

COMPLEMENTARY & ALTERNATIVE MEDICINE (CAM) IN AUSTRALIA



ASSESSMENT OF RISKS AND BENEFITS

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COMPLEMENTARY & ALTERNATIVE MEDICINE (CAM) IN AUSTRALIA



ASSESSMENT OF RISKS AND BENEFITS

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I. PURPOSE OF THIS DOCUMENT

The aim of this document is to provide background information regarding the assessment of safety and efficacy of products used in complementary and alternative medicine (CAM). As a result of recent political and medical events, there now exists a clear need for properly considered and agreed processes by which such therapies are assessed. The aim of such processes is to ensure safety for the Australian public, while retaining potentially valuable and cost-effective therapeutic agents. It is clear that this balance can only be achieved in an environment of open-minded, adequately funded clinical research. The resolution of this central need is dependent of good science and goodwill on the part of current proponents and opponents of CAM, and is not likely to be achieved in an environment of prejudice, reactionary regulation or legislation, or attempted political gain.

A reading list included with this document, drawn mainly from the orthodox, peer reviewed medical and scientific literature. The references are divided into sections appropriate to their content, so that the information used to author the various sections of this document can be readily gathered and reviewed. In places where important information or quotations are covered, the reference is provided in the text of the document.

II. COMPLEMENTARY AND ALTERNATIVE MEDICINE

A. GENERAL

There is considerable recent literature on the issue of what is increasingly becoming known as “complementary medicine”, and the appropriate use of what has previously been called “alternative medicine” within medical practice. In this document, the broader term, complementary and alternative medicine (CAM) is used for convenience, and because it has been adopted by the Office of Alternative Medicine (OAM) within the US National Institute of Health (NIH).

Many definitions of CAM have been attempted, ranging from restrictive to dismissive to all encompassing. Ernst and his colleagues have put forward the following definition, based on feedback from practitioners in orthodox and alternative medicine,

Complementary medicine is diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy, or by diversifying the conceptual framework of medicine

Ernst E et al, *Complementary medicine - a definition*, Br J Gen Pract Sept 1995;506

Many authors have noted the adoption of CAM by the public in many first world countries, and the best estimate is that Australians currently spend around \$A1 billion of CAM each year. Some administrators and anthropologists are aware of the potential for cost savings to the community in the use of CAM, especially for conditions which are chronic, self limiting, or for which no effective medical treatment exists. Mark Micozzi, an anthropologist and executive director of the American College of Physicians, has gone so far as to suggest that the constraining of the burgeoning health budget in the US will require judicious investment in research and appropriate utilisation of promising traditional and CAM practices.

There is some support for his viewpoint based on Australian research. In 1993, 20.3% of Australians consulted CAM practitioners, while 48.5% used CAM products, at a total cost of approximately \$A930 million. This is not funded by taxpayers, and represents an average “out of pocket” cost of \$84.56 per year, or \$1.63 per week for those who visit CAM practitioners, and \$71.13 per year, or \$1.37 per week for those who use CAM products. If divided over the entire population (as is done for medical costs), these figures are \$17.17/yr (\$0.33/wk) and 34.50/yr (\$0.66/wk) respectively.

In contrast, total expenditure for orthodox medical drugs alone now exceeds \$A3 billion, which equates to \$166 per year, or \$3.19 per week for each Australian. Australian Governments expend over \$A22 billion for orthodox medical care each year, representing a “taxpayer cost” of over \$A1,200 per year for each Australian, or around \$23.50 per person per week.

Medical costs not covered in the government expenditure (prescription and consultation “gaps”, private health cover, etc) may increase this figure by between 25% and 50%, meaning

that orthodox health care is now costing each Australian an average of around \$1,600 per year, or more than \$30 per week.

A decrease in the rate of growth of public expenditure in the health budget has primarily been achieved by “cost shifting”, in which the costs tend to fall increasingly on those who need health care most, and can afford it least. Measures such as removal of medications from the Pharmaceutical Benefits Scheme (PBS), altered legislation in workers compensation and social security payments, increasing cost of prescription medications and increasing private health fund premiums are tending to put high quality medical care beyond the reach of more Australians every year.

The introduction of costly new technologies, the rapid growth of expenditure for medications, and the adoption of evidence based medicine (EBM) are likely to continue to place pressure on Australia’s open-ended Medicare system. Without a “cap” to the health budget, the current “cost shifting” back to the patient will inevitably increase. This does not, however, cause any real decrease in medical expenditure for Australians. It places the cost burden on those who are sick, and can presumably least afford the costs. The result is likely to be financial and social stress, and further deterioration of the health of those people, either as a result of decreasing quality of medical care, or as a result of financial stress accompanying the payment for quality medical care.

In this way, “cost shifting” is likely to further escalate total medical costs in Australia without benefit from that expenditure, decreasing the cost-effectiveness of medical management, and further escalating the costs in the medium and long term.

A high proportion of the health consultations, investigations and interventions are ineffective at best, and dangerous at worst. Hospital admission in Australia is associated with accidental and unnecessary death and permanent injury at a rate comparable to that caused by cigarette smoking. Most GP consultations are for conditions which are trivial, self limiting, or not helped by medical intervention. In some other cases, the medical management may worsen or prolong the illness, or may lead to unintended adverse outcomes, such as antibiotic resistance.

