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CLINICAL PERSPECTIVES

Complementary medicine products: interpreting the evidence base

Marc Cohen [1] and Jennifer Hunter [2,3]

[1]School of Health and Biomedical Sciences, RMIT University, Melbourne, Victoria, and [2]National Institute of Complementary Medicine, Western Sydney University, and [3]Menzies Centre for Health Policy, University of Sydney, Sydney, New South Wales, Australia

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Correspondence
Marc Cohen, School of Health and Biomedical Sciences, RMIT University, PO Box 71, Bundoora, Vic. 3083, Australia.
Email: marc.cohen@rmit.edu.au

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Abstract

Many patients use complementary medicine (CM) products, such as vitamins, minerals and herbs as part of self-care without professional advice or disclosure to their doctors. While use of CM products is gaining awareness by the medical community and there is mounting evidence for their safety, efficacy and cost-effectiveness, there is also the potential for adverse events from inappropriate use and/or withdrawal, as well as interactions with other medicines. Due to the unique and complex properties of many CM products, research evidence is specific to individual preparations and this can lead to confusion when assessing label claims and interpreting the results of clinical trials and systematic reviews. While the Australian regulatory environment for CM products is the same as for prescription medicines and is based on risk, there is a great need for consumers and clinicians to have access to easily understood, evidence-based information to facilitate informed decision-making.

Introduction

Australians are some of the highest users of complementary medicine (CM)[1] and typically use CM alongside, rather than as an alternative to conventional healthcare.[2,3] In some regions, CM practitioners outnumber allopathic healthcare practitioners.[3] Consumers and health professionals seeking to make informed decisions about CM face significant challenges due to the complexities of interpreting the emerging, heterogeneous evidence of safety, efficacy and cost-effectiveness. While patients should anticipate an evidence informed discussion with their medical practitioners about whether to start or continue using a CM intervention, the most recent survey of Australian doctors conducted in 2008, found that many doctors (including those who routinely prescribe CM) were often uninformed about important evidence of efficacy, interactions and side-effects.[4] This paper discusses the challenges clinicians face when discussing CM use with patients and interpreting the evidence for CM products in light of their complexity and regulation in the Australian setting.

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Definitions

CM is an umbrella term that refers to a diverse range of health-related therapies and interventions that includes (but is not limited to) the practice of naturopathy, traditional Chinese medicine, Ayurvedic medicine, homoeopathy, chiropractic, osteopathy, massage therapy, yoga and meditation.[5,6] Similarly, CM products encompass a wide range of natural health products that include herbal medicines, vitamins, minerals, trace elements, nutritional supplements, homoeopathic preparations and certain aromatherapy preparations. CM products also vary widely with respect to their scientific evidence of efficacy and safety; clinical indications and claims; and availability and quality.

Australian regulation of CM products

All forms of medicine in Australia are regulated by the Therapeutic Goods Administration (TGA) through a risk-based system that is applied to both complementary and pharmaceutical medicines. As of 3 August 2016, there were 11 160 CM products on the Australian Register of Therapeutic Goods (ARTG) of which the TGA had formally evaluated and approved the claims of 35 CM products.[7]

Following the Therapeutic Goods Act 1989, the ARTG introduced two tiers of registration – AUST R and

AUST L.[8] Higher risk products, such as prescription medicines or CM products that make high-level or disease-specific claims, must be registered with an identifying AUST R number. Excluding grandfathered products (that includes a small number of CM products), the TGA has formally reviewed the quality, safety and efficacy of AUST R products.

AUST R registration is optional for most CM products. The majority are 'Listed' and assigned an AUST L number. AUST L products contain one or more pre-approved, low-risk ingredients that meet the TGA standards for quality and safety. Efficacy is not formally assessed and only general low-level claims about indications, such as health maintenance, nutritional supplementation and relief of non-specific symptoms, can be made.[9] Product sponsors are required to submit and hold a summary that outlines the history of use of the various ingredients and a critical scientific appraisal of the evidence for safety, efficacy and risk-benefit. In instances where the CM product aligns with its traditional use, the TGA also allows additional traditional evidence of safety and clinical indications to be included in the evidence review.

While the Australian regulatory system for CM is considered to be one of the most rigorous in the world, the regulatory framework controlling the supply and promotion of CM has been criticised by some as being 'weak' due to a lack of consumer awareness of the AUST L classification; issues around complaints handling, and the non-specificity of allowable evidence.[10] In response to a range of concerns, several recommendations have been endorsed in the Australian Government Response to the Review of Medicines and Medical Devices Regulation (2016).[11] This includes legislative changes to create a third tier of regulation that would sit between the AUST R and AUST L tiers. The proposed introduction of a third option would allow CM product sponsors to make higher-level claims about indications and efficacy that are commensurate with risk. Prior to market, the TGA would formally assess the submitted scientific evidence for these claims. Unredacted evaluation reports from a comparable overseas regulator may also be allowed.

