 2011\*

CAM subtype	Definition	Examples
Manipulative and body-based practices	Practices involving manipulation of musculoskeletal structures to affect physiology	Osteopathy, chiropractic, craniosacral therapy and massage therapy <sup>†</sup>
Mind and body practices	Practices that focus on the interactions among the brain, mind, body and behaviour, with the intent to use the mind to affect physical functioning and promote health	Exercise, meditation, acupuncture, yoga, massage therapy, <i>Tai Chi</i> , progressive relaxation, hypnotherapy and guided imagery
Natural products	Practices involving the use of substances found in nature, including diet	Herbal medicines, dietary supplements, probiotics, nutrition and diet manipulation
Other CAM practices	Practices that do not fall into the above NCCAM definitions	Energy medicine ( <i>reiki</i> , <i>Qi Gong</i> , healing touch <sup>‡</sup> ); alternate whole medical systems (homeopathy, naturopathy, traditional Chinese medicine, and Ayurvedic medicine)

CAM, complementary and alternative medicine; NCCAM, National Center for Complementary and Alternative Medicine. \*Using data from REF. 40. †Note that in the NCCAM Third Strategic Plan 2011–2015 (REF. 53), massage and healing touch are considered to be part of mind and body practices.

empirically know that, for example, homeopathy works<sup>93–96</sup>. Moreover, chemotherapy does not require postulating a mechanism that violates laws of physics or chemistry, as homeopathy does. After all, chemotherapeutic agents are chemicals, presumably with a receptor or molecule with which they interact for their effects, all phenomena that were easily encompassed by then-existing understanding of biochemistry and physiology, even if the details were not yet worked out. Even 50 years ago, chemotherapy drugs were often chosen for development on the basis of a broad mechanism of action<sup>91</sup>; for example, differential toxicity to rapidly dividing cells — the same reason that radiation therapy was tested as a treatment for cancer.

In contrast, the physics and chemistry that conclude that homeopathy and *reiki* are virtually impossible are so well established that, were healing phenomena due to homeopathy or *reiki* to be unequivocally demonstrated, then what we understand now about physics and chemistry would be proven to be very wrong. Worse, in RCTs testing modalities with low pre-test probability (that is, low plausibility), confounding effects are vastly magnified, producing many false positives<sup>97,98</sup>. Given that many CAM treatments have prior probabilities based on scientific plausibility that can only be characterized as very close to zero, if not zero, clinical trials of CAM are, in essence, identifying the noise in the RCT process. Admittedly, this is not a problem that is confined only to CAM<sup>98</sup>. Biomarker<sup>99</sup> and omics<sup>100</sup> studies are prone to it as well — but not to the same degree, as they have a higher pre-test probability. Owing to the infinitesimally low

pre-test probabilities associated with CAM modalities such as *reiki* or homeopathy, RCTs of CAM vastly amplify this problem<sup>101</sup>. In the case of CAM studies, this problem could begin to be alleviated using a Bayesian statistics approach taking into account the exceedingly low pre-test probabilities of such treatments<sup>97</sup>.

As an example, let us consider homeopathy. Its advocates tend to cite two positive meta-analyses<sup>102,103</sup> to counter the most frequently cited meta-analysis finding that homeopathy effects are most consistent with placebo effects<sup>93</sup> and to argue for the existence of definite clinical therapeutic effects due to homeopathy such that it is a mistake to dismiss homeopathy on basic science grounds alone. Unfortunately, the two positive meta-analyses are not particularly convincing. The first meta-analysis<sup>102</sup> has been supplanted by more recent studies, and reanalysis of its data provided clear evidence that studies with better methodological quality tended to yield less positive results<sup>104,105</sup>. The second meta-analysis<sup>103</sup> is a reanalysis by homeopaths of a widely cited negative meta-analysis<sup>93</sup> and was written with the explicit intent to refute it<sup>93</sup>; it makes the rather obvious conclusion that meta-analyses depend on the starting clinical trials chosen. Even if this second meta-analysis<sup>103</sup> is taken at face value, the reported effect sizes are tiny and almost certainly due to nonspecific effects that could be explained by random variation and bias. There are also multiple other systematic reviews and meta-analyses of homeopathy that conclude that homeopathy has no specific effects or that there is insufficient clinical evidence supporting it<sup>94–96</sup>, although

