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CLINICAL PERSPECTIVES

Complementary and alternative therapies in the palliative setting

Jennifer H. Martin [1,2] and Joanne Patel[1,3]

[1]School of Medicine and Public Health, University of Newcastle, [2]Division of Medicine, John Hunter Hospital, and [3]Department of Palliative Care, Calvary Mater Newcastle, Newcastle, New South Wales, Australia

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Correspondence
Jennifer H. Martin, School of Medicine and Public Health, Hunter Medial Research Institute, University of Newcastle, Newcastle, New South Wales 2305, Australia.
Email: jenniferh.martin@newcastle.edu.au

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Abstract

Complementary and alternative medicine (CAM) encompasses a wide range of medication, herbal, dietary and physical therapies that are not usually considered within the realm of conventional therapeutics. Approximately two thirds of the Australian population use CAMs and only around half of this number will discuss their use of these products with their doctor. Clinical use is commonly seen in patients with life-limiting illness, often because they experience a high burden of symptoms. However, it is also the case that many of these therapies do not have demonstrated efficacy, particularly for the often broad list of conditions and symptoms for which they are chosen to be used. Further, depending on whether they are sold as medications, sold as food supplements or imported illegally and distributed via nonstandard therapeutic channels, several products have had reports of toxicity, severe adverse effects, batch irregularities and drug interactions with other therapies. This awareness, together with lack of standardisation of products and lack of interchangeability between brands has made prescribers unwilling to put patients at risk of harm by supporting their use. In this article, we cover general pharmacological principles around use of a small selection of chemicals used in a medical setting to enable some guidance for use.

Introduction

Complementary and alternative medicine (CAM) encompasses a wide range of medication, herbal, dietary and physical therapies that are not usually considered within the realm of conventional therapeutics. Approximately two thirds of the Australian population use CAMs and only around half of this number will discuss their use of these products with their doctor. The annual Australian private expenditure on CAM therapies is AU $4 billion.[1]

What is driving this extraordinary private spending? Although there are many reasons, clinical use is commonly seen in patients with life-limiting illness, often because they often experience a high burden of symptoms. The desire to relieve symptoms, sometimes combined with the hope of managing (or curing) the underlying disease, leads to many palliative patients selecting to use CAMs.[2] However, it is also the case that many of these therapies do not have demonstrated efficacy, particularly for the often broad list of conditions and symptoms for which they are chosen to be used.[1]

Complementary medicines in Australia are either *registered* 'AUST R' meaning they have demonstrated safety, quality and efficacy, or *listed* 'AUST L' if they are assessed for some quality and safety but not efficacy.[3] Further, depending on whether they are sold as medications, sold as food supplements or imported illegally and distributed via nonstandard therapeutic channels, AUST L products have had reports of toxicity, severe adverse effects, batch irregularities and drug interactions with other therapies.[4] This awareness, together with a lack of standardisation of products and lack of interchangeability between brands has made prescribers unwilling to put patients at risk of harm by supporting their use. But are there any rules of thumb that can guide practitioners around potential use? Here we cover general pharmacological principles around the use of a small selection of chemicals used in a medical setting to enable some guidance for their use (Table 1).

Conflict of interest: None.

Table 1 Definitions. From: Clinical Oncology Society of Australia (COSA) Microsoft Word - COSA_CAM Position Statement_FINAL[5]

Conventional medicine is medicine practised by holders of medical degrees and by qualified allied health professionals, such as pharmacists, physiotherapists, psychologists, social workers and registered nurses.
Complementary medicine includes medicines and therapies that are not traditionally part of conventional medical practice, used together with conventional medicine to produce better health outcomes.
Alternative medicine is medicines and therapies that are not considered part of conventional medical practice and are used in place of conventional medicine.
Integrative medicine refers to the blending of conventional and complementary medicines with the aim of using the most appropriate, safe and evidence-based modality(ies) available.

