Why Randomised Placebo-controlled Trials are Inappropriate for Acupuncture Research

Abstract

Although real acupuncture usually outperforms usual care or no treatment in research studies, when compared to sham acupuncture the differences are often small. This has been described as a 'paradox in acupuncture research'. Is it because acupuncture is just 'theatrical placebo'? Or because sham acupuncture is not inert? Or perhaps because the real acupuncture used in the study was not optimal? This paper addresses the first two questions.

The randomised placebo-controlled trial (RCT), often referred to as the 'gold standard' for healthcare research, were designed to measure a single variable while attempting to control for all others. They were first developed to assess medications, but are problematic as a research model for assessing complex skill-based therapies including acupuncture, psychotherapy and surgery. There is now evidence that shows that sham acupuncture protocols used in trials to date have not been inert and in fact produce effects that real acupuncture does not. This has caused a consistent underestimation of the effect size of real acupuncture.

Another factor impacting on acupuncture research is the prevailing understanding of placebo, which according to popular science is responsible for 30 per cent of all treatment effects. In fact, research is now suggesting that placebo effects may be much more complex than previously imagined, and may involve the genetic predisposition of subjects. Estimates of both the effect size and prevalence of placebo in studies have varied wildly, suggesting serious problems with how placebo has been measured.

This article explores these problems with acupuncture research, and concludes that comparative trials - analysed using network meta-analysis to produce a ranked order of therapies in terms of effectiveness, safety and cost effectiveness - is much more useful for developing clinically relevant practice guidelines than the current model of RCTs analysed via systematic reviews.

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Introduction

A landmark paper published by The Society for Acupuncture Research in 2011 identified a paradox in acupuncture research.[1] While acupuncture usually outperforms usual care or no treatment in studies, real acupuncture is often not found to be superior to sham acupuncture. There are three possible explanations for this phenomenon. Firstly, acupuncture may be 'theatrical placebo' as some critics have suggested.[2] Secondly, sham acupuncture protocols may not actually be inert, leading to an underestimation of the effect size of real acupuncture. Thirdly, the real acupuncture protocols may not have been designed to allow the treatment to achieve maximum therapeutic benefit. This paper will address the first two of these possible hypotheses and explore developments in current understanding of placebo before documenting the serious limitations of typical research methodologies for measuring complex interventions.

Why are randomised placebo-controlled trials used in healthcare research?

The randomised controlled trial (RCT) model is explicitly designed to measure a single variable while controlling for all other variables as far as possible. In acupuncture RCTs, treatment is often a standardised protocol to reduce the number of variables at play; however this does not reflect usual practice where individualised treatments (which may vary with each treatment session) are the norm.[2] Therefore

the research question 'What are the outcomes when a standard acupuncture treatment protocol is used?' fails to answer the clinical question 'What are the outcomes when a skilled practitioner delivers individualised acupuncture treatments according to their clinical judgement?' The many variables which define an acupuncture treatment include: practitioner skill/knowledge; point selection; diameter, length and design of needles; needle manipulation; number of points selected; needle retention time; time of day; frequency and duration of treatment course; co-interventions (moxibustion, cupping, dietary and lifestyle advice, electroacupuncture, ear acupuncture, etc.). The greater the translation gap between what occurred in a study and the treatment that would be delivered in a real-world clinical setting, the less clinical relevance the study will have in informing clinical practice guidelines.

Professor Ted Kaptchuk from Harvard Medical School published a paper in 2001 entitled: 'The double-blind, randomized, placebo-controlled trial: Gold standard or golden calf?'.[3] In this paper, Kaptchuk explores the possibility of a number of sources of bias which may be inherent in 'gold standard' research methodologies. If limitations of the RCT as a research model are not appreciated, then the relevance of RCTs to inform clinical practice guideline development may be overvalued, even to the point of 'worship'; as Kaptchuk explains, 'While a gold standard is valuable, any worshipping at an altar of a golden calf, like the Biblical Exodus story, may obscure "reality"'.[3]

The same limitations of RCTs apply to all complex interventions, not just to acupuncture. Psychotherapy, surgery and physiotherapy all involve complex multi-faceted interventions which do not lend themselves to single-variable examination. Indeed, even pharmacy research - for which the RCT model was originally developed - tests medications one at a time, but very little research informs prescribing clinicians about concurrent use of multiple medications, which has been a common practice for many years. A study of 26,277 elderly Spanish people found that 21.9 per cent were taking five or more prescription medications concurrently (defined as 'polypharmacy'), and in a study of 822,619 people aged over 75 in Sweden, the polypharmacy rate was 45 per cent.[4, 5] This creates a serious gap between what is known about individual medications from RCTs and how multiple medications are actually being prescribed and taken in the real world.