It is appropriate to identify such problem areas within medicine, and to educate both the medical profession and the public about these limitations. It would seem likely that a potential starting point for the introduction of CAM exists in such “niches” in which medical intervention is either ineffective or has a high risk-benefit or cost-benefit ratio. Removing these poor performing areas from orthodox medical care would, in fact, improve the value gained from money invested in orthodox medicine. The money saved could be committed to quality outcome-based clinical research, with review of the safety and cost-effectiveness of a broad range of promising approaches for such conditions. In this way, after a minimal “priming” with research funds, CAM becomes “revenue neutral”, funding research in part from money saved due to improved cost-effectiveness of medical management, and in part from public money saved by “cost shifting” to private expenditure for health.

Without adequate money for clinical research into complementary medicine, orthodox medicine will consume increasing resources with reducing returns in health outcomes. With open-minded assessment of *all* diagnostic, preventive and management options, and with the money to perform the required research, all modalities will stand or fall according to safety and cost-effectiveness in managing these difficult medical conditions. Ernst has claimed that, even in the US, less than 0.08% of the medical budget is put towards research into CAM. In Australia, this would translate to a research budget of \$A17.6 million. The current expenditure is considerably less than this, and is probably less than \$A1 million. A considerable increase from the current level is clearly required to effectively organise and support basic research in CAM.

One issue is obvious and undeniable: there is an increasing use and acceptance of CAM in the general community, and this has occurred despite the heavy subsidising of orthodox medicine by the Medicare and Pharmaceutical Benefits Scheme. The use of CAM by a high proportion of Australians is a reality, and a commensurate allocation of funds for research into risks and benefits is urgently needed. This contribution may well provide unexpected cost and health benefits to an overstretched Australian Health Care system. Continuing to ignore CAM research will not diminish its use, may cost Australians dearly in loss of cost-effective therapies, and is incompatible with the goal of best health outcomes for all Australians.

B. DEALING WITH RISK - PERCEIVED VS 'REAL' RISK

Assessing risk is an inherently difficult problem, for a large number of reasons. In principle, exposure to any activity, process or chemical agent (natural or synthetic, therapeutic or otherwise) on the part of an individual, exposes that individual to a risk. It is axiomatic, then, that any such risk needs to be weighed by the individual against the perceived benefit of the activity or agent. This also involves the assessment of the risk of failing to perform the activity or use the agent in question. This leads to a concept of a risk-benefit ratio, in which the individual may be seen as seeking to minimise risks where possible, while gaining the maximum benefit.

Complexity emerges from this simple concept for many reasons. Sometimes, the risk is borne by a small subgroup of the population, while benefit is evenly distributed, or gained by only a few. On other occasions, benefits are gained in the short term, while risks become apparent later. On other occasions still, the subjective views of risk and benefit are not supported by statistical data, leading to distortions of perceptions of risk and benefit.

The processes of assessing risk-benefit are also difficult for an entirely different reason. The risks and the benefits may be far from agreed upon or accepted. In this case, agreed parameters for risk and benefit assessment can be followed by data collection for those agreed parameters. Neither risk nor benefit can be assumed to exist without adequate data to support that assumption, and the presence of data related to one side of the ratio cannot

be considered without adequate data related to the other side. In short, risk-benefit assessment assumes adequate, preferably complete, assessment of data relating to both risks and benefit.

In practice, complete data are never available. For this reason, a branch of statistical inference has emerged known as Bayesian statistics. "Prior probabilities" are assigned according to the best available data for both risk and benefit, and new information over time is used to modify those "prior probabilities" to more accurate "posterior probabilities". The "posterior probabilities" then become the new "prior probabilities", and the process moves forward again. This iterative approach, incorporating new knowledge as it becomes available, has recently been supported as a valid and useful compared to the "frequentist" statistical approach, typified by the high cost, placebo-controlled crossover cohort trials. This is especially true in situations in which funding for such a cohort trial is unlikely, especially where no party stands to gain financially from a patentable product or process at the end of a successful trial. This is frequently the case in CAM.

It is trite and somewhat hypocritical on the part of opponents of CAM to argue that the cost and running of such high cost trials is the responsibility of "proponents" of CAM. The issue being assessed is whether the community will gain from the use of a product or process, in terms of risk-benefit and cost-benefit. The financial gains to be made by producers and suppliers of CAM are orders of magnitude less than the potential financial gains for the developers of patentable products and processes, while the costs of appropriate trials are similar for equipotent products.

In fact, the aim of the scientific investigation of risks, benefits and cost of CAM is precisely the reduction of costs associated with the use of patented, high cost products and processes. Much of the health budget is now spent repaying the onerous R&D requirements of the developers and producers of new drugs. If equally safe and effective therapies can be found among CAM products in the public domain (ie they have the same risk-benefit ratio), then the issue becomes one of determining cost-benefit. In most cases, the cost benefit would fall on the side of the non-patented medication, as the payment of the costs of drug development would not need to be incurred.

