The other side of the coin: safety of complementary and alternative medicine

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ABSTRACT

- Most consumers consider complementary and alternative medicine (CAM) products inherently safe.
- The growing simultaneous use of CAM products and pharmaceutical drugs by Australian consumers increases the risk of CAM–drug interactions.
- The Therapeutic Goods Administration (TGA) has a two-tier, risk-based regulatory system for therapeutic goods — CAM products are regulated as low risk products and are assessed for quality and safety; and sponsors of products must hold the evidence for any claim of efficacy made about them.
- Adverse reactions to CAM products can be classified as intrinsic (innate to the product), or extrinsic (where the risk is not related to the product itself, but results from the failure of good manufacturing practice).
- Adverse reactions to CAM practices can be classified as risks of commission (which includes removal of medical therapy) and risks of omission (which includes failure to refer when appropriate).
- While few systematic studies of adverse events with CAM exist, and under-reporting is likely, most CAM products and practices do not appear to present a high risk; their safety needs to be put into the perspective of wider safety issues.
- A priority for research is to rigorously define the risks associated with both CAM products and practices so that their potential impact on public health can be assessed.

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The rising use of complementary and alternative medicine (CAM) by the Australian public raises the critical issue of safety. The primary concern for healthcare consumers is generally the potential benefits of the products or services they are considering. Safety, the other side of the coin, is assumed and seldom questioned. The general belief is that because these products or services are "natural" they are safe. The concept that "naturalness" is a guarantee of harmlessness is obviously both simplistic and untrue. Yet, an Australian survey of 3027 people in 2000 showed that 90% of users of CAM (especially the elderly) considered the products safe, compared with 65% of non-users.[1] The widespread availability of complementary medicines through health food stores and supermarkets, and the infrequency of litigation against CAM practitioners, has been suggested as evidence of safety.[2] However, these cannot be considered as appropriate measures of safety, and more appropriate measures are gradually emerging in the scientific literature.

It is important to realise that any therapy has the potential to cause harm, and that any pharmacologically active product is likely to have adverse effects. The critical issue in assessing any therapy is its risk to benefit. In conventional medicine, this can be often underpinned by hard data, with exact figures outlining the number of individuals experiencing an adverse event versus the number of people achieving a benefit. However, until more CAM therapies and products are rigorously assessed, clinicians should have a schema for considering safety issues.

Products and practices

The first issue in considering safety in CAM is to separate products from practices. Products are the medicines either purchased over the counter at pharmacies, health food stores or supermarkets or prescribed by CAM practitioners. Practices are the discipline-specific skills that complementary therapists are trained to use, and generally encompass a philosophy and rationale for the application of specific therapeutic techniques, such as acupuncture or massage, or the prescribing of specific medicines, such as herbs, vitamins or minerals.

The Commonwealth *Therapeutic Goods Act 1989* defines complementary medicines (Section 52F) as therapeutic goods consisting wholly or principally of one or more active ingredients, each of which has a clearly established identity and either a traditional use or any other use prescribed in the regulations.[3] The designated active ingredients are listed in Schedule 14 of the Act (Box 1).

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Risks associated with CAM products

Adverse reactions to CAM products may be either intrinsic or extrinsic.[4] Intrinsic reactions are directly related to the active medicine itself and consist of either predictable (Type A) reactions owing to their pharmacological effects, or idiosyncratic (Type B) reactions that are not predicted by their pharmacology (eg, anaphylaxis).[5] Extrinsic reactions are not related to the product itself, but result from failure of good handling and manufacturing procedures.

