

Does unconventional medicine work through conventional modes of action?

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It is often maintained that although conventional medicine works by means of pharmacotherapy with predominantly proved effects, unconventional therapies are more or less spiritual therapeutic approaches without a scientific basis. We hypothesize that both conventional and unconventional medicine might be effective because of similar modes of action. Certainly, this does not imply that every unconventional method has any effect. Conventional and effective unconventional medicine might both work by means of pharmacology (eg, substances in medical herbs), including pharmacologic interactions between the 2 treatment options (eg, herbs and drugs with coagulation effects). Both conventional and unconventional treatments involve a considerable risk of side effects, which are sometimes even severe. In general, the pattern of side effects of alternative treatments is similar to that observed with the use of conventional medicine. The placebo effect and suggestive aspects are also apparent in both treatments. Furthermore, mind-body medicine (eg, use of relaxation techniques) might be explained by pathophysiologic mechanisms. Overall, many aspects seem to contribute to the mosaic of joint modes of action involved in both conventional and unconventional medicine. This might demystify the aura of some of the complementary and alternative approaches and might help to bring both conventional and unconventional approaches together on a scientific basis. (*J Allergy Clin Immunol* 2006;118:569-73.)

Key words: Allergy, alternative medicine, complementary medicine, herbal medicine, homoeopathy, unconventional medicine

It is a common prejudice that although conventional medicine works by means of pharmacotherapy with predominantly proved effects, unconventional therapies are more or less spiritual therapeutic approaches without a scientific basis. Scientific medicine and unconventional medicine are usually believed to be mutually irreconcilable, both for diagnostic methods¹ and therapeutic methods.²

There seems to be a tendency for physicians-healers to attract like-minded patients and vice versa. Similarly, diagnostic or therapeutic measures will also tend to be acceptable to both parties (Fig 1).

We hypothesize that similar modes of action can be attributed to both conventional and unconventional medicine in many cases (Table I). Certainly, this does not imply that every unconventional method has some effect.

PHARMACOTHERAPY

Undoubtedly, pharmacotherapy is the mainstay of conventional medicine. In general, drug therapy includes aspects of pharmacokinetics and pharmacodynamics. Complementary and alternative medicine also uses pharmacotherapy, such as in phytotherapy and herbal medicine. Its use can be supported by 3 modes of knowledge about the efficacy: (1) confirmed efficacy of a known active substance; (2) supposed efficacy without knowledge of the active substance, without evidence from controlled trials, or both; and (3) deliberate use of a contaminant with proved efficacy.

First, the efficacy of certain herbal drugs on clinical symptoms or a disease has been proved in controlled trials, and the physicians inform patients and use the drug according to the state of the art in the literature. For example, Sheehan et al³ showed that in 40 adult patients with long-standing refractory atopic dermatitis, the reduction of the extent and severity of eczema with a formulation of herbs was statistically highly significant in a randomized, double-blind, placebo-controlled trial. Furthermore, there are studies of complementary and alternative medicine that have confirmed efficacies, but the active substance is not known. For example, the clinical trial of a derivative of the Chinese herbal formula MSSM-2 demonstrated beneficial effects in adults with moderate-to-severe asthma.⁴

Second, in some cases herbal medicine seems of benefit to the patients, but the responsible component or substance is not known and not characterized. Furthermore, well-controlled studies are not available. In such cases it might be possible that the herbal medicine contains an active component that has not yet been identified.