The proposed new third tier aims to promote informed consumer choices, greater flexibility in the market and create incentives for industry to fund more research.[11] Currently, the TGA allows the use of 'borrowed evidence' for Listed AUST L products whereby traditional, generic, scientific and product-specific evidence regarding the use of natural ingredients are all admissible and interchangeable. The use of 'borrowed evidence', however, may potentially result in misleading claims and creates little incentive for industry to fund clinical trials. It is not clear how such legislative changes will adequately address these concerns.

'Borrowing' product-specific evidence

The validity of borrowing evidence is questionable due to the biological complexity of many CM products and variations in their quality.[11,12] Regarding herbal medicine products, it must be recognised that plants themselves are not medicinal products. The results from one clinical trial or historical data on a traditional preparation do not necessarily support (nor discredit) the use of different preparations from the same plant.

Individual herbal medicines by their very nature consist of multiple chemicals with a variety of actions. There can be considerable variations between batches and brands.[13,14] Therefore, the clinical evidence for a herbal medicine is potentially most reliable when it is based on the specific end product rather than the plant.[12]

The limitations of using 'borrowed evidence' does not only apply to herbal medicines. The chemistry and pharmacology of vitamins, minerals and other micronutrients can be equally as varied. For example, the gastrointestinal absorption of mineral formulations is affected by the compounds they are bound to and minerals may even compete with each other for absorption.[15] Calcium-hydroxyapatite has different pharmacokinetic properties to other calcium compounds, and combining calcium with other nutrients, such as vitamin D and vitamin K can also alter its bioavailability and clinical impact on bone density.[16] It is also unclear if strains of Lactobacilli or Bifidobacterium can be used to substitute for specific strain/s tested in a clinical trial.[17] Finally, even if the individual ingredients in a CM product have specific evidence of efficacy, often the efficacy of combining these ingredients has not been evaluated.

Standardising complex biological products

Generic evidence can only apply to equivalent standardised products. Unlike pharmaceuticals, it is extremely difficult to manufacture 'generic' products from complex biological ingredients, such as plants. Herbal medicines are subject to considerable variation due to many factors including:

- Plant factors, such as the species, sub-species, plant part, and natural genetic variation
- Geographical and climatic factors
- Farming methods used for sowing, cultivation and harvesting
- Processing, extraction and standardisation methods

• Formulations of fresh or dried plant parts and extractions used in teas, oils, tablets, powders or tinctures[18]

Every part of this process must be standardised to produce a high-quality herbal product with minimal batch-to-batch variations. Without such rigour, the pharmacology and clinical outcomes are less reliable.[12,18,19] Yet, despite attempts by some manufacturers to standardise their products, there are no official standards and herbal products can vary widely with regards to their quality and pharmacology.

The TGA has addressed the need to standardised herbal medicines by requiring manufacturers to state the 'dry weight equivalent' on product labels. 'Dry weight equivalent' refers to the amount of dry plant material used to make the product. It does not equate to the potency of the end product and is therefore misleading as different processing and extraction methods will create very different medicinal products. An analogy is grapes: sultanas, grape juice, vinegars and wines may all be made from the same 'dry weight equivalent' of grapes despite being very different products with different pharmacological effects.

Challenges with applying the evidence

Whilst the variation and uncertainty around the exact constituents of different CM products does not preclude their use in Australia, it does add confusion when interpreting the evidence and matching this to available CM products. In many instances, it is unclear to what extent the results of clinical trials and meta-analyses of specific CM products can be generalised to other products with similar ingredients.

Clinical trials

Due to the increasing awareness of the complexities of CM products, a CONSORT extension for herbal medicinal interventions has been developed for the reporting of clinical trials that includes providing detailed information about the herbal product, its characteristics, treatment regimen and quality testing.[19] Guidelines have also been developed for the reporting of clinical trials testing other types of CM products; these are yet to be incorporated into Consolidated Standards of Reporting Trials (CONSORT).[20] Such statements are helpful when appraising the methodological quality of clinical trials and could also help clinicians and regulators select comparable 'generic' CM products.

Systematic reviews

Compared with generic pharmaceuticals where the active agent and its precise dosage is known and therefore comparable across studies, the product complexity of many CM products and the varied reporting of clinical trials contribute to the challenges of interpreting the results of systematic reviews and meta-analyses. Quality assessment generally only considers the risk of bias arising from the methods and reporting of the published clinical trials. The complexity and quality of the products along with the rationale for the treatment regimen are rarely appraised. Questions therefore remain about the validity of comparing different formulations of similar CM products as is the case for many meta-analyses.