Predictable (Type A) reactions

These are the most common form of adverse reactions to drugs and constitute about 80% of adverse drug reactions.[6] An example is the mineralocorticoid adverse effects reported with the use of liquorice (*Glycyrrhiza* spp.),[7] a plant used widely in both Western and Chinese herbal medicine, and estimated to affect up to 20% of patients who take large doses or receiving long-term therapy with Gan Cao (*Glycyrrhiza uralensis*), the form used in Chinese herbal medicine. Currently, there is no critically evaluated comprehensive list of CAM products with potential for causing predictable reactions. Given the widespread community use of these products, such a list would be a significant public health measure. Until such

1 Schedule 14 of the *Therapeutic Goods Act 1989* of designated active ingredients which can be used in complementary medicines available in Australia[3]

Item	Ingredient or kind of ingredient
1	Amino acid
2	Charcoal
3	Choline salt
4	Essential oil
5	Plant or herbal material (or a synthetically produced substitute for material of that kind), including plant fibres, enzymes, algae, fungi, cellulose and derivatives of cellulose and chlorophyll
6	Homoeopathic preparation
7	Microorganism, whole or extracted, except a vaccine
8	Mineral, including a mineral salt and a naturally occurring mineral
9	Mucopolysaccharide
10	Non-human animal material (or a synthetically produced substitute for material of that kind) including dried material, bone and cartilage, fats and oils and other extracts or concentrates
11	Lipid, including an essential fatty acid or phospholipid
12	Substance produced by or obtained from bees, including royal jelly, bee pollen and propolis
13	Sugar, polysaccharide or carbohydrate
14	Vitamin or provitamin

a list is available, it is recommended that clinicians obtain one of the plethora of desk references on both efficacy and safety issues of CAM products. Two reviews of the quality[8] and value[9] of these resources are useful guides for critical thinkers seeking to understand the developing literature in this field.

CAM–drug interactions are a specific category of predictable, intrinsic reactions. The most commonly suspected are herb–drug interactions, although many nutrient–drug interactions also occur.[10] Estimates of the concurrent use of CAM products with prescription drugs vary from 18% in a United States survey[11] to 39% in an Australian survey of patients using Chinese medicine.[12] Based on the Australian Bureau of Statistics' projected estimate of the Australian population of 20.048 million people in February 2004, the number of people potentially at risk of CAM–drug interactions lies between 1.8 million and 4.07 million. Yet, relatively few reports of interactions are published or submitted to government agencies such as the Adverse Drug Reactions unit of the Therapeutic Goods Administration (TGA). There is little doubt that such adverse reactions are under-reported,[4] although the extent of under-reporting is unknown. It is unlikely, however, that thousands of such reactions remain unreported in the community.[13]

Information on interactions is currently derived mainly from isolated case reports (where causality is not always rigorously assessed), and lists of theoretical or predicted interactions based on the known pharmacological effects of CAM products.[14] Where there has been extrapolation from known activity of chemical constituents within the substance or from in-vitro studies, the risks should be described as potential rather than real risks (ie, those that have been demonstrated in appropriately designed formal studies).[15] A 2001 systematic review of herb–drug interactions reported 17 formal clinical trials relating to five herbs; 10 of the 17 studies were performed on St John's wort (*Hypericum perforatum*).[16] That review found only 41 case reports relating to the same five herbs (garlic [*Allium sativum*], ginkgo [*Ginkgo biloba*], ginseng [*Panax ginseng*], St John's wort [*Hypericum perforatum*] and kava [*Piper methysticum*]). Thus, the real risks from hundreds of medicinal plants remain either unknown or hypothetical. Box 2 provides a summary of the major herb–drug interactions currently documented for these herbs.

Idiosyncratic (Type B) reactions

Idiosyncratic reactions are usually allergic responses, and account for 6%–10% of adverse drug reactions to pharmaceutical drugs.[6] An example is the reaction to the commonly used herb chamomile (German, *Matricaria recutita* and Roman, *Chamaemelum nobile*, syn. *Anthemis nobilis*). An allergic reaction to chamomile was reported in a 69-year-old Ukrainian immigrant who was given a chamomile enema for constipation by his wife, a trained medical practitioner.[17] Within minutes he developed dyspnoea, flushing and an urticarial rash on the inside of his arms. He was treated immediately with oral prednisolone and later received nebulised salbutamol. Skinprick testing was positive to the chamomile tea bag used to prepare the enema. These types of allergic reactions are impossible to predict. Vigilance by doctors in recognising symptoms of different types of allergic reactions will enable these unpredictable reactions to be quickly identified and appropriately treated.

