



Complementary and alternative medicine therapies for the anesthesiologist and pain practitioner: a narrative review

Traitements de médecine complémentaire et alternative pertinents pour l'anesthésiologiste et le clinicien de la douleur: un compte rendu narratif

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Abstract

Purpose This narrative review provides an overview of the complementary and alternative medicine (CAM) therapies that anesthesiologists and pain management practitioners commonly encounter along with recommendations for evaluation and implementation.

Source A literature search of PubMed was performed using the comprehensive MeSH term, “Complementary Therapies OR Dietary Supplements”, and a search was conducted of the various licensing organizations and books published on the topics of CAM and integrative medicine.

Principal findings In North America, the most commonly encountered CAM therapies include 1) manipulation and procedural therapies; 2) herbs, nutritional supplements (nutraceuticals), and dietary therapies; and 3) mind-body and energy therapies. Controversy exists regarding many of these therapies, particularly those with a higher risk of harm, such as chiropractic manipulation, acupuncture, and nutraceutical use. Several well-conducted studies were analyzed to show how research in CAM can control for placebo responses. Practical considerations are provided

for patients and practitioners interested in pursuing or already employing CAM in perioperative and chronic pain management settings.

Conclusions Complementary and alternative medicine therapies in general may provide a useful adjunct in the management of chronic pain. Nevertheless, many patients are not aware of the risks and benefits of individual therapies. In the perioperative setting, the most concerning CAM therapy is the use of herbs and other supplements that may produce physiologic and metabolic derangements and may interact with prescription medications. Resources exist to aid pain specialists, anesthesiologists, and patients in the evidence-based utilization of CAM therapies.

Résumé

Objectif Ce compte rendu narratif propose une vue d'ensemble des traitements de médecine complémentaire et alternative (MCA) que les anesthésiologistes et les spécialistes de la douleur rencontrent fréquemment ainsi que des recommandations pour leur évaluation et leur mise en œuvre.

Source Une recherche de la littérature dans PubMed a été réalisée en utilisant le terme MeSH global « Complementary Therapies OU Dietary Supplements » (Traitements complémentaires OU suppléments alimentaires), et une recherche a été effectuée à propos des divers organismes de brevet et des livres publiés au sujet des MCA et de la médecine intégrative.

Constataions principales En Amérique du Nord, les traitements de MCA les plus fréquemment rencontrés sont 1) les traitements de manipulation et procéduraux; 2) les herbes, les suppléments nutritionnels (nutraceutiques) et les traitements alimentaires; et 3) les thérapies corps-esprit et énergétiques. La controverse existe concernant nombre

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de ces traitements, particulièrement ceux présentant un risque plus élevé d'effets néfastes, tels que la manipulation chiropratique, l'acupuncture et l'utilisation de nutraceutiques. Plusieurs études rigoureuses ont été analysées afin de montrer comment la recherche en MCA peut tenir compte des réponses placebo. Nous offrons des considérations pratiques destinées aux patients et aux médecins intéressés à continuer à ou employant déjà des techniques de MCA dans des contextes périopératoires ou de prise en charge de la douleur chronique.

Conclusion *Les traitements de médecine complémentaire et alternative en général peuvent être un ajout utile pour prendre en charge la douleur chronique. Toutefois, bon nombre de patients ne connaissent pas les risques et les bienfaits des traitements individuels. Dans le contexte périopératoire, le traitement de MCA le plus préoccupant est le recours à des herbes ou d'autres suppléments qui pourraient provoquer des déséquilibres physiologiques ou métaboliques et pourraient interagir avec les médicaments prescrits. Il existe des ressources à la disposition des spécialistes de la douleur, des anesthésiologistes et des patients concernant l'utilisation des traitements de MCA fondés sur des données probantes.*

The use of complementary and alternative medicine (CAM) has gradually risen in many countries, along with an increased demand for skilled practitioners and evidence-based assessment and a push towards assimilation into mainstream medical practices.^{1,2} As a result, the idea of “integrative medicine” has developed, which involves incorporating CAM therapies to better patients’ emotional and physical well-being while simultaneously continuing more conventional treatments. In particular, CAM therapies seem to be gaining acceptance within the field of pain management. This may be due in part to the subjective nature of pain experiences, which are heavily influenced by psychosocial situations and emotional well-being.³

Imagine you are a patient who is about to undergo a procedure. You are a little nervous. You enter a waiting area and find yourself bathed in your favourite colour of soft warm light. You close your eyes and breathe deeply, taking in the pleasant aromas around you. You are soothed by the sounds of your favourite calm and meditative music. You smile as your anesthesiologist greets you and gently explains all the steps of the procedure, making you feel safe, secure, and protected. The music continues as you are taken to your procedure room. Any anxiety you had dissipates as you allow yourself to drift confidently into the healing hands of your providers.

As a patient, you have just experienced aspects of integrative medicine. As a reader, you have just experienced guided imagery. This example touches on several CAM modalities that are easy to implement: music therapy, aromatherapy, guided imagery, and meditation. Some of these modalities may have already been integrated into your practice without your conscious awareness. Arguments have been made regarding the validity of CAM therapies and whether their effects are distinguishable from placebo. For some of these therapies, such as those exemplified above, the risk to benefit ratio is so low that rigorous investigation may not be warranted prior to implementation.