For example, in a meta-analysis of vitamin and antioxidant supplements for the prevention of cardiovascular disease, there was considerable heterogeneity in the ingredients, the dosages, and potentially the quality of the supplements included in the analysis.[21] Along with the main analysis, subgroup analyses based on individual ingredients, dosages, and manufacturer were conducted. Although not explicitly stated by the authors, it might be reasonable to use the manufacturer (i.e. whether the product was supplied by the pharmaceutical industry) as a proxy measure of CM product quality. Information about pharmaceutical industry funding was also collected to assess further possible bias. The only positive findings from the meta-analysis were in a few of the subgroup analyses.[21] Vitamin B6 supplementation was associated with a decreased risk of cardiovascular mortality and vitamin E with myocardial infarction. These positive findings only remained in the subgroup analyses of trials with high methodological quality and for supplements manufactured by the pharmaceutical industry. Conversely, although low dose vitamin B6 was associated with a decreased risk of all major cardiovascular events, this association was not significant for the subgroup analysis of high-quality trials.

It is commendable that the authors attempted to address the complexity of the various interventions included in their meta-analysis.[21] Unfortunately however, the authors did not appraise the validity of their approach. With so many subgroup analyses, the likelihood of type 1 errors increases. Furthermore, the analyses did not assess the possible synergistic and antagonistic effects of the different combinations of antioxidants and vitamins in the various products. The effects of other potential confounders, such as calcium, fish oil, aspirin and ramipril that were included in some of the interventions were also ignored.

The authors of the second Cochrane review of St John's Wort for the treatment of major depression took a different approach to managing the known variability

between products and quality concerns, such as batch-to-batch variation. In this review, only high-quality products were included and the authors used a qualifying statement that cautions extrapolating their results to untested products.[22] The trade-off from this approach is that only one of the St John's Wort extracts in the Cochrane review, Ze119 is currently registered in Australia. Interestingly, the Ze117 formula has a low hyperforin content. Along with clinical trials demonstrating its efficacy,[23,24] there is pharmacokinetic data showing that Ze117 does not result in any alteration in the bioavailability of an oral contraception.[25] The other St John's Wort products included in the review had higher amounts of hyperforin and some had low hypericin content. Although each product is potentially effective, their potential for drug interactions will vary considerably. Without detailed reporting of the hypericin, hyperforin and even pseudo-hypericin content in a St John's Wort product, it is difficult for clinicians to prescribe confidently such products, particularly for patients using other medications. Currently, the TGA does not require the amounts of all potentially active ingredients to be stated on the product label.

Doctors' perceptions and use of CM

Increasingly medical practitioners are prescribing or recommending CM.[4,26] An estimated 30–40% of Australian general practitioners (GP) integrate CM into their clinical practice and over 75% refer their patients for such therapies.[4,27] Based on the opinions of surveyed GP, CM effectiveness can be grouped into (i) non-medicinal or non-manipulative therapies, such as acupuncture, massage, meditation, yoga and hypnosis, which most GP considered to be highly effective and safe; (ii) medicinal or manipulative therapies, such as herbal medicine, nutritional therapies, homoeopathy, Chinese medicine, naturopathy, chiropractic and osteopathy, which more GP considered potentially harmful than potentially effective; and (iii) esoteric therapies, such as spiritual healing, aromatherapy and reflexology, which were seen to be relatively safe yet also relatively ineffective. The perceived risks of CM according to the surveyed GP were seen to arise from incorrect, inadequate or delayed diagnoses and interactions between complementary medications and pharmaceuticals, rather than the specific risks of the therapies themselves.[27]

A survey of Australian rehabilitation physicians found similar results to the GP survey regarding perceived effectiveness and safety of various types of CM.[26] Other recent surveys of medical practitioners outside of Australia include surveys of different types of doctors in Germany,[28] paediatricians in the Netherlands,[29] GP in North West England[30] and gastroenterologists in the United States.[31] These surveys found that a significant proportion of medical practitioners consider there is a role for CM in their clinical practice, and many prescribe CM or refer patients for a limited range of CM interventions.

Evidence-based clinical practice

Issues specific to standardising and evaluating CM products must be understood by clinicians seeking to make informed clinical decisions.[12,32] Along with evidence of safety and efficacy, evidence-based practice utilises the expertise of the clinician and considers modifying factors, such as patient preferences and values; affordability, cost-effectiveness and opportunity costs; feasibility and available resources.[32–34] Even when the evidence of efficacy is inconclusive or unknown, information about modifying factors and the safety of a CM product is often available to guide clinical decisions and recommendations.