Table 3 | Subtypes of CAM as defined by OCCAM\*

CAM subtype	Definition	Examples
Alternative medical systems or whole medical systems	Alternative medical systems are built upon complete systems of theory and practice. Often, these systems have evolved separately from and earlier than the conventional medical approach used in the United States	Ayurveda, homeopathy, traditional Chinese medicine and Tibetan medicine
Energy therapies	Biofield therapies are intended to affect energy fields that purportedly surround and penetrate the human body. The existence of such fields has not yet been scientifically proven	<i>Qi Gong</i> , <i>reiki</i> and therapeutic touch
	Electromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating current or direct current fields	Pulsed electromagnetic fields and magnet therapy
Exercise therapies	Exercise therapies include health-enhancing systems of exercise and movement	<i>Tai Chi</i> and yoga
Manipulative and body-based methods	Manipulative and body-based methods in CAM are based on manipulation and/or movement of one or more parts of the body.	Chiropractic, therapeutic massage, osteopathy and reflexology
Mind–body interventions	Mind–body medicine uses a variety of techniques that are designed to enhance the mind's body to effect bodily function and symptoms	Meditation, hypnosis, art therapy, biofeedback, imagery, relaxation therapy, music therapy, cognitive behavioural therapy and aromatherapy
Nutritional therapeutics	Nutritional therapeutics are an assortment of nutrients and non-nutrients, bioactive food components used as chemo-preventive agents, and specific foods or diets used as cancer prevention or treatment strategies	Macrobiotic diet, vegetarianism, Gerson therapy, Kelley/Gonzalez regimen, vitamins and soy
Pharmacological and biological treatments	Pharmacological and biological treatments include the off-label use of certain prescription drugs, hormones, complex natural products, vaccines, and other biological interventions not yet accepted in mainstream medicine	Antineoplastons, low-dose naltrexone, immunoaugmentative therapy and laetrile
	Complex natural products are an assortment of plant samples (botanicals), extracts of crude natural substances, and unfractionated extracts from marine organisms used for healing and treatment of disease	Herbs and herbal extracts, mistletoe and mixtures of tea polyphenols
Spiritual therapies	Spiritual therapies are therapies that focus on deep, often religious beliefs and feelings, including a person's sense of peace, purpose, connection to others, and beliefs about the meaning of life	Intercessory prayer, and spiritual healing

CAM, complementary and alternative medicine; OCCAM, Office of Cancer Complementary and Alternative Medicine. \*Using data from REF. 39.

there is one positive Cochrane review for radiation-induced stomatitis and dermatitis<sup>106</sup>. However, for these studies, herbal remedies that were not diluted to the usual homeopathic range were used, meaning that active ingredient was detectably present<sup>107,108</sup>. Considering this body of literature, which is more likely, that homeopathy is placebo medicine supported by a few bias- and error-prone clinical trials, or that physicists and chemists are wrong about fundamental principles of physics and chemistry? One must always concede that it is possible, albeit remotely so, that our scientific theories explaining these matters, built up over hundreds of years and supported by vast evidence, might be wrong, but it would take more than equivocal clinical trials to demonstrate that. To show that homeopathy works would require evidence of approximately the same quality and quantity as the evidence that concludes that it cannot work.

Basically, CAM is a term that lumps together the highly implausible with the plausible. But what CAM treatments

might be plausible and therefore potentially useful? Integrative treatments that might have a basis in science tend, from a scientific perspective, to be relatively mundane<sup>68</sup>. These include interventions that tend to fall under either mind and body (NCCAM) or exercise therapies (OCCAM), such as *yoga* and *Tai Chi*, the biologically based (NCCAM) or pharmacological and biologically based treatments or nutritional therapeutics (OCCAM), for which there are scientific studies identifying specific mechanisms of action of diet or specific chemicals in herbal remedies. For these, as is the case with experimental therapeutics, many supplements that have been tested for their effect on cancer prevention have failed, such as selenium and vitamin E for prostate cancer (SELECT)<sup>109,110</sup>, and  $\beta$ -carotene, which actually increased the risk of lung cancer<sup>111,112</sup>. In CAM, as in science-based medicine, prior plausibility is no guarantee of positive results, but prior probabilities that are as close to zero as those

of homeopathy are a good guarantee of negative results. Moving from cancer prevention to treatment, high-dose vitamin C, even if one interprets existing clinical trials<sup>113–115</sup> in the most generous possible light, is ineffective against cancer.