Third, a cause of great concern is the deliberate contamination of phytotherapeutics with corticosteroids by some practitioners of alternative systems of medicine.^{5,6} Screening for corticosteroids of 120 samples of

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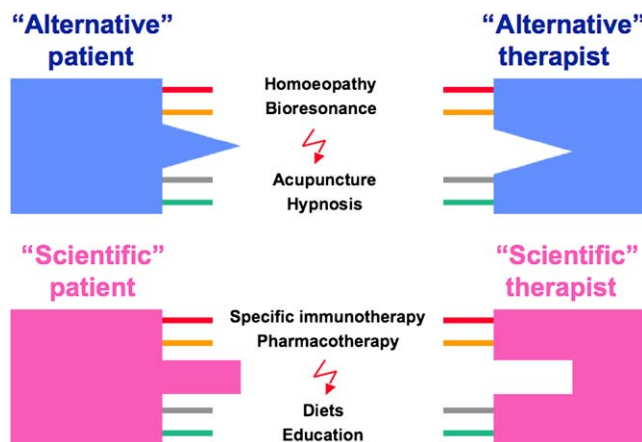


FIG 1. Patients and therapists: like attracts like. Adapted with permission from Niggemann B, Grüber C. Unconventional and conventional medicine—who should learn from whom? *Pediatr Allergy Immunol* 2003;14:149-55, Blackwell Publishing.²

TABLE I. Common modes of action of conventional and unconventional medicine

- Pharmacotherapy
- Side effects
- Pharmacologic interactions
- Placebo effect
- Suggestion
- Relaxation techniques
- Time
- Costs
- Combinations

alternative medicines dispensed to patients with mainly asthma or arthritis showed that 38.3% of these samples were adulterated with steroids.⁵ Another study found dexamethasone in 8 of 11 creams investigated, with a mean concentration of 456 $\mu\text{g/g}$ (roughly equivalent to 0.05% betamethasone valerate).⁷ In a further case report, the Chinese herbal cream given to a 53-year-old woman with psoriasis was investigated by means of liquid chromatography, and a significant concentration of clobetasol propionate was found.⁸ Tablets labeled as an herbal drug but containing 0.75 mg of dexamethasone acetate were given to a 2-year-old child for atopic eczema, leading to adrenal suppression and clinical signs of steroid toxicity.⁹ A similar case of a 5-year-old boy with eczema receiving a potent topical steroid for several months without any warning was reported from England.¹⁰ Adulteration of traditional Chinese medicines has been reported not only with corticosteroids but also with a wide range of other substances and drugs.¹¹

The immunologic basis for possible clinical effects was shown in an animal model in which the Chinese herbal formula MSSM-002 suppressed airway hyperreactivity and eosinophilic inflammation in a murine model of allergic asthma. These effects were comparable with those of dexamethasone but were not accompanied by the suppression of T_H1 responses seen with dexamethasone.

In vitro studies demonstrated that MSSM-002 significantly decreased antigen-induced T_H2 cytokine secretion by murine T_H2 -polarized splenocytes and human mucosal T_H2 cell lines.¹² Other studies showed similar results.¹³ In human subjects immunologic changes have been observed in patients with atopic eczema¹⁴⁻¹⁶ and perennial allergic rhinitis¹⁷ after treatment with a Chinese herbal therapy.

In summary, complementary and alternative medicine can have clinical effects with or without proved pharmacologic or immunologic modes of action. Deliberate adulteration of herbal medicine with drugs might delude patients with the risk of severe side effects.¹⁸

SIDE EFFECTS

Although it has always been clear that conventional medicines can have adverse side effects, it is often claimed that unconventional therapeutic approaches are free of adverse effects. The statement that “a drug that has no side effects has no main effects” is probably true for both conventional and unconventional medicine. It has been shown that complementary and alternative medicines have the potential for side effects, such as sensitizing capacity (eg, herbal medicine), mechanical injury (eg, pneumothorax caused by acupuncture), infectious complications (eg, outbreaks of hepatitis B associated with acupuncture), organ toxicity (eg, content of heavy metals or hepatotoxic and nephrotoxic effects of some herbal remedies), cancerogenic properties (eg, urothelial carcinoma associated with herbal medicine), and nutritional hazards (eg, severe nutritional deficiencies resembling “kwashiorkor” in infants caused by strict alternative diets).¹⁸

It has been well established that formation of reactive metabolites of drugs is associated with drug toxicity. Similarly, findings increasingly suggest a role of reactive metabolites-intermediates through bioactivation in herbal toxicity and carcinogenicity. It has been hypothesized that reactive metabolites resulting from herbal bioactivation

covalently bind to cellular proteins and DNA, leading to direct cytotoxicity and oncogene activation.¹⁹

In summary, complementary and alternative medicine can exert clinical benefits. However, some methods also harbor a considerable risk of even severe side effects. In general, the pattern of side effects of alternative treatments is similar to that observed with conventional treatments.