This situation clearly presents a problem for government and for business in acting responsibly on behalf of the community. Availability of safe and effective CAM therapies represents a financial risk for businesses engaged in research, development and marketing of novel, synthetic, patentable and potentially profitable medications. These businesses are frequently multinational pharmaceutical industries with enormous financial reserves and political influence. Their financial risks are minimised by restriction of competitive products, especially products available in the public domain which may have similar or better risk-benefit or cost-benefit ratios. The community's needs, however, are best served by access to safe, effective and low cost health care.

Government is often caught between the desire to support commerce and novel research on the one hand, and its need to keep the growing costs of this type of industry under control, so that the community can afford effective health care. To date, industries within medical care have marginalised those groups seeking to introduce CAM for the management of many health problems, by claiming that the “gold standard” of large prospective trials as the only means of scientifically determining risk-benefit and cost-benefit. Such trials require an investment of time, money and resources usually only available to government and large, profitable industries.

Bayesian statistical methods is only the first of a number of changes in assessment of health care options required to ensure that safe and effective CAM approaches are not lost to the community, to the detriment of the health of that community. The development of approaches which prevent the loss of potentially cost-effective health care products and processes, while ensuring safety for the community, is one of the challenges for the coming century. It is one that has so far not been addressed by the Department of Health and Family Services, the National Health and Medical Research Council, or the Therapeutic Goods Administration, but is a necessary challenge if they are to perform their duty of providing for better health outcomes for all Australians. Without adequate and timely research into CAM, the opportunity to reverse the escalating health costs and looming health funding crisis in Australia may well be lost.

Finally, it must be noted that all therapeutic intervention is associated with risk. Casarett & Doull's *Toxicology: The basic science of poisons*, is the classic textbook in this field of risk assessment. It is appropriate to quote from the section on “Risk Extrapolation”,

An acceptable risk depends upon a number of factors, including benefits of the chemical to the society. Some factors considered in establishing acceptable risk factors are:

Beneficial aspects of the chemical

- Economic growth*
- Employment*
- Increased standard of living*
- Increased quality of life*
- Taxes generated*

Detrimental aspects of the chemical

- Decreased quality of life*
- Emotional difficulties*
- [Adverse] Health effects*
- Lawsuits*
- Loss of environmental resources*
- Loss of work*
- Medical payments*

In addition, more recently, issues of economic and environmental sustainability must also be factored in to this complex evaluation.

As can be seen, CAM practices and products are able to contribute in all of the categories related to “beneficial aspects”, with the added benefit of economic and environmental sustainability. They are not usually associated with any of the “detrimental aspects”, apart from possible adverse health effects, and possibly loss of employment (if the use of CAM reduces the need for research and development costs of drugs).

Finally, a risk of death or cancer below one person per million in the population is generally currently considered zero risk. This applies to agents as diverse as agricultural chemicals, foodstuffs, medications and activities. One reason for this is that it is impossible to distinguish between a cause and effect relationship and chance association between events at this level of risk.

The more commonly a product or process is used or adopted by the community, the greater the likelihood that a poor health outcome will occur around the time of use of the process or product. Asthma is a common illness, affecting around 3 million Australians. The use of various CAM products is also now very common, with nearly 50% of the population using some form of CAM therapy in a given year. In some people, the asthma and use of a CAM product or procedure, though unrelated to each other, will occur in close temporal proximity, and can give rise to the view that one “caused” the other. This was a personal view expressed by a number of the experts in a 1997 Coroner’s Inquest regarding a possible death from Royal Jelly, based on a small number of apparent associations.

Such personal viewpoints are inadequate to establish a cause and effect relationship. There is much research to support the view that “active surveillance for events which support a prior belief” leads to a gross overestimation of the true risks of a product or process. The only valid method of assessment of risk is a prospective trial which does not suffer from such selection bias. All studies have drawn attention to this need for further clinical research, yet the research has not been commenced.

It is also useful to place this issue of risk in a context of use of other therapeutic agents, food additives, and foods.

- Breast implants are therapeutic devices which carry a risk of local rupture, associated with painful scarring, pain and contracture in excess of 35% over a ten year period. The best estimate of risk of autoimmune disease is about 25% increase over those without silicone breast implants, although it would appear that the type is a specific subtype peculiar to people with certain types of silicone exposure. The use of implants involves virtually all of the detrimental aspects listed above, while the benefits are limited to profits for surgeons and manufacturers, and a possible short term improvement in quality of life for the consumer. While the cost of the original cosmetic implant is borne by the individual, the cost of revisions and other medical care for the person who has received an implant is born by the community, under Medicare. Estimates of the added medical costs to the community range from \$8,000 to \$30,000 over the lifetime of a person who receives cosmetic implants in her third decade of life.

This cost is significant, yet is rarely addressed in cost-benefit assessment as it becomes invisible, and absorbed into general medical costs for the community.