Common examples of pharmacological therapies used

There are a large number of pharmacological therapies that are considered in the CAM space due to their 'natural' or 'herbal' origins yet with some scientific rationale to guide toxicity and efficacy in particular patient groups; however, few have quality clinical trial data. Commonly used therapies include cannabis products, capsaicin topical preparations for neuropathic pain, evening primrose oil for uraemic pruritus and melatonin for sleep disturbance.[6] Of note, though, whilst guidelines are clear on chemical name and derivation, there is a paucity of literature on dose–response curves, toxicity and issues around drug interactions.

In this article, we have predominantly focussed on therapies used in the palliative and supportive medicine space. Here, CAM therapies are sometimes trialled after conventional treatments have failed to deliver the desired outcome or have led to unacceptable side effects.

Cannabinoids

Cannabis, also known as marijuana, is a plant first grown in Southern and Central Asia that is now grown in many parts of the world including Australia and New Zealand. The plant makes a resin containing a complex mixture of more than 500 chemicals, including cannabinoids and noncannabinoid-type constituents. *Cannabis sativa* has had 125 cannabinoids isolated and/or identified as cannabinoids, which are C21 terpeno-phenolic compounds. The noncannabinoid constituents include many other chemical groups including phenols, flavonoids, terpenes, alkaloids and others.

The use of cannabinoids is complex, because 'use' has conflated cannabinoids extraction from plant, synthetic development (e.g. dronabinol) and whole plant, for example, as used in vaping. Both extraction methodologies, plant or synthetic, compound or compounds extracted and route of administration affect dose–response (efficacy and toxicity). Comparison of different compounds, different routes of administration, different doses and combinations cannot therefore be easily compared or systematically reviewed, a fact that is often lost in the media when the overarching hypothetical Venn diagram describing 'cannabis use' and 'cannabis benefits' are discussed.

Added to this is the context in which these therapies are administered (see section Drug interactions below). Patients' physiology, comorbidity, diet and drug interactions are all highly variable and prevalent, and all affect drug disposition. In addition, pharmacodynamic effects and interactions with disease are very common; for example, cannabinoids concomitantly used during immunotherapy have been observed to be associated with lower survival.[7]

So why do people take cannabinoids as complementary therapies? A scan of Therapeutic Goods Administration (TGA) data shows that the highest use is in people with chronic noncancer pain, cancer symptoms and other symptoms such as insomnia, anxiety and post-traumatic stress disorder.[8] The cannabinoid cannabidiol (CBD) has been touted for a wide variety of symptoms, but the strongest scientific evidence is for its effectiveness in treating drug-resistant childhood epilepsy syndromes, such as Dravet and Lennox–Gastaut syndromes, where randomised controlled trials (RCTs) were undertaken.[9] It is noted that placebo response rates are high, and even in the cannabinoid group, it is unclear whether the response is always caused by CBD or by the fact that CBD inhibits the enzyme that breaks down benzodiazepines, which are commonly coprescribed.[10]

Based on this evidence, Epidyolex, in which CBD is the active ingredient, is the first CBD product to be TGA listed.[11] The TGA has also registered Sativex, a combination of tetrahydrocannabinol (THC) and CBD for muscle spasticity in multiple sclerosis.[12] Animal studies and self-reports or research in humans suggest that CBD may also help some people with anxiety, sleep, chronic pain, arthritis inflammation, inflammatory pain and addiction of heroin and tobacco, although dose or relative benefit over registered therapies is unclear. Animal models of addiction suggest it may also help lessen cravings for alcohol, cannabis, opiates and stimulants.

Although large case series and observational data suggest an antianxiety effect of some doses of CBD in some patients,[13] RCTs comparing CBD with current best practice have not been undertaken. Further, other drugs that appear to act on the same pathways of fear, sleep, hunger, for example, the 'z' drugs, orexin or even GABA

antagonists such as diazepam, have not been compared for relative safety or efficacy.