PHARMACOLOGIC INTERACTIONS

Many herbal medicines have a significant pharmacologic activity and thus a potential for adverse effects.²⁰ It is increasingly being acknowledged that herbs can interact with drugs in the same way that drug-drug interactions occur.^{21,22} This is illustrated by the report of the Ayurvedic syrup “Shankhapushpi,” which caused a decrease in the plasma concentration of phenytoin, impairing seizure control in epileptic patients.²³ St John’s wort (*Hypericum perforatum*) interacts with substrates of the drug efflux transporter P-glycoprotein and decreases fexofenadine plasma concentration.²⁴ It can also decrease the bioavailability of theophylline.²⁵

Inhibition of coagulation leading to postoperative bleeding requiring surgical re-exploration after preoperative use of mostly herbal preparations was reported in a 60-year-old woman with breast carcinoma.²⁶ Several other herbal medicines carry the risk of potential coagulation effects, such as *Ginkgo biloba*, which interacts with aspirin and warfarin,²⁷ or the Chinese traditional medicine formula *Kangen-Karyu*, which interacts with ticlopidine.²⁸

In summary, complementary and alternative medicine can clearly exert conventional pharmacotherapeutic effects. Physicians must be aware of possible drug interactions associated with herbal remedies and should ask patients about the use of these products.²⁷ Finally, many more studies are warranted to further investigate possible important interactions of conventional and unconventional drugs.

PLACEBO EFFECT

The Latin word “*placebo*” means, “I will please.” The “placebo effect” implies that positive expectations after administration of a drug or use of a method will improve or cure symptoms. On the other hand, many patients show signs of a “nocebo effect”; that is, negative expectations induce or enforce adverse effects of drugs and methods.^{29,30}

A placebo effect has been proved in numerous pharmacotherapy studies (eg, in asthmatic patients).³¹ Some typical placebo enhancers are a garish color, a large size, a bitter taste, a painful administration, exoticism, impressive apparatus, and a high price.² The placebo effect is not restricted to pills or methods but also characterizes the beneficial effects derived from a positive physician or healer-patient relation.

A recent comparative study showed that biases are present in placebo-controlled trials of both homoeopathy

and conventional medicine. When these biases were taken into account, there was weak evidence for a specific effect of homoeopathic remedies but strong evidence for specific effects of conventional interventions. This finding is compatible with the notion that the clinical effects of homoeopathy are placebo effects.³²

In summary, medical science often makes the mistake of considering the placebo effect predominantly in a negative sense (ie, to prove that patients have no evident or real pain). The placebo effect could be integrated in our medical work in some cases by carefully exploiting the positive effects. Both conventional and unconventional approaches might take advantage of placebo effects.

SUGGESTION

Suggestive aspects of a therapeutic approach might be useful: the personal charisma of the physician or healer definitely plays an important role in gaining the patient’s confidence. Furthermore, although an impressive apparatus with a high-tech character (eg, in bioresonance) and imposing names and titles of persons (professor, specialist, certificates in the waiting room) or institutions (eg, research institute for XYZ, center of XYZ) might promise more than they can offer, these factors might enhance the patient and physician-healer interaction, leading to an improved therapeutic success. Again, this holds true for both conventional and unconventional approaches. However, the border of responsible therapeutic action is exceeded if the patient is saddled with a therapeutic burden when this should be borne by the physician or healer.

In summary, suggestive aspects, such as the charisma of the therapist or impressive apparatus and imposing titles, might lead to an improved therapeutic success in both conventional and unconventional medicine.