Another problem with CAM arises when CAM practitioners make claims based on the fallacy that natural must be better, making the assumption that crude supplements and herbal preparations are as effective as, or even more effective than, pharmaceutical medicines that have been purified. These claims are based on ideas such as that in their natural state in the plant, active ingredients produce synergistic effects. Such synergy has been reported<sup>116–118</sup>, but it is uncommon and, although relatively easy to demonstrate *in vitro*, very difficult to demonstrate in animal models, and even more so to demonstrate in humans. Be that as it may, such synergy, if it exists in herbal medicines, is a property that can be studied using existing pharmacology, with no need to label it as alternative or integrative.

Furthermore, a major problem with herbal medicines is that it is very difficult to control lot-to-lot variations in content of active ingredient. There is a reason why patients who need digoxin are not asked to ingest foxglove leaves<sup>119</sup>.

**What is the harm?**

Another common response to criticisms of the pseudoscientific nature of many of the treatment modalities considered to be part of integrative oncology is, ‘what is the harm?’. As long as CAM is used solely for symptom relief and not as a primary treatment for the cancer itself, on the surface, this, too, seems to be a compelling argument. There are two responses, one scientific and one ethical. They are intimately related. The scientific argument rests on the observation that the hard-won improvements in mortality from cancer and quality of life of cancer patients over the past 80 years have come about not from diluting the scientific basis of cancer care, but rather from the ever-more rigorous application of evidence<sup>91</sup> in a progression from basic science to animal models to RCTs. It is true that the process is not as linear and neat as that. Clinical observations cross-pollinate basic science observations and *vice versa*. However, in EBM, it is nonetheless generally assumed that treatments do not reach the stage of RCTs without having amassed sufficient preclinical evidence supporting biological plausibility to justify the effort, time and expense of RCTs, and, above all, the use of human subjects. Indeed, so integral to this process are biological plausibility and preclinical evidence that they are enshrined in the Declaration of Helsinki<sup>120</sup>.

Before CAM, in the era of RCTs, treatments without biological plausibility and compelling preclinical evidence rarely, if ever, progressed to the stage of RCTs. Indeed, it is rare to find laboratory and animal experimentation supporting CAM modalities other than natural products- and acupuncture-related studies. Such preclinical studies, even when they exist, are often over-interpreted and/or have little relevance to humans. Here is a brief example. It has been proposed on the basis of mouse studies that acupuncture relieves pain through the local release of adenosine, which then activates nearby A1 receptors. Unfortunately, the key studies<sup>121,122</sup> that made this conclusion suffered from the awkward grafting of concepts of ‘*qi*’ and meridians onto what would otherwise have been straightforward interesting

neuroscience studies of the role of the A1 receptor in pain modulation. Instead, needles were inserted into an ‘acupuncture point’ on the mouse that, relative to the mouse leg, was far larger and far closer to a major nerve than in the human. In essence, because this caused more tissue damage and inflammation relative to the size of the animal in mice than in humans, such studies unnecessarily muddled a finding that local inflammation can result in the local release of adenosine with analgesic effect, and they still fail to demonstrate a sufficiently biologically plausible mechanism to justify clinical trials.

This phenomenon goes beyond basic science. When acupuncture is tested in the clinic, overall, with possibly one exception (for example, to treat nausea<sup>123</sup>), recent evidence strongly suggests that its effects are nonspecific and indistinguishable from placebo effects<sup>124–128</sup> that are highly dependent on practitioner–patient interaction<sup>129,130</sup>. Moreover, meta-analyses almost always conclude that there is insufficient clinical evidence to make a determination of efficacy<sup>123,131–133</sup> and include studies with a high risk of bias<sup>134–136</sup>. Also, contrary to the claimed mechanism of redirecting the flow of *qi* through meridians, researchers usually

find that it generally does not matter where the needles are inserted, how often (that is, no dose-response effect is observed)<sup>137</sup>, or even if needles are actually inserted<sup>138</sup>. In other words, ‘sham’ or ‘placebo’ acupuncture generally produces the same effects as ‘real’ acupuncture<sup>138–142</sup> and, in some cases, does better<sup>143</sup>. Even what is arguably the most persuasive meta-analysis<sup>144</sup> concluding that acupuncture has some efficacy against chronic pain included studies without sham acupuncture controls, and the reported difference due to acupuncture was still less than the minimal clinically important difference in pain for osteoarthritis<sup>145,146</sup>, strongly suggesting that acupuncture effects are probably not clinically relevant. The most parsimonious explanation for this body of evidence is that acupuncture almost certainly has no specific effects greater than placebo for any condition<sup>19</sup>, with the possible exception of nausea<sup>123</sup>.