- Aspirin and paracetamol are responsible for a considerable number of deaths per year, the former from adverse reactions to salicylate, the latter from hepatic necrosis following overdose. Both are also associated with increased risk when used with alcohol, paracetamol more so than aspirin. This is of particular concern, as paracetamol is promoted as a “gentle to the stomach” pain reliever, and is thus frequently used for the headaches which follow heavy alcohol use (“hangovers”). Both products, therefore, have readily definable and clear risks. Despite this, both products are easily available from supermarkets, carry no warnings of interactions with alcohol, do not carry warnings about asthma, and are found in the medicine chests in almost all homes. The benefits relate to short term pain relief, most often for conditions such as headache which are self limiting.
- Food additives such as benzoates and sulfites, as well as colourings and artificial flavourings, are commonly used by the food processing industry without adequate regard for safety or appropriate labelling. A recent study by Hodge and Loblay has shown that sulfites are a common cause of asthma. This asthma occurs up to an hour after ingestion, and may be serious or even life threatening. Sulfites have been largely banned in the US for this reason, although they remain in common use in Australia, and was the most likely cause of death in a recent case involving Royal Jelly. The risk of asthma and anaphylaxis from adverse reactions to such food additives is significant, and could be better controlled if sulfites were banned apart from certain situations in which they are considered necessary for food preserving reasons. In these cases, clear and appropriate labelling would be required.
- Finally, foods such as shellfish, peanut, soy, egg, wheat, citrus and milk contain common allergenic proteins, and each is capable of causing anaphylaxis and death in highly sensitive individuals. The number of deaths attributable to each is uncertain (specific data are not collected), but is clearly greater than one in a million. While there is clear benefit for the community in the availability of many of these, the difficulties arise when people who have known sensitivities inadvertently consume products which contain the food to which they are allergic. Adequate labelling and warnings on packages and in restaurants of ingredients would help minimise risks for such sensitive people, but has not so far been considered.

The view put forward by one expert researcher during the Coroner’s Inquest into Royal Jelly, when he rhetorically asked why any risk should be considered acceptable, is also relevant here.

It is initially an appealing prospect, that therapeutic agents should carry zero risk, but as many authors have pointed out, any agent which has a potential for benefit has a potential to harm. It is the qualification and quantification of the benefits and the risks which allow

for a decision to be made on whether the potential benefit(s) are worth the risk(s). Were this not so, medicine would have ground to a halt in its infancy, reduced to trivial and irrelevant practices in an obsessive attempt to prevent any harm. The concept of *primum non nocere* (first do no harm) is now interpreted as meaning that the doctor should always ensure that intervention has a greater potential to benefit the patient than to harm the patient. On many occasions, the use of therapies with a high risk of mortality can be justified if the failure to use them carries with it a greater risk of mortality or extreme morbidity. Such a situation regularly exists in cancer management, and even in the management of HIV.

The point of dealing with these issues is that many day to day activities and products carry measurable and easily modifiable risks, yet we accept these with minimal or absent regulation and control of use. If regulation and restrictions are applied to one agent, the logical follow on will be to identify all those products of equal or greater risk, and regulate or restrict those agents in a consistent fashion. The dividing line between safe and unsafe may prove to be arbitrary at present, but once a de facto benchmark is set by the regulation of one product, a great many of our commonly used foods, food chemicals and medications will be drawn into the cycle of consistency of such risk minimisation.

C. EVOLUTIONARY BIOLOGY AND THE HISTORY OF CAM

Some general questions need to be addressed in the issue of the use of CAM, in order to assign “prior probabilities” on safety and effectiveness. Is CAM safe? Is it effective? What assumptions can be made?

Without adequate research, prior probabilities for these questions require that we look to the history of the use of CAM. Evolutionary biology (EB) would suggest that the current universal use of CAM by societies is evidence that the use of CAM is a trait which improves the likelihood of survival and procreation of the members of those societies.

All cultures that we know of have developed shamanistic or other health practices, most often incorporating the use of naturally occurring agents derived from animal or plant sources. EB proposes that those traits which we observe will generally exist because the presence of the trait on the whole led to improved survival and reproduction. Thus, one large “trial” has led to an outcome suggestive of a long term, sustainable benefit. Any “prior probability” would clearly have to place the benefit higher than the risk of using CAM. In addition, the long history of use of CAM would support the view that benefits gained from CAM are ecologically and (recently) financially sustainable, a claim that cannot be made for the use of western orthodox medicine as yet.

There is no suggestion that the prevalence of CAM in societies is “proof” of a low risk-benefit ratio, nor that other therapeutic approaches may not improve on the risk-benefit

ratio of CAM. It is simply prior evidence that survival of humans is likely to have been enhanced rather than hindered by the use of CAM, and that the use of CAM has led to a sustainable benefit over a long period of time. This makes for a low “prior probability” of risk, with a high “prior probability” of benefit. This estimate may well be modified in either direction with the discovery of further facts related to these specific questions, but suggest that it is both unwise and unscientific to ascribe “prior probabilities” of high risk and low benefit for CAM. The added benefit of long term sustainability of benefits over risks in CAM can be also be assumed, as there appear to be no traditional communities where financial or ecological concerns have led to abandoning of the use of CAM practices and products. If there are examples of this, then I have been unable to find them in the scientific literature.