A large systematic review[14] examined CBD use across a variety of symptoms and doses. It concluded that 'although promising results have been identified, considerable variation in dosage schemes and route of administration were employed across studies. There was evidence to support single dose positive effect on social anxiety disorder, short medium-term effects on symptomatic improvement in schizophrenia and lack of effect in the short medium-term on cognitive functioning in psychotic disorders'. In general, studies were heterogeneous and showed substantial risks of bias' Adverse events were common and most focussed on nervous system disorder, gastrointestinal disorders, infections and infestations and psychiatric disorders.[14]

As well as CBD, the other common cannabinoid in the plant, often extracted for human use, is delta-9-THC. Although both THC and CBD are psychoactive (affecting brain function), CBD does not appear to cause psychosis, unlike THC. However, based on some animal and low-grade trials, it appears THC may have some efficacy in nausea, cachexia and neuropathic pain for some people. It is interesting that synthetic THC, i.e. dronabinol and nabilone, are approved by the US Food and Drug Administration for the prevention or treatment of nausea and vomiting caused by chemotherapy. These have been accessed in Australia on SAS-A before relatively newer antinausea classes were developed (e.g. neurokinin 1 and more selective D2 antagonists).

A current large observational study is underway in New South Wales (NSW) that is recruiting patients with advanced cancer to examine scientifically and investigate the potential indications, symptom benefits and patient harms.[15]

Capsaicin

Capsaicin is a chilli pepper extract with analgesic properties. Used topically, capsaicin can cause sensory nerve blockade through activation of TRPV1 and release of substance P. Its application often initially induces a burning pain but repeat application can produce desensitisation. Low-concentration capsaicin creams may relieve pain by inducing heat in the application area but are typically no more effective than placebo. Higher-concentration patches (8%) have efficacy in localised neuropathic pain and can be accessed via the Special Access Scheme.[6] The burning sensation means that capsaicin is not well tolerated in large areas but may have a role for smaller areas of neuropathic pain or itch.[6,16]

One of the biggest issues with the use of this product is the lack of standardisation of dose and release kinetics, due to skin type and condition, and amount of tissue area, proportion and ratio of fat to lean tissue and vascularisation.

Evening primrose oil

Uraemic pruritus is a commonly experienced symptom in patients with end-stage kidney disease. A study of dialysis patients found that over 40% of patients with progressive kidney disease reported moderate to extreme pruritus, associated with decreased quality of life (QoL), depression and poor sleep. In uraemic pruritus, itch is not mediated via the histaminergic pathway and antihistamines have not been demonstrated to be beneficial. First-line treatment for uraemic pruritus is low-dose gabapentinoids, but these do not always relieve symptoms, are addictive and can be misused. Small trials have shown benefits for evening primrose oil. Gamma-linolenic acid (an active constituent of evening primrose oil) has been suggested to reduce pruritus by modifying plasma concentrations of essential fatty acids; however, quality comparative data are lacking.[16]

Melatonin

Many chronic diseases, including dementia, can cause disturbance in circadian rhythm cycles and insomnia. Melatonin, a hormone that regulates circadian rhythm and sleep, may reduce sleep-onset time and small doses improve sleep quality in adults with insomnia; however, the clinical significance of improvements is small and may only be short-lived. At low doses, melatonin is generally well tolerated and does not appear to have abuse potential or cause daytime sedation.[16,17] Low-dose tablets containing 2 mg or less are now registered for the short-term treatment of primary insomnia characterised by the poor quality of sleep for adults aged 55 or older; however, it is unclear how much off-label use is occurring. To advance our knowledge, there is a current RCT investigating whether the administration of melatonin in patients with advanced cancer can prevent delirium.[18]