Unfortunately, the infiltration of CAM into oncology risks both degrading the rigorous science behind cancer clinical trials and compromising the ethics of clinical trials by subjecting subjects to interventions that are so implausible that it is reasonable to conclude there is no realistic probability

**Glossary**

**Bayesian statistics**

A method based on Bayes’ theorem for calculating the degree to which new data changes the probability that the hypothesis being tested is true.

**Cantron**

A liquid developed by James V. Sheridan and promoted as a treatment for cancer since the 1930s, containing chemicals such as inositol, sodium sulphite, catechol, and others. There is no evidence it has anticancer activity.

**Declaration of Helsinki**

A statement of ethical principles for medical research involving human subjects developed by the World Medical Association. It stipulates, ‘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’.

**German New Medicine**

A system of medicine created by German physician Ryke Geerd Hamer that attributes cancer to an unresolved psychic conflict, evidence of which can be seen on computed tomography scans of the brain. Resolving this conflict, according to Hamer, allows the body to ‘heal itself’ of cancer.

**Gerson protocol**

An alternative cancer treatment involving extreme dietary modifications, including large doses of supplements, as well as coffee enemas.

**Laetrile**

Mandelonitrile-beta-glucuronoside, a modified form of the natural substance amygdalin, which is found in almonds and the pits of apricots. There is no evidence it has anticancer activity, and its use can result in cyanide poisoning.

**Natural products**

Medicines from natural plant or animal sources that are used as either extracts or purified active components.

**Pre-test probability**

Under Bayesian statistics, pre-test probability is the estimated probability that a hypothesis being tested is true prior to executing the study and analysing new data.

**Tongue diagnosis**

In traditional Chinese medicine, a system of diagnosis that maps various organs to specific areas on the tongue, much like reflexology maps specific organs to locations on the soles of the feet and palms of the hands.

**Traditional Chinese medicine**

An ancient system of medicine based on the Taoist belief that everything is interconnected. It includes herbal medicine, acupuncture and tongue diagnosis, and attributes causes of disease to imbalances in the ‘six *qi*’.

**Vitalism**

A concept that living creatures are fundamentally different from non-living objects because they possess a non-physical element that gives them life, referred to as ‘*qi*’ (traditional Chinese medicine), *prana* (Ayurveda), and the ‘vital force’ (naturopathy and homeopathy).

of a positive result. Although the most infamous example of this phenomenon was not a cancer RCT<sup>147,148</sup>, in oncology there is one particularly egregious example of an NCCAM-funded trial to test a protocol for pancreatic cancer, which involved extreme dietary modifications, consumption of large quantities of vegetable juices and supplements (81 capsules per day), skin brushing, salt and soda baths, and twice-daily coffee enemas. After many years and abandonment of the RCT format for an unblinded ‘patient’s choice’ design, the results showed that one-year survival rates of patients undergoing the dietary protocol were nearly four-fold worse than patients receiving standard-of-care chemotherapy<sup>149</sup>. Survival rates were also worse than expected based on historical controls, and subjects in the experimental group had poorer quality of life scores. By any reasonable measure, this trial was a disaster for patients.

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 modalities achieve that level of preclinical evidence in oncology, RCTs testing them cannot be scientifically or ethically justified. Unfortunately, in integrative oncology, biological plausibility as established through rigorous preclinical research no longer seems to be a prerequisite for RCTs, and strong scientific and clinical evidence are no longer prerequisites for widespread adoption. Acupuncture, *reiki*, and, less frequently, homeopathy are increasingly practiced at academic medical centres, including NCI-CCCs<sup>14,150</sup>, despite little or no convincing scientific evidence<sup>19</sup> for specific effects for any condition, cancer<sup>151,152</sup> or non-cancerous<sup>93,106</sup>, that is distinguishable from placebo. Indeed, the evidence that most non-pharmacological or dietary CAM modalities, such as acupuncture, are little more than ‘theatrical placebos’ (REF. 19) is so compelling that some proponents of acupuncture have, in essence, conceded this point by advocating the ‘harnessing of placebo effects’ or developing ‘meaningful placebos’ (REF. 153) (even though placebos do not seem to have significant objective effects on pathophysiology<sup>2</sup>), and the use of placebo effects ‘without deception’ (REF. 154) (even though subjects were told that placebos have “powerful mind–body effects”). This use of placebos is ethically problematic, because physicians should not

deceive their patients, nor should they recommend treatments without solid scientific evidence of efficacy and safety.