RELAXATION TECHNIQUES

Physical and psychologic stress is a well-known trigger of many symptoms and complaints, including heavy breathing and dyspnea in bronchial asthma. Therefore it seems reasonable that mind-body medicine, such as relaxation techniques, Buteyko breathing, yoga, hypnosis, and biofeedback, should be used to avoid or manage asthmatic symptoms. Some studies show a positive effect of relaxation techniques,³³ Buteyko breathing,^{34,35} and yoga³⁶ on lung function or the need for β -agonists in patients with asthma. As a consequence, relaxation techniques have become an integrated element of asthma education measures.

The underlying modes of action leading to positive clinical effects of relaxation techniques on asthmatic symptoms and lung function can be explained by “conventional thinking.” Bronchial obstruction can be induced in asthmatic patients by means of tachypnea, hyperventilation, or forced breathing on the basis of their bronchial hyperreactivity. Conversely, patients who relax and

reduce stress and thereby normalize their breathing might be able to avoid or minimize bronchial obstruction.

In summary, mind-body medicine using various therapeutic approaches, such as relaxation techniques, can contribute to the patient's well-being and health in diseases such as bronchial asthma.

TIME

One of the main complaints patients express about their physicians is that they do not have (enough) time for them. However, a therapist who pays attention to the patient and listens carefully will build up confidence. If the patient has gained confidence, successful management of symptoms might appear more likely, and symptoms might be perceived as less severe and might be more likely to improve or disappear. This is of potential benefit for both the unconventional healer and the physician.

For instance, homoeopathy might be successful for some patients, because it ideally combines the following²:

1. a long and thorough session (around 1 hour) in which the patient might be asked a range of personal questions for the first time and in which the physician listens carefully;
2. individual and holistic pharmacotherapy, usually free from side effects; and
3. the principle of "primary deterioration": many symptoms and diseases improve during the next weeks or months because of the natural or spontaneous course of disease, irrespective of the medical intervention.

Thus the factor of time might work through 2 modes of action: (1) on a short-term basis through personal attention leading to confidence and hope and (2) on a long-term basis as a result of the spontaneous course of disease. Practitioners of conventional medicine, however, all too often feel the pressure to change therapy if symptoms do not improve or vanish soon.

In summary, time plays an important role in the interaction between the patient and physician or healer. Unconventional medicine seems to exploit this fact extensively. Although conventional medicine suffers from financial restraints, it would be well advised to integrate this resource to a larger extent.

COSTS

A high price is one of the well-known placebo factors leading to an intended effect, especially if paid out of pocket. A patient who pays \$250 for a treatment might more easily perceive an effect than somebody who has never seen the bill. "The bill is the pill" or "if it doesn't cost anything, it cannot be worth anything": this also holds true in medicine for many persons, irrespective of conventional or unconventional medicine.

However, the aspect of the price as an integral element of the placebo effect might not be applicable in some

health care systems. If patients do not know what costs are induced by the diagnostic and therapeutic measures, they cannot profit from the financial part of the placebo effect.

In summary, costs seem to play a role as placebo for both conventional and unconventional therapies.

COMBINATIONS

Frequently, both unconventional and conventional methods are used by patients and physicians to treat particular symptoms. Not too long ago, some unconventional therapists claimed that their therapy would not work if conventional drugs (eg, corticosteroids) were used at the same time, even if administered locally. It has increasingly been accepted by both sides that several therapeutic approaches can be used in parallel. As one example, conventional physicians might administer mistletoe extracts in oncologic patients in some cases. On the other hand, unconventional therapists often agree on complementary rather than solely alternative therapeutic approaches.

CONCLUSIONS

Overall, many aspects seem to contribute to the mosaic of mechanisms involved in both conventional and unconventional medicine. This might demystify some of the complementary and alternative approaches and might help to bring both conventional and unconventional approaches together on a scientific basis because the plural of anecdotes is not evidence.³⁷

Unconventional methods will remain attractive for patients with allergic or other chronic disease and will continue to be offered by physicians and healers. Our concern as allergologists is not that some patients might be helped by unconventional methods but that others using unconventional methods as a replacement for conventional medicine will not receive sufficiently effective therapy, so that their disease worsens.