Often, CAM therapies are discovered from observation of the biological effects of the use of the original product. A strongly positive, or beneficial, biological response of an unrelated species to an agent provides some degree of assurance, namely that at least one “natural experiment” with the agent in question has occurred. The queen bee, for example, apparently survives entirely upon Royal Jelly, the milky secretions of the mandibular glands of the “nursing” bees, and displays extraordinary longevity and fecundity compared to other bees, and to other insects of similar size, generally. This proves nothing about safety or efficacy in humans, but provides a degree of prior evidence that the components of the Royal Jelly have the capacity to produce biological responses of the type needed for beneficial outcomes in humans.

Indeed, the entire field of ethnopharmacology relies upon the observations and usage of traditional societies and cultures to identify potentially beneficial naturally occurring products, with a view to categorising their benefits and risks from these accumulated historical observations. Whether these products are derived from exotic herbs, rainforest tree bark or leaves, plant or animal toxins, or foods is immaterial. The generally held view is that we as a species should be paying greater attention to the rediscovery of this accumulated knowledge, rather than discarding it. The view that all therapeutic agents of value are synthetic and novel chemical creations ignores the fact that many of our best known drugs are little more than the so-called “active ingredients” of naturally occurring products.

New information, derived from appropriate research targeted at the issues of risk-benefit and cost-benefit are now required. This document provides a survey of the evidence from the popular and scientific literature on the possible and probable benefits derived from the use of Royal Jelly, balanced against a review of the possible and probable risks of Royal Jelly, taken from the same sources. This is proposed as a useful starting point in the modification of the suggested “prior probabilities”, and as a pointer to the type of research required in the future to further refine the assessment of the risk-benefit and cost-benefit of this product.

D. SAFETY AND EFFICACY IN CAM

There is a peculiar problem in assessing safety and efficacy in CAM products and processes, especially where such products and processes have been used for a prolonged period. It is instructive to deal with this issue before proceeding, as it provides an important insight into the problems which may arise in the absence of a formal process of assessment of CAM.

Briefly stated, most orthodox medical products and processes appear to have a low risk-benefit ratio early in their cycle of use, and this ratio increases over time. Most CAM products and processes appear to have a high risk-benefit ratio at some point in their use, and this ratio decreases over time. Stated another way, most new drugs initially appear safer and more effective than is truly the case, while most CAM products appear less safe and less effective (at some point) than is really the case.

Why would this be so?

Orthodox medical products are usually designed with a specific therapeutic goal in mind. One of the easier questions to answer is usually, "Does this agent do what it is designed to do?". Those agents which do not perform the job they are designed to do are discarded, and only those which do perform the desired action which move into further stages of testing.

Thus, the benefit side of the equation is likely to be prominent early in the life-cycle of the product. Those which do show a benefit are then subjected to assessment of adverse effects, initially in animal species unrelated to humans, and later in human trials. Those agents which pass through these trials with least demonstrable risk are then likely to be pursued by commercial interests in order to market the drug or other agent.

I will not deal with the complexities of the shortcomings of toxicological assessment of novel drugs, except to say that there is a recognition of those shortcomings implied by the requirement for post-marketing surveillance. Post-marketing surveillance has its own clear shortcomings, not the least of which is the failure of medical practitioners to report the majority of adverse reactions. It is not reasonable that the surveillance be carried out by the prescribers of the drugs in question, especially in an increasingly litigious age, and given the poor training of medical practitioners in recognising adverse reactions. Whatever the cause, all authorities and research agrees that under-reporting of adverse reactions is the rule rather than the exception.

This leads to a situation where the short term benefits are appreciated by doctors and the consumer, while long term risks to the individual and the community are discounted to an undetermined extent. Two examples of this would be the use of beta-agonist drugs in asthma (which clearly improve symptoms short term, but which are now suggested to be associated with increased mortality and morbidity from asthma), and the use of antibiotics (where apparent, though possibly nonexistent, short term benefits in individuals have led to a long term, community health problem of antibiotic resistant infections).

Thus, in general, the product development cycle in medicine tends to suggest high benefit

with low risk in the early period of use, while the knowledge of true risks accumulate as time passes, often ending with the banning of many drug therapies as unsafe and ineffective.

In contrast, CAM products and practices commonly exist in the community prior to formal assessment of safety or efficacy. The lack of clear beneficiary following formal efficacy trials (where no patent or commercial advantage is conferred upon the sponsor of such a trial) means that the CAM products tend to accumulate only cultural, historical and anecdotal evidence of benefit. As well, in complex pharmacological products such as herbal medications, many benefits are often ascribed to a single agent, making assessment of true benefit even more difficult. An example would be garlic, where anti-atherosclerotic and anti-infective properties are ascribed to one product. This means that many genuinely beneficial products are unlikely to have been formally assessed for benefit by the costly methods used in orthodox drug development.

It is important to distinguish between the phrase, “no evidence of benefit”, and the phrase, “evidence of no benefit”. For many CAM products and processes, the former is true, while the latter is false. The reason is that most CAM products and processes have not been adequately or appropriately studied for benefit. The literature is in almost unanimous agreement that adequate studies are urgently needed to establish the degree and type of benefit for most products and processes in CAM.