What do we know about the nature of placebo responses, their prevalence and effect sizes?

'Placebo' was defined in Robert Hooper's Quincy's *Lexicon Medicum* in 1811 as 'an epithet given to any medicine adapted more to please than benefit the patient'. Placebo has also been defined as an inert substance or treatment.[6] By this definition any intervention which produces any effect is not a placebo. Hence 'placebo' becomes a response to an inert intervention. For this reason, the terms 'sham acupuncture' and 'minimal acupuncture' are now frequently used in studies, in acknowledgement of evidence that demonstrates that they are not inert, and hence cannot be called 'placebo' controls.[7, 8]

In 1955, Beecher published a landmark paper entitled 'The Powerful Placebo', in which he estimated that 35.2 per cent of the subjects in the placebo control groups across 15 studies exhibited a placebo response.[9] In popular science this has morphed into the belief that 30 per cent of all treatment effects for all therapies are due to placebo. In fact, estimates of both prevalence and effect size of placebo responses in studies have been massively variable (see Tables 1 and 2). Indeed, Walsh et al (2002) in their review of 75 RCTs observe that prevalence of placebo responses ranged between 12 and 51.8 per cent, and that there was an association between year of publication and response rate.[10] In other words, over the years, researchers' estimates of the prevalence of placebo response have grown consistently (and have continued to grow since 2002). The extreme inconsistency of estimates of both placebo effect sizes and prevalence strongly suggests that there are fundamental problems with the process of measurement.

Table 1. Effect size of placebo response

- Non-existent (Hrobjartsson & Gotzsche, 2004)[44]
- 20% - 30% of clinical improvement (Jospe, 1978)[45]
- 40% of clinical improvement (Sartorius, 2006)[46]
- 56% analgesic effect of morphine (Evans, 1985)[47]
- 46% - 57% pain reduction [cream] (Benedetti et al,1999)[48]
- up to 90% in pain reduction (Haour, 2005)[11]
- 100%+ - "At times more potent than the pharmacologic agent " (Wolf, 1950) [44]

Table 2. Prevalence of placebo responders

- Non-existent (Hrobjartsson & Gotzsche, 2004)[44]
- 35.2% (Beecher,1955)[9]
- 39% (Levine et al,1979)[49]
- 12.5 - 51.8% (Walsh et al, 2002)[10] [Review of 75 RCTs – association between year of publication and response rate]
- 56% (Petrovic et al, 2002)[50]
- 70% (Turner et al, 1994)[51]
- 90% (Roberts et al, 1993)[52]
- Nearly 100% (Liberman, 1964)[53]
- 100% (Moerman, 1983)[54]

Some researchers have suggested that placebo response can be predicted by various psychological parameters.[11] However, Whalley et al found 'that personality predictors [of placebo response] (acquiescence and absorption) will not be consistent across contexts'.[12] This was echoed

by Kaptchuk et al who stated that evidence of the existence of reliable and consistent placebo responders is 'contradictory and methodologically weak'.[13]

A new frontier has now opened up in placebo research, with the discovery of 'The Placebome'. In an assay of an array of genetic markers, Zhang and colleagues found association clusters linked to specific forms of placebo response. For example, the presence of dopamine transporter gene SLC6A2 modulates an individual's response to placebo alcohol.[14] This adds a whole new layer of complexity to the placebo story, even before considering the impact of epigenetic modulations. Perhaps the problems to date in measuring the placebo response derive from a current lack of understanding of its complex nature.