Extrinsic risks

The suspension of Pan Pharmaceuticals' manufacturing licence in 2003 for breaching its obligations to maintain pharmaceutical good manufacturing practice (GMP) standards[18] is a clear example of extrinsic risks. These can include:[4,12]

2 Important herb–drug interactions*

St John's wort
- Lowers blood concentrations of cyclosporin, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline.
- Causes intermenstrual bleeding when used with oral contraceptives
- Causes mild serotonin syndrome when used with loperamide or selective serotonin reuptake inhibitors.

Ginkgo
- Causes bleeding when used with warfarin
- Causes raised blood pressure when used with a thiazide diuretic

Ginseng
- Lowers blood concentrations of alcohol and warfarin
- Induces mania when used with phenelzine

Garlic
- Lowers blood concentration of warfarin
- Changes the pharmacokinetics of paracetamol
- Causes hypoglycaemia when used with chlorpropamide

* Adapted from Izzo and Ernst.[16]

- misidentification of materials (particularly of herbal materials where there is not appropriate botanical identification);
- lack of standardisation (failure to identify appropriate marker compounds within herbal materials and ensure a minimal concentration of these);
- contamination (of crude plant material by pesticide residues, microorganisms, aflatoxins, radioactive substances and heavy metals);
- substitution (of one herb with another, potentially more toxic herb);
- adulteration (the illegal practice of adding conventional pharmaceuticals to CAM products or decreasing the proportion of active components by increasing that of inactive components);
- incorrect preparation or dosage (mistakes in the safe preparation or appropriate dosage of a specific herb); and
- inappropriate labelling or advertising (claims made on labels and advertisements being untruthful, invalid or misleading).

Risk-management framework

In cooperation with state and territory governments, the TGA is responsible for the regulatory arrangements for complementary medicines. The TGA has developed a risk-management framework which differentiates low-risk and high-risk medicines. This is based on community expectations that therapeutic products will be safe, effective and of good quality, and industry expectations that regulation should be the minimum necessary, appropriate and commensurate with the assessed risk of the products and consistent with international practice.[18] Low-risk medicines, which include most complementary medicines, are listed on the Australian Register of Therapeutic Goods (ARTG) and have been assessed by the TGA for quality and safety. They are not assessed for efficacy, but their sponsors must hold the evidence for any claims made, and these need to be consistent with the guidelines for the types and levels of claims for therapeutic goods.[19] High-risk medicines, which include over-the-counter pharmaceuticals and prescription drugs, are registered on the ARTG and are assessed for quality, safety and efficacy. The recent Expert Committee on Complementary Medicines in the Health System found that:

- the current single regulatory framework for medicines in Australia is appropriate for complementary medicines; and
- the current two-tier, risk-based regulatory system should be maintained, with some enhancements.[18]

One enhancement recommended by the committee is that the TGA should increase random and targeted auditing of sponsors of complementary medicines to ensure that evidence for efficacy is held for any claim made for a specific product. This is expected to result in more meaningful marketing claims substantiated by appropriate evidence.

Risks associated with CAM practices

Risks associated with the practice of CAM can be either risks of commission or risks of omission.[12] Examples of risks of commission include:

- removal of appropriate medical therapy (which can lead to loss of the benefit of that therapy, increased morbidity and, in some cases, death);
- incorrect prescribing (poor prescribing, failure to observe contraindications, inappropriate dosage, inappropriate duration of therapy, failure to avoid known interactions with pharmaceutical drugs); and
- negligent practice (eg, use of non-sterile acupuncture needles).