Other CAM modalities exist that are far more controversial in terms of risk and benefit, requiring a comprehensive evidence-based review of how each of these therapies can be best utilized. Chiropractic and spinal manipulation, for example, is often used for various pain syndromes, despite some literature reviews that fail to show any benefit over sham procedures and also show the potential for harm.^{4,5} Another heavily investigated therapy is acupuncture, which is generally considered more invasive and carries with it the potential for adverse events.

The goal of this narrative review is to provide a broad overview of the types of CAM therapies most commonly encountered by anesthesiologists and pain management practitioners. It is not our intent to provide a systematic review of the literature, as each individual therapy warrants its own systematic review. Nevertheless, where appropriate, we attempt to summarize relevant Cochrane systematic reviews and meta-analyses for anesthesiologists and pain management practitioners. The number of reviews regarding individual CAM therapies continuously grows as medical systems become more integrated and therapies move from “alternative” into “mainstream”. This review provides a summary of relevant information for practitioners within the specialty and subspecialties of anesthesiology and pain management.

We focus on three broad categories of CAM therapy: 1) manipulation and procedural therapies; 2) herbs, nutritional supplements (nutraceuticals), and dietary therapies; and 3) mind-body and energy therapies. Within these categories, the primary emphasis is on the therapies that generate the most controversy due to their risk to benefit potential, i.e., acupuncture, chiropractics, and herbal/nutraceutical therapy. Many therapies exist that do not fall exclusively into any of these categories and will not be as thoroughly addressed. We also examine several well-conducted studies to exemplify how to optimize CAM research by controlling for placebo responses and provide clinically relevant practical considerations for both patients and practitioners who are either interested in pursuing or already employing CAM.

For this review, we performed a literature search of PubMed and a search of the various licensing organizations and books published on the topics of CAM and integrative medicine. We searched the PubMed database using a list of pertinent keywords, and we reviewed nutraceuticals, vitamins, and other micronutrient/functional foods as they relate to the perioperative period. Search terms (MeSH) included “Complementary Therapies OR Dietary Supplements”. We focused on recently published, highly cited, randomized controlled trials, human studies, translational animal studies, and reports relating to the perioperative period, in particular, those reporting adverse outcomes. Articles in languages other than English were excluded from our search.

Categories of complementary and alternative medicine

The term, CAM, has been used to encompass the wide variety of therapies that are outside the scope of conventional medicine. In a systematic review of surveys in the United Kingdom, it was found that, on average, the prevalence of CAM usage in one year was 41.1%, and the average prevalence of use in a lifetime was 51.8%.⁶ National surveys of the frequency of CAM usage have investigated anywhere from five to 36 different therapies. Some types of CAM are all-inclusive alternative medical systems that address multiple aspects of well-being, such as diet, lifestyle, and mental and emotional health. Other types of CAM offer treatments directed only at specific symptoms or diseases.^{7,8} Table 1 comprises a non-exhaustive list of therapies that are currently not emphasized by most traditional mainstream medical education programs. We loosely categorized these therapies into three separate groups. The Centers for Disease Control and Prevention and the National Center for Health Statistics conducted the National Health Interview Survey (NHIS) to ascertain the approximate frequency of usage of each CAM therapy by the US population.^{7,9}

Manipulation & procedural therapies

Manipulation and procedural therapies include massage, chiropractic manipulation, and acupuncture. Massage and neuromuscular release involve manipulating soft tissues. The claimed benefits from massage are broad, but they primarily include inducing a sense of well-being, relaxation, and improved blood flow to affected areas. Chiropractic manipulation involves attempting to perform spinal and joint adjustments with purported benefits that include influencing the body's nerves and natural defenses, although sufficient evidence to support these claims is still lacking. Both therapies are commonly used in the treatment

Table 1 Non-exhaustive list of different forms of complementary alternative medicine (CAM) and the percentage of the US population older than 18 yr who used each therapy in a one-year period

Manipulation & Procedural Therapies	Usage in US (%)
Acupuncture	1.4
Chiropractics	8.6
Massage	8.3
Nutraceutical & Dietary Therapies	
Herbal Remedies	17.7
Special Diets	3.6
Megadose Vitamins	2.8
Homeopathy	1.8
Mind-body & Energy Therapies	
Prayer	43
Guided Imagery	2.2
Biofeedback	0.2
Hypnosis	0.2
Meditation	9.4
Yoga	6.1
Tai Chi	1.0
Energy Healing	0.5

Usage statistics gathered from NHIS surveys conducted in the United States (2002, 2007)

NHIS = National Health Interview Survey

of pain syndromes. Indeed, 8.6% of the US adults on the 2007 NHIS survey responded that they visited a chiropractor in the last 12 months.⁷ Acupuncture, one of the branches of traditional Chinese medicine (TCM), is based on a theoretical flow of “*Qi* energy” along “meridians” throughout the body. In 2007, 1.4% of US adults responded that they received acupuncture treatment in the last 12 months.⁷ There has been intense interest in its benefits and efficacy, leading to extensive study by evidence-based medical practitioners.