Analyzing the modes of action in unconventional medicine might help us to understand why some patients seek or stick to unconventional methods despite our efforts. In selected situations deliberate use of modes potentially common to unconventional and conventional medicine, such as placebo effects, might be warranted to optimize efficiency by better compliance. The second possibility to optimize efficiency is to increase efficacy. For many indications, we have good reason to believe that we can offer conventional treatment with similar or different modes of action but with an efficacy superior to unconventional methods. We should not miss the chance to introduce efficacy for a shared vision of disease management between patients and physicians.

REFERENCES

1. Niggemann B, Grüber C. Unproven diagnostic procedures in IgE-mediated allergic diseases. *Allergy* 2004;59:806-8.

2. Niggemann B, Grüber C. Unconventional and conventional medicine— who should learn from whom? *Pediatr Allergy Immunol* 2003;14:149-55.
3. Sheehan MP, Rustin MHA, Atherton DJ, Buckley C, Harris DJ, Brostoff J, et al. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet* 1992;340:13-7.
4. Wen MC, Wei CH, Hu ZQ, Srivastava K, Ko J, Xi ST, et al. Efficacy and tolerability of anti-asthma herbal medicine intervention in adult patients with moderate-severe allergic asthma. *J Allergy Clin Immunol* 2005;116: 517-24.
5. Gupta SK, Kaleekal T, Joshi S. Misuse of corticosteroids in some of the drugs dispensed as preparations from alternative systems on medicine in India. *Pharmacoepidemiol Drug Saf* 2000;9:599-602.
6. Graham-Brown RAC, Bourke JF, Bumphrey G. Chinese herbal remedies may contain steroids. *BMJ* 1994;398:473.
7. Keane FM, Munn SE, Du Vivier AWP, Taylor NF, Higgins EM. Analysis of Chinese herbal creams prescribed for dermatological conditions. *BMJ* 1999;318:563-4.
8. Wood B, Wishart J. Potent topical steroid in a Chinese herbal cream. *N Z Med J* 1997;110:420-1.
9. Hughes JR, Higgins EM, Pembroke AC. Oral dexamethasone masquerading as a Chinese herbal remedy. *Br J Dermatol* 1994;130:261.
10. O'Driscoll J, Burden AD, Kingston TP. Potent topical steroid obtained from a Chinese herbalist. *Br J Dermatol* 1992;127:543-4.
11. Huang WF, Wen KC, Hsiao ML. Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. *J Clin Pharmacol* 1997;37:344-50.
12. Li XM, Zhang TF, Sampson H, Zou ZM, Beyer K, Wen MC, et al. The potential use of Chinese herbal medicines in treating allergic asthma. *Ann Allergy Asthma Immunol* 2004;93(suppl 1):S35-44.
13. Srivastava K, Teper AA, Zhang TF, Li S, Walsh MJ, Huang CK, et al. Immunomodulatory effect of the antiasthma Chinese herbal formula MSSM-2 on TH2 cells. *J Allergy Clin Immunol* 2004;113:268-76.
14. Banerjee P, Xu XJ, Poulter LW, Rustin MHA. Changes in CD23 expression of blood and skin in atopic eczema after Chinese herbal therapy. *Clin Exp Allergy* 1998;28:306-14.
15. Latchman Y, Banerjee P, Poulter LW, Rustin M, Brostoff J. Association of immunological changes with clinical efficacy in atopic eczema patients treated with traditional Chinese herbal therapy (Zemaphyte). *Int Arch Allergy Immunol* 1996;109:243-9.