Risks of omission include

- misdiagnosis (failure to detect underlying abnormality which can allow a disease to progress);
- failure to refer (often associated with misdiagnosis, but also occurs when practitioners are unaware of the limitations of their discipline); and
- failure to explain precautions (which may equate to failure to obtain informed consent, but can also have direct and serious consequences for a patient unaware of any risks).

During the review of Chinese traditional medicine conducted for the Victorian, New South Wales and Queensland state health departments, most medical practitioners consulted provided examples from their clinical practice of adverse events resulting from acts of commission or omission by CAM practitioners.[12] To date, no study of this has been reported in the medical literature.

Safety of CAM practices

There is a small but growing body of evidence supporting the safety of CAM practices. Most of the research to date has been in the fields of acupuncture and spinal manipulation. A systematic review of prospective studies on the safety of acupuncture identified nine surveys.[20] While the results were not uniform, they indicated that minor adverse events were common (eg, needle pain, 1%–45%; tiredness, 2%–41%; and bleeding, 0.03%–38%). The serious adverse event of pneumothorax was rare, occurring only twice in about 250 000 treatments. A large United Kingdom study reported after this systematic review described the adverse events following acupuncture in a prospective survey of 32 000 consultations with medical doctors and physiotherapists.[21] There were no serious adverse events and 2135 minor events, giving an incidence of 671 per 10 000 consultations, or 6.71%. The most common adverse events were bleeding (3.1%) and needle pain (1.1%). Aggravation of symptoms occurred in 0.96%, but subsequently improved in 70% of cases. While these total figures are low, they show that the highest adverse event rates for individual acupuncturists (as a percentage of their consultations) were 53% for bleeding, 24% for pain and 11% for aggravation of symptoms. While there may be a number of explanations for the wide range in rates of adverse events, a potential causative factor is educational standards relating to the practice of CAM. A retrospective Australian study of adverse events in Chinese medicine,[22] primarily acupuncture, found that adverse event rates for practitioners with 0–12 months of CAM education were significantly higher than for those with 37–60 months' education. In 2000, the Victorian government passed the Chinese Medicine Registration Act, which established a minimum educational standard for practitioners of Chinese medicine, including acupuncturists. Similar legislation by other states is yet to follow, but was recommended by the recent expert committee.[18] Outside of chiropractic and osteopathy, other CAM practices remain unregulated and the capacity to set and enforce education and practice standards is problematic.

Reviews on spinal manipulation by chiropractors and osteopaths emphasise the infrequency of adverse events from spinal manipulations compared with the number of such manipulations performed throughout the world on a single day.[23,24] However, under-reporting is likely to significantly distort the evidence, and

large, rigorous studies of cervical spinal manipulation are needed to accurately define the risks.[24]

Achieving perspective

Any discussion about the safety of CAM needs to consider wider public safety issues and levels of acceptable risk. There are 7.2 million cases of food poisoning in Australia each year; in 2002, 103 people were hospitalised and two died of food poisoning.[25] Moreover, 5.7% of hospital admissions in Australia are related to pharmaceutical drugs.[26] Yet, risks from food and conventional medicine are seen as acceptable public risks. It has been estimated that, if the number of cases of adverse events recorded as resulting from Chinese medicine over the past 20 years were multiplied by 100, the number of adverse events would still not be comparable to those related to pharmaceutical drugs in one year of medical practice.[12] Discussions about the safety of CAM need to be contextualised and not seen as a means of devaluing widely used health products and practices.

There is no doubt that both CAM products and practices have real risks associated with their use in the community, but, overall, these are most likely minimal.[12] A priority for research is to rigorously define these risks so that their potential impact on public health can be assessed. It is probable that the data will point towards specific products or practices that need to be modified or ceased to bring them into line with community expectations of acceptable risk. In addition, occupational regulation of CAM practitioners will minimise practice risks by restricting practice to individuals with acceptable educational qualifications and by enforcing appropriate practice standards. Furthermore, effective education of both the public and CAM practitioners will be the key to minimising risks and maximising safety.

Competing interests

None identified.

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