In the absence of such studies, it is illogical and profoundly antiscientific to assume that no benefit exists. Such a false assumption could lead to the loss of potentially beneficial, low cost therapeutic products or processes. In the extreme, all untested products could be eliminated rather than assessed, which is clearly absurd.

The CAM will most frequently come to the attention of the community following an apparent severe problem, possibly a death, which may have been caused by the product. This is followed by a rapid search by researchers for other such cases of adverse outcomes. Other cases which appear to confirm the initial suspicion rapidly escalate the apparent risk of the product, even when the risk does not actually exist.

To explain this, Jonas has written,

The occurrence of an event during a therapy is not equal to causation of that event by the therapy. ...

Non-random, cohort, or case-control evaluations of adverse events often overinflate estimates of risk, with odds ratios of even two to three subsequently being found to be false.

Most reports of adverse events in complementary and alternative medicine occur because of single case reports or small case series. These reports can only tell us that they can occur, not that they must occur, nor how frequently, and are likely to lead to an over-interpretation of the significance of the event. Specifically searching for adverse events among a population can lead to a search intensity bias, even in case-control studies, and must be conducted using objective outcome measures, equal opportunity for finding and extracting information from exposed and unexposed groups, and blinded evaluators as to the nature of the intervention.

To date, the studies regarding adverse effects of Royal Jelly, for example, have led to the selection bias discussed above. The shortcomings of the current information requires a trial based on the principles outlined above. Again to quote Jonas,

Events that occur rarely, less than 1 in 1,000 exposures, require large numbers (3 x 1 over the inverse ratio of events) to be 95% confident that even one adverse event would be detected. Interventions with significant public health implications, because of their widespread use, may require post-marketing surveillance of upwards of 3,000 individuals. As complementary and alternative medicine gains in popularity, the risk of these therapies becoming significant public health issues rises.

Thus, the risks become overly prominent before studies of efficacy begin in CAM, leading to an exaggerated risk-benefit ratio soon after the product achieves public notoriety, having been used for a considerable period of time. This generality does not apply when novel CAM products are introduced and promoted by producers and suppliers using unsubstantiated claims of benefit and an assertion of “safety of natural products”. This is usually not the case, however, with the majority of traditional CAM products.

It is often the dramatic claim of risk which acts as a catalyst for research, as it rightfully should. Two issues need to be decided - the real risk (as opposed to the likely initial overestimated claim of risk), and the likely benefits. This work requires time, money and research, leaving the unsubstantiated claims of risk standing until the time that actual valid data are accumulated. As the initial estimate of risk is reduced to more realistic levels (often the risk disappears entirely, as suggested by Jonas), and the evidence for beneficial biological effects increases, the risk-benefit ratio drops from an unreasonably high level to a level more closely reflecting reality. Until this occurs, it is neither reasonable nor scientifically valid to come to any judgement of the true risk-benefit, or to set in place actions which may unfairly prejudice the final assessment of the product.

Let us take a hypothetical example of Royal Jelly. The aim is to place reasonable figures on this so that the difficulties in assessing the risk of use of CAM products can be appreciated.

Let us say that the initial data, and cause for concern, is that three deaths from asthma may have been caused by Royal Jelly over three years. Let us further assume that one in five Australians are asthmatic, that 18,000 people use Royal Jelly regularly in Australia, and that Royal Jelly use was equally likely in asthmatics and non asthmatics. This would mean that about 3,600 Australian asthmatics use Royal Jelly. Finally, let us assume a mortality rate of 1 in 1,000 for asthmatics in Australia. What is the evidence of a cause and effect relationship between Royal Jelly and death from asthma?

The question appears straightforward. Of the 3,600 regular users, the expected number of deaths due to asthma in the year would be 3.6. Over three years, the value would be 10.8 deaths. The reported number (3) is less than the predicted number (10.8), suggesting that Royal Jelly may have some *protective* effect against asthma. Is this a reasonable assumption?

The answer is “No”. Under-reporting of adverse reactions could mean that the actual number of deaths was higher than three. Accidental or intentional misreporting could mean that there was less than three. The method of data collection, and the degree of uncertainty surrounding interpretation make the question impossible to resolve from these raw data, and further study is required.

However, let us now say that after the first death, media reports began to carry a message that Royal Jelly *does* cause death in asthma. What now happens to the subsequent assessment of risk. Firstly, the 3,600 asthmatics and their doctors are likely to believe that an association exists between Royal Jelly and asthma, even though it does not. Even if Royal Jelly *prevented* asthma in 50% of the asthmatics (ie it had a marked benefit in the illness in question), there would remain 1,800 Australians and their doctors who may suspect that Royal Jelly *causes* asthma, even though it reduces asthma by half. Of this 1,800, around two deaths from asthma would be expected by chance in the following year. The doctor, family and community, seeking reasons for the otherwise inexplicable deaths, may erroneously assume that the Royal Jelly was the cause of the asthma and death. There is, at this point, no credible data to support this viewpoint, but attribution of cause by humans is usually carried out even in the absence of scientific data.