Are there credible sham controls for complex interventions which are demonstrably inert?

a. Sham controls in acupuncture research

To date, five main types of sham control have been employed in acupuncture research: superficial needling of appropriate acupuncture points, needling 'irrelevant' channel points, needling non-channel points, non-penetrating sham needle devices and pseudo-acupuncture interventions (such as touching the skin with a toothpick).[15] In a meta-analysis of 37 acupuncture trials involving 5,754 subjects, Linde et al found that non-specific effects from sham acupuncture controls have been consistently 'moderately large'.[16]

Superficial needling of the same acupuncture points needled in the real acupuncture group, and the use of non-penetrating 'placebo needle' devices are clearly not inert controls. Indeed, two of the 'Nine Needles' documented in the *Ling Shu* (Divine Pivot) were blunt non-penetrating instruments, and stimulation of skin without penetration is included in a number of acupuncture traditions such as Shonishin. This makes non-penetrating stimulation at acupuncture points a type of real acupuncture and therefore not suitable for sham control protocols. A study by MacPherson et al compared fMRI activations/deactivations in response to superficial and deep needling and found 'marked similarities' of BOLD (blood oxygen level dependent) signals between the two needling methods.[17]

Three placebo needle devices have been commonly used in acupuncture research with the goal of blinding the subject. All three of these devices included a guide tube with a supporting pedestal or ring, and a placebo needle which retracts into the handle like a stage dagger on 'insertion'. When placebo needle devices were compared in a meta-analysis it was found that neither the Streitberger nor Park placebo needle devices were actually inert; there was no finding on the Takakura placebo needle device due to a lack of included studies.[18] While it has been suggested that the Takakura device may permit practitioner blinding as well as subject blinding, Takakura's own research concluded that the Takakura device was 'not suitable for double-blind testing of the needle effect'.[19]

Needling channel points which are deemed to be clinically irrelevant to the condition treated as a form of sham control has its hazards. While historical literature can provide clues about which points might produce particular effects, there is no literary record of which points have no effect on a target action. Longhurst, performing numerous studies on hypertension in rats, succeeded in demonstrating that the channel points he chose for his sham protocol were in fact not influencing blood pressure in any way, and hence could be established as inert.[20] If trials of potential sham control points were first conducted to establish their inert nature regarding the condition studied, this could provide a valid sham protocol, however this is rarely done.

Needling channel points was compared to needling non-channel points in an fMRI study by Wu et al. While some activations/deactivations were common to both channel and non-channel points, there were also specific activations/deactivations of brain centres which were seen only in response to needling channel points.[21] This demonstrates that needling non-channel points is not inert and overlaps to some extent with the effects of real acupuncture. Similar overlapping effects were found in an EEG and fMRI study by Nierhaus et al.[22] Pseudo-acupuncture interventions used as sham controls in acupuncture studies have included pressing a point with an empty guide tube without needle insertion, pressing a point with sharp object such as a wooden toothpick (cocktail stick), inactivated TENS and inactivated laser. As previously discussed, any stimulation of the skin with non-penetrating instruments will produce some effects and is therefore not inert. The use of inactivated TENS or laser is not suitable as a sham control, as even although they may be inert (which has not been established), they are not credible to subjects as an experience of acupuncture.

b. Sham controls in psychiatry and surgery research

So how does psychiatry research manage to create credible but inert sham controls? A meta-analysis of cognitive behavioural therapies for major depression and anxiety disorders found that 80 per cent of trials used a waiting list as a control and that these trials showed large effect sizes. However, when the controls used were usual care, placebo pill or relaxation, much smaller effect sizes were seen.[23] This closely resembles the 'paradox in acupuncture research' described above.

In a systematic review of placebo-controlled trials of surgery, placebo was described as 'a surgical placebo, a sham surgery, or an imitation procedure intended to mimic the active intervention'.[24] In 74 per cent of the 53 included

trials there was improvement in the placebo arm, and in 51 per cent of the trials there was no difference between surgery and placebo. In the remaining 49 per cent of trials showing surgery to be superior to placebo, the effect sizes were 'generally small'.[24] In complex interventions including acupuncture, psychiatry and surgery, it seems that sham/placebo-controlled trials consistently produce small effect sizes.

One of the possible reasons for the acupuncture research paradox may be that the sham protocols used in acupuncture studies have not been inert.[25] There is now substantial evidence to support this view for all five main types of sham controls used in acupuncture studies to date.[7, 8, 16, 26] When a sham protocol is active, the difference between the real and sham will be reduced by the degree of activity of the sham control. In other words, highly active sham controls will produce large underestimates of the effect size of real acupuncture. As Birch pointed out: 'This bias increases if the effects of the noninert placebo are larger and especially if they are specific to the condition under study'.[27] Birch also states that the problem of non-inert sham protocols is not exclusive to acupuncture, but is also a challenge for other complex interventions such as surgery (as mentioned above), for which researchers struggle to design a sham protocol which is both credible and inert.[27]

"A research model which is capable of including the practitioner's expertise and the patient's values while evaluating the evidence is likely to produce much more clinically relevant and useful outcomes."