Examples of nonpharmacological therapies

Nonpharmacological CAM therapies include acupuncture, massage, hypnotherapy, meditation, music therapy and reiki. These therapies are sometimes recommended in addition to evidence-based pharmacotherapies because of patient enthusiasm for nonpharmacological options and a lack of long-term side effects. However, there appears to be a lack of efficacy above that seen in placebo and studies are impacted by limitations in blinding or placebo control. Randomised studies in massage therapy have shown small numerical improvement

in some pain and QoL measurements compared with control; however, across the evidence base, these differences were not always statistically or clinically significant. No significant difference in QoL or symptom improvement has been demonstrated in hypnotherapy trials.[2] Restless legs syndrome is commonly experienced by patients with end-stage kidney disease on dialysis. Small (14–26 patients) studies have shown improvement in restless legs from short bursts of aerobic exercise during dialysis sessions, with mixed results on QoL.[16]

Guidance for practitioners

When discussing or prescribing CAMs, practitioners should apply the same rigorous pharmacological framework they apply to conventional therapies, taking into consideration the chemical properties of the CAM, patient variables and the level evidence base to support use.

1 The CAM

- Active ingredient

All users and prescribers of CAMs need to ensure that they are aware of the active pharmaceutical ingredient in the product, the dose and the dose response for each of those ingredients.

- Excipients

Often CAMs have different excipients depending on the brand and formulation. These affect the drug release, half-life, drug distribution and clearance; all of this affects safety and efficacy and the likelihood of drug interaction.

- Batch variability

Batch variability is common with CAMs and users should be aware of the effects of this not just on the CAM itself but also on the interactions with other drugs, issues with purity and unknown excipients.

- Stability in different desktop conditions

CAMs are not always tested as stringently as registered medicines for stability, effects of UV light and temperature. This means the likelihood of efficacy and safety is unpredictable.

- Contaminants

CAMs used by patients may or may not have been examined for contaminants, depending on the source of production. The TGA mandates that medications are examined for the presence of contaminants, including pesticides, heavy metals and bacterial or fungal components, referenced with respect to cannabinoids by TGO93.[a] CAMs that have been imported or produced outside of TGA guidance may contain contaminants which could cause adverse health outcomes. Medicinal cannabis, for example, must meet TGA guidance for testing criteria including heavy metals, pesticides and foreign matter, but 'black market' cannabis is not examined in the same way. A review of cannabis contaminants found evidence of pesticides, heavy metals and bacterial and fungal contaminants, which may cause adverse health outcomes.[19]

Drug interactions

Pharmacokinetic drug–CAM interactions. Pharmacokinetic drug–drug interactions may occur in the absorption, distribution and elimination stages and result in increased or decreased plasma drug concentrations. Further, particularly if the drugs are lipid soluble and liver metabolised, the concentrations of both drugs will be affected. The more drugs a patient is taking, the greater the risk of significant pharmacokinetic drug–drug interactions. A common mechanism of drug–drug interaction is the induction or inhibition of enzymes involved in drug metabolism. CYP450 enzymes are involved in the metabolism of many drugs and all plants, which by nature are lipid soluble. This is seen particularly with use of cannabinoids in clinical practice.

Individual patient genetic polymorphisms occur in CYP450 enzymes. Patients may be 'poor metabolisers' and others 'ultrametabolisers' and genetic variation can markedly alter the severity of drug–drug interactions. Drug transporters present in the liver, kidney, blood–brain barrier and intestine are involved in the absorption, distribution and elimination of some drugs. Efflux transporters include P-glycoprotein, multiresistance-associated protein and breast cancer–resistant protein. Genetic polymorphism and the inhibition or induction of these transporters by one drug may result in changes in plasma drug concentrations of another drug. Clinical effects are commonly seen in the combination of cannabidiol and epilepsy therapies.[20] UDP-glucuronosyltransferase (UGT) enzymes also represent an important pathway of metabolism. The UGT family of enzymes catalyse glucuronic acid conjugation and play an important role in the metabolism and detoxification of many small molecule drugs, CAMs and endogenous compounds.