It has also been suggested and reported<sup>155,156</sup> that psychosocial interventions can prolong cancer-specific survival, improve immunity and decrease recurrence, with the implication that patients can to some extent control the time of their deaths on the basis of the purported observation that people tend to die after, rather than before, birthdays and major holidays. However, the idea that people die after important days has no evidence to support it<sup>157,158</sup>, and the consensus in psychology is that psychological interventions almost certainly do not prolong survival, although they can certainly improve quality of life. Furthermore, there is a dark side to claims telling cancer patients that the ‘power of positive thinking’ is so powerful; namely, the implication that, if a cancer patient is dying of the disease, it is at least in part because he or she does not have a ‘positive enough’ attitude and/or is not fighting hard enough.

“ Therein lies a key problem with integrative oncology. The less ‘alternative’ the intervention, the more it resembles conventional oncology; the more ‘alternative’ the intervention, the more it resembles the quackery from which integrative oncologists rightly distance themselves. ”

#### Is integrative oncology of value?

To the extent that conventional medicine might underemphasize non-pharmaceutical health-promoting activities, such as lifestyle interventions and nutrition, integrative oncology could be argued to be useful in its reintroduction of an emphasis on consuming a balanced diet, exercising, and doing things that promote general wellness, some of which could conceivably at least improve the quality of life in cancer patients, if not their overall chances of surviving their disease. However, this reintroduction is not without a price, and it is questionable whether the claimed benefits are worth this price. Integrative oncology integrates unscientific practices into science-based medicine, and, worse, the

pseudoscience at the heart of so many of the non-biologically based subdivisions of CAM is so pervasive, so embedded in the very fabric of integrative oncology, that it opens the door to clinical trials of dubious efficacy and the wasting of time and resources. The scientific ‘wheel’ is being reinvented and, in the process, turned back by a discipline that embraces crude supplements rather than pure drugs and that tolerates what can only be described as magical thinking in the form of energy medicine and acupuncture.

However, integrative medicine, including oncology, as replete as it is with the questionable treatments listed above, has not only found respectability in medical academia, but is now increasingly taught in the undergraduate medical curriculum<sup>159–162</sup>, often as part of popular electives<sup>163</sup>, and in primary care residencies as a recommended core competency<sup>164</sup>. Such programmes have not gone without criticism for being strongly biased towards CAM rather than evidence-based standards<sup>165,166</sup>. Scientific rigor aside, in the United States, there is now a board certification in integrative medicine (see the [American Board of Integrative Medicine](#) (see Further information)). Although it is granted by a less widely recognized board than the American Board of Medical Specialties, given the trajectory of integrative medicine, it is not beyond the pale to imagine a time in the not-too-distant future when integrative medicine and integrative oncology are fully accepted specialties. Although there does not yet seem to be a similar certification in Europe, a recent review of the literature identified ten integrative oncology programmes in England and two in Germany<sup>9</sup>. Even more evidence of this increasing acceptance occurred this year, in the form of a well-attended session on integrative oncology at the 2014 meeting of the American Society of Clinical Oncology, where not only diet and yoga but also acupuncture and mind–body interventions were discussed approvingly.

Can anything useful be salvaged from integrative oncology? Unfortunately, it is difficult not to conclude that, in its current form at least, integrative medicine integrates a great deal of pseudoscience and bad science with science-based oncology. It does not need to be this way. Returning to Glymour and Stalker<sup>1</sup>, practicing truly holistic oncology does not require rejecting science and embracing pseudoscience. It is possible to introduce scientifically supportable elements of CAM, such as certain

dietary and lifestyle interventions<sup>167</sup>, into oncology as science- and evidence-based supportive modalities, in essence reversing the rebranding that integrative oncology has been so successful at. The question is whether the mainstreaming of integrative oncology has already passed the point of no return. There should be no such thing as alternative or integrative medicine. There should only be medicine with strong evidence supporting efficacy and safety. Unfortunately, most of what is being 'integrated' with science-based medicine in integrative oncology is either unproven or has been proven not to work. Patients with cancer deserve better.

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#### Competing interests statement

The author declares [competing interests](#): see Web version for details.

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