Does sham acupuncture produce effects which real acupuncture does not?

A pattern emerges from studies which have compared the effects of real acupuncture with various sham controls. In fMRI studies of brain connectivity and BOLD signals of various brain centres, there is substantial overlap between the effects of real and sham acupuncture. However, there are also distinctive effects for real acupuncture and sham acupuncture.[21, 28-30] Liu et al also found that while there is substantial overlap in fMRI changes between real and sham acupuncture measured immediately, delayed fMRI changes occurred exclusively in the real acupuncture group.[31] In a study on acupuncture for fibromyalgia pain, mu opioid receptor binding potential was found to increase in response to real acupuncture but remained unchanged or decreased in response to sham acupuncture.[32] Again, this suggests that real and sham acupuncture are activating different pathways.

Sham controls not being inert is one problem. However, if sham controls are having effects which real acupuncture does not produce, then it is invalid to 'subtract' the effects of sham acupuncture from those of real acupuncture to differentiate between non-specific and specific effects. It would be more appropriate to speak of the 'specific effects of real acupuncture' and the 'specific effects of sham acupuncture'; the overlap between the two might be regarded as the 'non-specific effects' (see Figure 1).

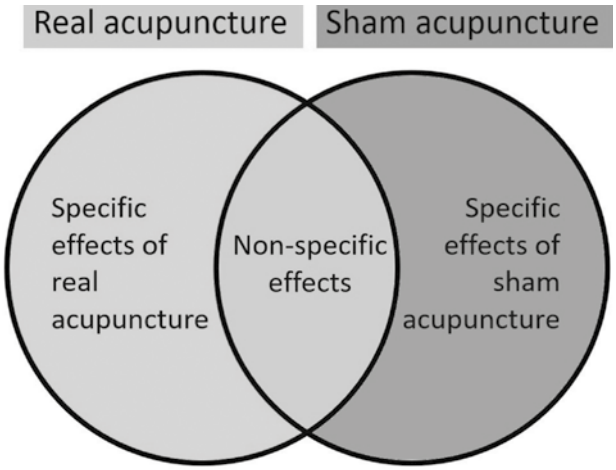

Figure 1: Non-specific effects of acupuncture

What alternative research methodologies are available to inform the development of clinical practice guidelines?

Comparative effectiveness research has been suggested as a way to reduce the gap in clinical relevance between RCTs and real-world clinical practice in developing clinical practice guidelines.[1, 33, 34] Open pragmatic head-to-head trials comparing two or more therapies do not need to have controls, as the research question is not about efficacy: 'How much of the treatment outcomes are due to specific effects' but 'How do the treatment outcomes of these interventions, delivered in the context of usual clinical practice, compare in terms of effectiveness, safety and cost-effectiveness?' The answers to the latter question are far more useful to inform the development of clinical practice guidelines, with much less translation gap.

There are a number of advantages to such comparative trials. Apart from reducing the research translation gap, the open pragmatic comparative trial gives greater clinical autonomy to therapists to use their experience and clinical judgement to deliver individualised treatments tailored to their patients' preferences and needs. The original definition of 'Evidence Based Medicine' (EBM) offered by Sackett et al had three aspects: 'The integration of best research evidence with clinical expertise and patient values'.[35] The RCT removes both the practitioner's clinical judgement and the patient's values from the equation to attempt to evaluate evidence in isolation. However, when evidence is applied in a clinical setting to inform clinical decision-making, it is vital that both the practitioner's

clinical judgement and the patient's values form part of the 'shared decision-making' (SDM) process.[36, 37] A research model which is capable of including the practitioner's expertise and the patient's values while evaluating the evidence is likely to produce much more clinically relevant and useful outcomes.

Another advantage of the comparative trial model addresses one of the ethical dilemmas involved in trial designs, where many subjects miss out on receiving any benefit. For example, in a three-arm study involving real acupuncture, sham acupuncture and no acupuncture, only one third of the subjects are likely to benefit (plus those who might derive benefit from an unintentionally active sham). In comparative trials every subject can receive a treatment which has been designed for their benefit. This is likely to improve both recruitment and retention of subjects in trials. It is also likely to increase researcher satisfaction, as delivering sham or no treatment is often an uncomfortable experience for researchers, whose instinct is to provide an intervention that is of benefit to the patient.