[a] https://www.tga.gov.au/conforming-therapeutic-goods-standard-medicinal-cannabis-tgo-93-order-2017

Pharmacodynamic drug–CAM interactions. Pharmacodynamic drug-CAM interactions occur when a medication and a CAM have either additive or opposing effects. For example, using melatonin for sleep may enhance the sedative properties of benzodiazepines or 'z' drugs in an additive effect.[21] Interactions that cause sedation may occur between cannabis and other central nervous system depressants, such as sedatives or hypnotics, via potentiation of central effects. CBD has been reportedly associated with fatigue and somnolence, potentially compounded by coadministration with other central nervous system–active medications.[22]

CAMs–food-drug interaction. There are several different dietary patterns and dietary supplements that are purported to reduce cancer risk or have direct tumour effect. Whilst diet, physical activity and body weight have been shown to influence outcomes from cancer, there is no specific dietary regimen that has been clearly demonstrated to cure cancer or increase overall survival.[23] In the cancer prevention space, there is a small body of evidence that some dietary interventions act as chemoprevention, with sulforaphane (from leafy green vegetables) and ketogenic diets just an example of current areas of research.[24,25] Interestingly, chemoprevention researchers are also looking into repurposed medicines to see whether established drugs with other indications have a role in preventing or treating malignancy. For example, there are trials underway to investigate the potential for valproate to prevent head and neck cancer[26] and the role of metformin as chemoprevention in breast cancer.[27]

The overarching guidance is to encourage discussion about CAM use and dietary variances with patients, as there are known drug–food interactions including a potential interaction between green tea and bortezomib (an anticancer drug used in multiple myeloma)[23] and the potential interaction of vitamin C in reducing the cytotoxic effects of some antineoplastic agents. Spirulina (blue-green algae) is purported to have a myriad of beneficial effects including lowering cholesterol, treating attention-deficit/hyperactivity disorder and stimulating the immune system. Whilst evidence for these benefits is variable, spirulina is known to inhibit CYP1A2 and CYP2E1 and may interact with drugs metabolised by these enzymes, such as pain (e.g. paracetamol) and mental health drugs (e.g. fluvoxamine) that are currently coprescribed.[28]

There is a huge number of dietary and herbal supplements available to purchase, attached to a multitude of claims about potential benefits with often no standardisation or evidence of benefit. In the event that a patient wishes to pursue a particular diet or supplemental approach, consultation with a clinical pharmacist could help identify potential drug–drug and food–drug interactions. The About Herbs database from the Memorial Sloan Kettering Cancer Centre provides a comprehensive resource of herb–drug interactions in cancer care.[28]

2 The Patient

Consideration should be made to the patient's individual factors, which will impact the pharmacokinetics and pharmacodynamics of the drug, remembering the dynamic nature of the body during a disease process. For example, whilst a patient is taking a steady administered dose of the drug they may have changing weight, organ function or simply age, which impacts the exposure and effects of the drug. As patients get more unwell, they may have drugs added or deprescribed, affecting pharmacokinetics. Cancer itself has effects on drug enzyme activity.[29] Hepatic impairment can reduce the absorption of lipid-soluble drugs. Hypoalbuminaemia increases the active unbound drug concentrations in medications, which are highly protein bound. Renal impairment impairs excretion and may lead to accumulation of toxic metabolites.

Cachexia, where present, can impact the absorption of topical transdermal preparations and also lead to a reduced volume of distribution. The simultaneous loss of fat and lean body mass reduces the space into which drugs can distribute, leading to higher peak concentrations.[30] Animal studies have shown that food deprivation enhanced the concentrations of THC (a lipophilic drug) in the blood of rats that had previously been exposed to THC, although this has not yet been demonstrated in humans.[31]

3 When to use?

Patients usually request to use CAMs for several main reasons. First, people may believe the product is 'natural', and there are various lay descriptions of natural. Second, there is an erroneous expectation that the CAM has efficacy without toxicity. Third, their experience with registered medicines has not successfully managed the symptom. Finally, patients may be keen to use therapies that they do not believe to be associated with the wider pharmaceutical industry.