Academics, clinicians, researchers and even Coroners can become so convinced that a cause and effect association exists, that evidence to the contrary is discarded as “not sensible”, or at odds with commonly held beliefs. Anecdote is submitted as further evidence of harm, as happened when a medical expert stated during a recent Coroner’s Inquest that he had “just become aware of another Royal Jelly death” from hearsay, adding this to the proceedings as if it were evidence of equal value to the scientific literature. Thus, a false view of the true risks becomes “common knowledge”, and is assumed to be true without critical assessment.

This, in turn, may lead to increased surveillance for “cases” supportive of this causal association. In a large allergy clinic, asthmatics who use Royal Jelly may well be found, leading to an exhaustive characterisation of those cases, and further apparent confirmation of the causal link. This approach would lead to this result, remember, even if Royal Jelly were strongly protective against asthma!

What is needed, clearly, is an assessment of users and non-users of Royal Jelly, both in asthmatics and non-asthmatics. Such clinical trials have been proposed by all researchers to date, but no such trials have been commenced. One critical issue for the credibility of such a trial is that it be carried out by dispassionate researchers with no demonstrable prior bias or conflict of interest, and that the researchers and the conduct and running of the trial be accepted by all stakeholders prior to commencement.

It can be seen, therefore, that the focus on perceived risks of CAM products and methods can lead to a view that risks exceed benefits early on, while research over time tends to characterise the benefits, while determining that the original risk estimates were unrealistically high.

The effect of this is that orthodox medical products and processes initially appear safer and more effective than they actually are, while CAM products and processes appear less safe and less effective than they actually are. The determination of actual safety and efficacy of all therapeutic agents, both orthodox and CAM, requires active and ethical ongoing research, and effective post-marketing surveillance. The issue of who should cover the costs of such research depends to a large extent on who stands to profit most from the information.

E. THE “WAR” WITHIN MEDICINE - WHO CAN BE BELIEVED?

There is a difficult problem which needs to be addressed with regards the relationship between orthodox medicine and CAM. It is frequently described as a “paradigm war”, and many of the supposedly objective scientific papers are in fact emotionally charged with extreme and unsupportable viewpoints. This has been pointed out by Ernst, in his paper entitled *Complementary medicine: common misconceptions* (J R Soc Med 1995;88;244-247). Ernst’s publications have tended to enrage the extreme proponents of both orthodox and complementary medicine, suggesting that his view strikes a reasonable balance.

The paper deals with the unwarranted criticisms of CAM, as well as the unsupportable claims of CAM, and proposes that a commitment to high quality scientific research is a valid and useful means of reaching conclusions about the true place of CAM in the modern health care system.

In particular, Ernst notes (the claim precedes the quotation, in parentheses),

(CM is unscientific while orthodoxy is scientific)

“... not all the procedures of orthodoxy have sound scientific bases; it was estimated that about 85% of our current therapeutic repertoire do not fulfil this criterion.

(CM is known to be ineffective)

“...Some approaches of CM (complementary medicine) have been shown to be utterly wrong, and of not specific worth to patients. Yet to generalise in the above manner [that CM is known to be ineffective] is problematic, if not antiscientific. As long as a remedy has not been tested, it cannot be labelled either effective or ineffective.

(Effects of CM are proven)

“...One has to carefully separate ‘effects’ from ‘effectiveness’ when discussing CM. To be a useful treatment, each complementary remedy must be demonstrated to be clinically effective in defined conditions through randomised controlled trials, and these are still a rarity in the area of CM

(CM is natural, and therefore harmless)

“...There is no such thing as a treatment without potential harm. CM can be directly harmful ... can ... induce side effects and complications ... is hazardous when it prevents proper diagnosis or effective (orthodox) therapy ... is definitely dangerous when used incompetently ... [and] is harmful when it is needlessly wasting financial or other resources.”

Ernst's proposals for a way forward are instructive for promoting discussion on this general philosophical disagreement between "competing paradigms". They include,

"...both 'sides' must free themselves from those deep-rooted prejudices. Neither over-enthusiastic belief, nor stubborn disbelief will help patients or advance medicine.

"...Proponents and opponents might consider discontinuing their habit of 'selective quotation', ignoring facts that do not fit the arguments.

"...We urgently need more and better research into CM. It should systematically address effectiveness, its safety, and subsequently its cost-effectiveness. ... Without funds there will be no research. Thus, potential funding bodies might reconsider their policy of the past to support CM research to a nominal degree at least.

It would be of great benefit if the resolution of CAM issues were to address these prejudices and shortcomings in a constructive way, as the general resolution of these issues will eventually be required on many occasions.

There is a philosophical divide between CAM and orthodox medicine which requires an urgent resolution. This may indeed be at the heart of the difference of paradigms. In general, CAM holds a view that good health is, itself, a valid and useful defence against disease and illness. To this end, the pursuit of optimal health of the individual is a valid and useful goal of CAM.

Western orthodox medicine, as currently practiced, implicitly holds that illness and disease simply occur, and that the analytical approaches of diagnosis and therapeutic intervention are valid means of controlling, diminishing or eliminating illness. For orthodox western medicine, the absence of disease is often indistinguishable from good health, whereas for CAM, there is a clear area between health and disease which deserves attention, as identification of declining health provides an opportunity for early intervention with a view to preventing overt disease.