Comparative trials lend themselves to Bayesian network meta-analysis, which can produce a ranked order of interventions, even though many of the interventions within the matrix may never have been specifically tested against each other.[38] As a simplistic example, if therapy A is superior to therapy B, and therapy B is superior to therapy C, then without a specific study we can safely impute that therapy A is superior to therapy C. In a network meta-analysis on sciatica treatments by Lewis et al, acupuncture was superior to most other therapies in global effect and pain relief.[38] This included several therapies which were recently recommended by the National Institute for Health and Care Excellence (NICE) in the UK for low back pain and sciatica, such as radio frequency denervation and exercise (see Table 3).[38] Even though acupuncture was recommended by NICE in 2009 for chronic low back pain, the recommendation was removed in their 2016 review. It is noteworthy that shortly after NICE's removal of the recommendation for acupuncture for low back pain, the American College of Physicians updated their low back pain clinical practice guidelines to give a strong recommendation for acupuncture for both acute and chronic low back pain.[39] Similarly, in a network meta-analysis of physical treatments of knee osteoarthritis pain by Corbett et al, not only was real acupuncture superior to all of the physical interventions currently recommended by NICE, but sham acupuncture was also superior to most other interventions (see Table 4).[40]

At the Society for Acupuncture Research Conference at Harvard Medical School in 2015, a speaker from The National Center for Complementary and Integrative Health (NCCIH) announced that further placebo-controlled trials on acupuncture for pain were a 'low research priority', as such trials are uninformative and a poor use of limited research resources.[41] The NCCIH outlines one of their current research strategies as: 'Conduct pragmatic clinical trials to address questions about the integration of complementary health approaches into health care systems, or to study the effectiveness of complementary or integrative approaches in comparison to standard care'.[42]

The Society for Acupuncture Research has also called for a reorientation towards more pragmatic 'whole system' research supported by mechanism studies.[1] Given that attempts to create a credible but inert sham protocol for acupuncture research for almost 70 years have clearly failed, and given that sham acupuncture protocols have been shown to produce effects that are distinct from real

Table 3. Ranked order of effect size for interventions for sciatica (from Lewis et al., 2015)[38]

Global effect	Pain intensity
Biological agents (TNF-α modulators)	Biological agents (TNF modulators)
Acupuncture	Acupuncture
Manipulation	Intra-operative interventions
Intra-operative interventions	Neuropathic pain modulators
Epidural injections	Epidural injections
Spinal cord stimulation	Disc surgery
Disc surgery	Manipulation
Non-opioids	Chemonucleolysis
Education/advice	Exercise therapy
Chemonucleolysis	Non-opioids
Passive physical therapy	Conventional care
Neuropathic pain modulators	Traction
Bed rest	Passive physical therapy
Traction	Opioids
Percutaneous discectomy	Percutaneous discectomy
Opioids	Radiofrequency treatment
Exercise therapy	Education/advice
Conventional care	Bed rest
Intradiscal injections	
Radiofrequency treatment	

Table 4. Ranked order of physical treatments for knee osteoarthritis pain (from Corbett et al., 2013)[40]

acupuncture
balneotherapy
sham acupuncture
muscle exercise
Tai chi (Tai Ji Quan)
weight loss
aerobic exercise
no intervention

acupuncture, and considering the problems with using a single-variable measuring tool (the RCT) to evaluate complex interventions, more appropriate ways to evaluate the place of acupuncture in healthcare systems are urgently needed.

In addition to conducting comparative trials, which can be analysed either with conventional systematic reviews or with network meta-analysis, further studies of acupuncture's underpinning mechanisms are also needed, for three reasons. Firstly, a better understanding of mechanism increases the credibility of acupuncture in the minds of many, especially other health professionals and researchers. Secondly, understanding mechanism may suggest new treatment directions. For example, it is known that acupuncture can stimulate the production and release of oxytocin.[43] Could this perhaps indicate clinical value for preventing post-partum depression, especially in the high-risk group of mothers who have undergone a caesarean section and have elected not to breast-feed (two main natural sources of oxytocin stimulation)? Thirdly, talking about how acupuncture works makes it easier for acupuncturists to explain their therapy to patients, other health professionals and the public in general.

"Further studies of acupuncture's underpinning mechanisms are also needed ..."