The common misconception that 'natural equals safe' drives increased uptake of these unregistered and unstandardised products. It has long been known that many 'natural' remedies, e.g. digoxin from the foxglove plant, have their own uses and toxicities. Natural remedies become conventional medicines after rigorous

research and approval processes determine their use and efficacy. Patients who are suspicious of 'big pharma' motives and monetary incentives may be interested to learn that complementary medicine is a US$30 billion a year industry in the United States.[32]

The desire for alternative treatments sometimes arises when conventional medicine fails to achieve a 'cure'. Registered medicines do not always cure disease or completely address all symptoms, particularly for complex symptoms. For example, in postherpetic neuralgia, pregabalin has a number needed to benefit of 3.9, i.e. for every four patients taking pregabalin for postherpetic neuralgia, on average only one will get a 50% reduction in pain.[33] For comparison, the number needed to benefit for a 50% improvement in neuropathic pain with cannabis-based medicines is 20.[34] It is not uncommon that patients will get unsatisfactory results with registered, conventional medicines, but alternative medicines are still unlikely to add benefit and will potentially cause side effects.

CAM use falls into three broad categories. It may be safe and beneficial, safe with uncertain benefit or, in the worst-case scenario, harmful to the person. It may cause harm through financial stress, due to drug–CAM interactions or the interruption of the conventional medicine plan, for example, by leading to exclusion from clinical trials. Overall, as with other complementary therapies, it is always safer and more effective if the treating doctors know of all the registered therapies together with any additional complementary products including dose, route of administration and frequency. Interactions can only be detected if practitioners have a full medication list. Recent data collected from the NSW Cannabis Medicines Advisory Service has demonstrated several concerns from general practitioners who have patients accessing only their cannabinoids in a cannabis clinic.[35] These make it difficult for the treating doctor to know about likely drug interactions, drug–disease interactions or new toxicities.

In palliative care, CAMs are sometimes used by patients alongside first-line treatments; this may be appropriate dependent on individual patient factors and the specific drug. However, it is vitally important to recognise that these might also interact with the other treatments, causing toxicity and also reducing efficacy. Further, by definition, CAMs are so named because they do not at this time have the required peer-reviewed robust evidence to be formally considered as 'conventional medicine'. Supporting their use may thus have legal and professional effects for a prescriber. It is important for practitioners to maintain open, nonjudgemental discourse with patients to try and come to the best possible individualised plan. There are resources available from the Cancer Council,[36] the National Health and Medical Research Council[1] and the Clinical Oncology Society of Australia[2] to aid physicians in the discussions around CAMs with patients. Prescribing or suggesting CAMs should be reserved for instances where there may be some evidence to suggest benefit and a low risk of harm.

Table 2 Key resources

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Conclusion

Most commonly, the use of CAM is initiated by patients themselves. It is rare that a practitioner would prescribe a CAM because of the prescribing risk of using unregistered products, lack of evidence of benefit and safety or drug interaction concerns. Often there is a lack of knowledge of dose–response curves for different products and unknown pharmaceutic and contaminant risks. In this instance, it remains important for the prescriber to be aware of their use because of the potential for drug–CAM interactions as well as the possible complication of nonadherence to a conventional medicine plan or lack of therapeutic alliance between physician and patient. There are numerous available CAM products, and it is not possible for prescribers to be aware of the pharmacological properties of each, nor the batch or formulation differences. Our guiding principles include those of good prescribing: openness to asking about CAMs in the history taking, a knowledge of resources to gather CAM information, a robust understanding of basic pharmacology and how to apply this to CAMs and conventional medications with the goal of minimising patient risk (Table 2).

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