This often leads to problems in understanding of the varied approaches. Many studies have shown that people who consult CAM practitioners are "healthier" than those who consult medical practitioners. This has led to claims by orthodox medical practitioners that the apparent therapeutic successes of CAM practitioners is illusory, as they are treating healthy people, whereas doctors are treating sick people. The logical flaw in this argument is that it is equally plausible that the healthier state of patients of CAM practitioners may be due to their use of CAM practitioners, and that the focus on early identification and management of declining health is effective in preventing or delaying the onset of disease. Orthodox medical practitioners may, in this scenario, be missing opportunities to institute effective health promotion and prevention strategies, inadvertently allowing health problems to progress to the point of overt disease before action is taken.

There may be a way of thinking about this problem which identifies the training and strengths of each approach, assuming that research confirms such strengths. Recognition of the value of traditional and CAM health approaches in health maintenance, while also recognising the primacy of orthodox medical care in disease diagnosis may help organise

more effective health care. By way of analogy, car maintenance and smash repair are separate aspects of automotive care. Good maintenance is likely to be a cost-effective means of minimising the risk of an accident, but does not guarantee against one. When an accident does occur, smash repair is required whether or not the vehicle is well maintained.

While there are obvious deficiencies in the above analogy, the issue is clearly an important one to resolve if there is to be cooperation between orthodox medicine and CAM. Such cooperation, as has been noted by many authors, is essential to achieve optimal health outcomes for the community.

It is less than ideal that academics and medical practitioners who have promulgated and published inflammatory and unreasonably critical opinions regarding the use of CAM, should be involved in the process of advice and assessment of CAM, or in the assessment of CAM products. The advice provided by such individuals needs to be scrupulously clear of such personal biases, and this is best achieved by reliance upon the relevant medical and scientific literature without 'selective quotation'.

Some may hold a view expressed in a recent issue of *American Scientist*, that strong advocacy and selective quotation to support personally held views is a valid and useful means of progressing science. If this is the view taken, then it needs to be expressed overtly. The reason for this is that, for this approach to 'work' (and there is some doubt that this approach really can achieve the goals achieved by more objective and less biased approaches to a subject), it must be in the context of a process in which all viewpoints are equally represented, and where the information and advocacy of all proponents is given equal weighting. Otherwise, the process is open to abuse of position and qualification, allowing the "best qualified" proponent's personal viewpoint to continually dominate the process.

In the assessment of CAM, I would propose that the concepts and recommendations of Ernst (qv) be adopted instead, and that an effort be made on the part of all involved to eliminate personal and professional biases. For those unwilling to do so, or unable to recognise such biases, an overt decision needs to be made with regards their participation in the process. On the whole, this would lead to the exclusion of such individuals, unless the person's experience and expertise was deemed essential to the functioning of the process. In such cases, the person may be willing to participate as an advisor in the process, under the guidance of a moderator aware of the biases likely to emerge.

Finally, I include documents related to research priorities of the National Health and Medical Research Council (NHMRC) for the coming three years. It is both surprising and disappointing that an organisation such as the NHMRC has made no provision for, nor mention of, research into safety, efficacy and appropriate use of CAM in Australia. It is especially difficult to reconcile this with the mission statement of the NHMRC that it is committed to community-relevant research, given that more Australians now consult CAM practitioners than consult medical practitioners. The reality of this choice on the part of the

community requires a response from the body given the responsibility of setting medical research priorities, and allocating public money for medical research. Their claim of accountability for decisions of the NHMRC needs to be called into question if the organisation persists in its failure to adequately commit funds for assessment of safety, efficacy and cost-effectiveness of CAM.

In addition, I have reviewed the health programs of the Federal Department of Health and Family Services, and there appears to be no recognition of the need for responsibility in the issues of safety, efficacy or cost-effectiveness of CAM. The responsibility is simply asserted to end with the assessment of these factors for publicly funded diagnostic and therapeutic products and processes. Despite this, the TGA clearly has the responsibility for assessment of therapeutic products and claims, whether publicly funded or not. Thus, the current government approach is problematic for the adequate assessment of safety and efficacy of many of the agents which it regulates. In the absence of adequate research and data, the approach of the TGA to these products may become arbitrary and incomprehensible, decided more by unstated prejudices and philosophies than by science.

III. SUMMARY

If the Federal Government is to fulfil one of its clear election policies regarding access to safe and effective CAM products in Australia, then a commitment of funding to support this election promise is urgently required.

The benefits from properly funded research is that the 40% of Australians who currently utilise CAM will be provided with information on the safety and value of their chosen therapeutic modalities, bringing “evidence based medicine” to the public. The resolution of risk-benefit and cost-benefit issues will allow Australians to regain quality, affordable health care. This, in turn, leads to better health for all Australians, whilst simultaneously reducing PBS expenditure. This opportunity needs to be grasped now. How we deal with CAM and its products will most likely determine whether we can make our health care system sustainable, and may prove to be the greatest and most exciting challenge in the coming decade.

Signed

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