Conclusions

The goal of the double-blind RCT in medical research is to reduce bias while evaluating efficacy of health interventions. However, there is growing evidence that when this research model is used to investigate complex interventions it actually introduces negative bias and leads to underestimation of effect sizes. This can be seen not only in acupuncture research but also in surgery and psychotherapy research. The common thread appears to be placebo controls which are not inert. The extreme variation in outcomes of studies attempting to measure the effect size and prevalence of placebo responses suggests serious methodological problems in the measurement of placebo. Recent research into the placebome suggest that placebo responses may be influenced by genetic (and possibly epigenetic) factors, and hence are far more complex and less understood than was previously thought.

Comparative pragmatic studies are likely to be more useful to inform the development of clinical practice guidelines. There are numerous advantages to comparative trials, including reducing the translational gap between outcomes of research and usual clinical practice, all subjects receiving treatment which is likely to be beneficial, and the potential for comparative trials to feed into network meta-analyses. This reorientation of the direction of acupuncture research is supported by the Society for Acupuncture Research and the National Center for Complementary and Integrative Health in the US. Both of these bodies also recommend that comparative research be reinforced by further investigations of acupuncture's physiological mechanisms.

Evidence Based Medicine was originally created as a model for shared decision-making where the best available evidence is interpreted using the practitioner's clinical judgement in the context of the patient's preferences. This is a conversation between patient and therapist which includes research evidence, but in which this evidence in isolation does not dictate the treatment. Ultimately the purpose of health research is to provide practitioner and patient with the most accurate and useful data to inform shared decision-making. This is more likely to be achieved through comparative trials plus mechanism studies than by continuing to use placebo-controlled RCTs.

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The Journal of Chinese Medicine

Newsbites

Oolong tea may help prevent breast cancer

Oolong tea is a partially oxidised tea, with different kinds of oolong varying from almost green in appearance (lightly oxidised) to darker (more oxidised). While previous research has shown that unoxidised green tea plays a role in inhibiting breast cancer cell growth, proliferation and tumour progression, no studies have been conducted on oolong. Now a lab study carried out at Saint Louis University has confirmed that oolong has a similarly beneficial effect on breast cancer cells, while black (fully oxidised) teas showed no benefit. Epidemiological data from Fujian province in China also showed that high consumers of oolong tea had a 68% lower incidence of breast cancer compared to the general population. And on top of this, of course, high quality oolong tea is a wonderful and delicious drink (Anticancer Research, November 2018).

Exercise, body shape and longevity

It's no surprise that exercise extends lifespan, but some interesting data has come out about the differences between men and women. For women, exercising for up to an hour a day increases the chances of reaching the age of 90, but exercising for longer appears to offer no added benefit. In men, however, the more they exercise, the more likely they are to reach 90. The chances of greater longevity also seem to be greater for tall and slim women who don't put on excess weight during life, although there is no similar advantage for taller men. (Journal of Epidemiology and Community Health, January 21st)

Decline of traditional medicine stores in Taiwan

Around 200 small scale herbal pharmacies are closing every year in Taiwan, despite the widespread popularity of traditional medicine. It's all down to a 1998 decision by the government not to issue any new licences and not to allow them to be passed down to the younger generation. The idea was to better regulate the mostly 'mom-and-pop' family stores by encouraging trained Chinese medicine doctors and pharmacists to take over the industry – something they have singularly failed to do, mostly because of low profitability. The average age of store holders at 61 means the future is bleak unless the government changes tack.

Climate change threatens cordyceps

Cordyceps (dong chong xia cao in Chinese, yarchagumba in Nepalese) is the highly prized and – at three times the price of gold - astonishingly valuable caterpillar fungus. Wild cordyceps is only found in locations above 3500 metres and is formed when the fungus penetrates caterpillars and slowly consumes them. This 'half plant half animal' substance is thought to have an ideal yinyang balance and act as a potent tonic. The fungus grows only in conditions where winter temperatures are below zero but the ground is not permanently frozen. Global warming, however, has changed the climate of the fungus-growing areas of Bhutan and the Tibetan plateau, with average winter temperatures rising by 3.5 to 4 degrees over the last three decades. The fungus does not appear to be adapting by moving to higher regions, and increasing scarcity threatens the livelihoods of the local cordyceps hunters (Proceedings of the National Academy of Sciences, October 2018).