16. Novak N, Haberstok J, Kraft S, Siekmann L, Allam JP, Bieber T. Standardized extracts from Chinese herbs induce IL-10 production in human monocyte-derived dendritic cells and alter their differentiation in vitro. *J Allergy Clin Immunol* 2001;108:588-93.
17. Yang SH, Hong CY, Yu CL. Decreased serum IgE level, decreased IFN- γ and IL-5 but increased IL-10 production, and suppressed cyclooxygenase 2 mRNA expression in patients with perennial allergic rhinitis after treatment with a new mixed formula of Chinese herbs. *Int Immunopharmacol* 2001;1:1173-82.
18. Niggemann B, Grüber C. Side-effects of complementary and alternative medicine. *Allergy* 2003;58:707-16.
19. Zhou S, Koh HL, Gao Y, Gong ZY, Lee EJD. Herbal bioactivation: the good, the bad and the ugly. *Life Sci* 2004;74:935-68.
20. Barrett B, Kiefer D, Rabago D. Assessing the risk and benefits of herbal medicine: an overview of scientific evidence. *Altern Ther Health Med* 1999;5:40-9.
21. Pinn G. Adverse effects associated with herbal medicine. *Aust Fam Physician* 2001;30:1070-5.
22. Silverstein DD, Spiegel AD. Are physicians aware of the risks of alternative medicine? *J Community Health* 2001;26:159-74.
23. Bateman J, Chapman RD, Simpson D. Possible toxicity of herbal remedies. *Scot Med J* 1998;43:7-15.
24. Wang Z, Hamman MA, Huang SM, Lesko LJ, Hall SD. Effect of St John's wort on the pharmacokinetics of fexofenadine. *Clin Pharmacol Ther* 2002;71:414-20.
25. Fugh-Berman A. Herbal-drug interactions. *Lancet* 2000;355:134-8.
26. Norred CL, Finlayson CA. Hemorrhage after the preoperative use of complementary and alternative medicines. *AANA J* 2000;68:217-20.
27. Cupp MJ. Herbal remedies: adverse effects and drug interactions. *Am Fam Physician* 1999;8:1239-45.
28. Makino T, Wakushima H, Okamoto T, Okukubo Y, Deguchi Y, Kano Y. Pharmacokinetic and pharmacological interactions between ticlopidine hydrochloride and *Kangen-Karyu*—Chinese traditional herbal medicine. *Phytother Res* 2003;17:1021-4.
29. De Craen AJM, Kaptchuk TJ, Tijssen JGP, Kleijnen J. Placebos and placebo effects in medicine: historical overview. *J R Soc Med* 1999; 92:511-5.
30. Butler C, Steptoe A. Placebo responses: an experimental study of psychophysiological processes in asthmatic volunteers. *Br J Clin Psychol* 1986;25:173-83.
31. Joyce DP, Jackevicius C, Chapman KR, McIvor RA, Kesten S. The placebo effect in asthma drug therapy trials: a meta-analysis. *J Asthma* 2000;37:303-18.
32. Shang A, Huwiler-Müntener K, Nartey L, Jüni P, Dörig S, Sterne JAC, et al. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. *Lancet* 2005;366:725-32.
33. Loew TH, Siegfried W, Martus P, Tritt K, Hahn EG. Functional relaxation reduces acute airway obstruction in asthmatics as effectively as inhaled terbutaline. *Psychother Psychosom* 1996;65:124-8.
34. Bowler SD, Green A, Mitchell CA. Buteyko breathing techniques in asthma: a blinded randomised controlled trial. *Med J Aust* 1998;169: 575-8.
35. Cooper S, Osborne J, Newton S, Harrison V, Thompson Coon J, Lewis S, et al. Effect of two breathing exercises (Buteyko and pranayama) in asthma: a randomised controlled trial. *Thorax* 2003;58:674-9.
36. Nagarathna R, Nagendra HR. Yoga for bronchial asthma: a controlled study. *BMJ* 1985;291:1077-9.
37. Bielory L. The science of complementary and alternative medicine: the plural of anecdote is *not* evidence. *Ann Allergy Asthma Immunol* 2004;93(suppl):S1-4.