Evidence to cease, verses evidence to start

Rather than dismissing the use of a CM product due to inadequate scientific evidence supporting its use, a more measured approach might be to consider what evidence (efficacy, safety, costs, opportunity cost, etc.) is needed to advise strongly a patient to cease using a CM, versus the evidence required to recommend proactively a CM. Obviously, higher quality evidence is required for the latter, particularly when there is an alternative option with proven efficacy or cost-effectiveness. However, unless there is high-quality evidence that a CM is ineffective, evidence of safety (e.g. side-effects, interactions and risks associated with cessation) and costs (e.g. patient affordability and opportunity costs of using CM as an alternative) have been suggested as the most compelling reasons for a medical practitioner to recommend strongly cessation.[35]

Managing conflicting views

In most instances, a balance must be found between respecting patient autonomy and the clinical opinion of the medical practitioner.[35,36] The 2013 Clinical Society for Oncology in Australia (COSA) position statement on patients' CM use suggests that if a CM product is deemed to be safe, after determining the outcomes the patient is seeking and their reasons for use (that may be as an alternative to other recommended treatments), the clinician could consider negotiating a trial period

with the patient to assess further potential benefits and risks.[35]

Ceasing CM

Regarding cessation of CM products, a 2015 Position Statement of the Council of Australian Therapeutic Advisory Groups (CATAG) points out that in most instances Australian hospitals cannot legally prevent CM use by their in-patients.[36] CATAG also recommends that if a CM is ceased during a hospital admission, this is recorded in the clinical notes and discharge summary.[36]

Prescribing evidence-based CM products

As the evidence for the safety, efficacy and cost-effectiveness of CM products continues to build, clinicians will be more likely to recommend their use. However, due to the complexities of extrapolating the research on a specific CM product to other products, there may be instances where the clinician will choose to prescribe the exact product tested in clinical trials.[12]

Discussing CM use with patients

While the use of CM in the Australian population is high and is increasingly being recommended by doctors, there is evidence that many people self-select CM and do not routinely disclose CM use to their healthcare professional.[3,37–39] For the most part, patients use CM alongside, rather than as an alternative to conventional care.[2,3,37–39] This raises concerns about patient safety, including the risk of interactions, adverse effects and inappropriate use.

Communication between healthcare professionals and patients is essential, yet it seems that a '*don't ask – don't tell*' scenario is common, whereby clinicians do not actively seek information and patients do not voluntarily disclose it.[39] Reasons for clinicians failing to inquire includes poor awareness of CM safety issues, a belief that few of their patients take CM, lack of confidence in dealing with this subject, or an assumption that information will be volunteered unsolicited.[31] For some, there is the perceived threat that by respecting the patient's choice to use an unproven CM, the principles of evidence-based medicine will be undermined and the patient will mistake this for endorsement.[40,41] Common reasons for patient non-disclosure include the fear of a negative response, the belief that the clinician does not need to know, and the clinician not asking.[37,39]

In response to the concomitant use of CM by patients, COSA has published a position statement and a guideline that encourages health professionals to discuss openly CM use with their patients; familiarise themselves with reputable CM information sources (Table 1); discuss the concept of evidence-based medicine with their patients; recognise their own limitations and seek expert CM advice when necessary; and respect the patient's right to autonomy.[18,35,42] The statement includes practical advice about discussing and documenting CM use, and strategies to support patient-centred clinical decision-making.[35]

Table 1 Recommended evidence-based CM product information resources†

Herbs and Natural Supplements – An Evidence Based Guide. 4th ed
Integrative Medicine IM Gateway (also available through eMIMS) http://www.imgateway.net
National Centre for Complementary and Integrative Health https://nccih.nih.gov
University of Maryland Medical Centre – Complementary and Alternative Medicine Guide http://umm.edu/health/medical/altmed
Natural Medicines Comprehensive Database (recommended by COSA with free access for members) http://naturaldatabase.therapeuticresearch.com/
Natural Standard http://3rdparty.naturalstandard.com/frameset.asp

†Information includes: monographs; results of clinical trials and systematic reviews; side-effects, interactions and contraindications; and references.

Conclusions

Many patients use CM products without professional advice or disclosure to their doctors despite a growing awareness of CM by the medical community. Clinicians should actively inquire about CM use and not wait for patients to disclose this information. The decision to recommend a CM product can be complex. Evidenced-based practice combines clinical experience with an assessment of the available scientific evidence and consideration of patient preferences and values. Factors to consider include the quality of the CM product; patient preferences and characteristics; direct costs and affordability; availability of alternative proven therapies, immediacy of treatment and opportunity costs; and the benefits and safety of continuing a CM product versus the risks of cessation. High-quality CM products, with product-specific evidence, broaden the therapeutic options for clinicians and patients. The proposed legislative changes to the regulation of CM products in Australia behoves clinicians to be aware of the nuances and challenges with borrowing 'generic' evidence and applying this to other products. Access to easily understood, evidence-based information is needed to support open, respectful and informed discussions between patients and clinicians.

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