A 1998 National Institutes of Health (NIH) consensus on acupuncture concluded that acupuncture is effective for adult postoperative and chemotherapy-induced nausea and vomiting as well as for postoperative dental pain.¹⁰ In addition, it has been reported to be variably effective for several other pathological states, including addiction, asthma, carpal tunnel syndrome, fibromyalgia and other myofascial pain syndromes, headaches, low back pain, menstrual cramps, osteoarthritis, and tennis elbow.¹⁰ Acupuncture has been used successfully in a variety of chronic pain conditions ranging from osteoarthritis to chronic migraines.^{8,11,12} There is some evidence that acupuncture may be beneficial for idiopathic headache as well.¹³ Acupuncture combined with non-narcotic analgesics may obviate the need for opioid therapy and reduce side effects associated with higher dosages of medication.¹⁴ Assertions in recently performed literature

Table 2 Summary of select Cochrane systematic reviews and meta-analyses for manipulation & procedural therapies relevant to anesthesia and pain management

CAM Therapy	Condition Treated	Number of Trials Analyzed	Primary Outcomes Measured	Results	Reference
Acupuncture	Peripheral joint OA	11, 16	Pain and joint function	+	(12) (107)
	Tension HA	11	HA days, pain scores	+	(17)
	Migraine HA	22	HA days, pain scores	+	(18)
	PONV	40	Nausea, vomiting, need for rescue antiemetics	+	(108)
	Pregnancy-related pain	26	Low back and pelvic pain	+	(109)
	Labour pain	13	Pain intensity, analgesic use, patient satisfaction	+	(15)
	Fibromyalgia	9	Pain, physical function, fatigue, sleep, total well-being, stiffness	+/-	(8)
	Low back pain	35	pain score, function	+/-	(110)
	Shoulder pain	9	Pain, time to maximum pain relief, range of motion	+/-	(111)
	Rheumatoid arthritis	2	Pain, ESR, CRP, number of swollen joints, reduction of analgesics	-	(112)
Depression	30	Depression scores, self-reported remission of depression	-	(113)	
Chiropractic & Spinal Manipulation	Neck pain	27	Pain, function, patient satisfaction	+ for short-term; no evidence available for long-term	(114)
	Chronic low back pain	26	Pain, disability, back-related function, patient satisfaction	+ for short-term; +/- for long-term	(115)
	Acute low back pain	20	Pain, back specific functional status, patient perception	+/-	(4)
Massage	Cancer pain	12	Pain	+	(116)
	Fibromyalgia	10	Pain, fatigue, stiffness, anxiety, depression, sleep	+ for short-term; +/- for long-term	(117)
	Neck pain	15	Pain, function, disability	+/-	(118)
	Elbow and knee tendinitis	2	Pain, function, quality of life, patient satisfaction, adverse events	+/-	(119)

CAM = complementary and alternative medicine; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HA = headache; OA = osteoarthritis; PONV = postoperative nausea and vomiting; + = positive evidence (low-strong), sufficient research has been performed to support the therapy for the selected indication; +/- = inconclusive, more studies need to be performed before evidence of benefit can be assessed; - = negative evidence (low-strong), sufficient research has been performed to conclude that the therapy should not be supported for the selected indication

reviews suggest that acupuncture may be effective for peripheral joint osteoarthritis, neck pain, tension-type headaches, migraine prophylaxis, and labour pain (Table 2). For example, in 2011, Lee and Ernst published an analysis of Cochrane reviews that thoroughly addresses the specific evidence on acupuncture for pain.^{12,15-20} They found that most of the evidence for the effect of acupuncture in pain related to migraines, neck disorders, tension-type headaches, and peripheral joint osteoarthritis. They also noted a lack of effect for rheumatoid arthritis and inconclusive results for some other types of pain, suggesting that acupuncture is effective for some types of pain but clearly not all.

Mind-body & energy therapies

The group of mind-body and energy therapies is the most frequently used subtype of CAM.⁷ The 2002 NHIS survey showed that 43% of US adults used prayer specifically for their own health in the past 12 months.⁹ There is some evidence to suggest that certain mind-body and energy therapies may be helpful for stress reduction and reducing pain intensity (Table 3). There are many types of mind-body and energy therapies with various intended purposes.

Guided imagery employs positive detailed mental imagery to relax the patient. It has been commonly applied for the treatment of chronic medical conditions

Table 3 Summary of select systematic reviews and meta-analyses for mind-body and energy therapies relevant to anesthesia and pain management

CAM Therapy	Condition Treated	Number of Trials Analyzed	Primary Outcomes Measured	Results	Reference
Hypnosis	Disability-related pain	10	Pain, depression, medication usage	+ short-term	(120)
	Perioperative effects	26	Pain, post-op anxiety, pain medication requirement, nausea	+ for anxiety and pain	(121)
	Labour pain	7	Pain, analgesic use, patient satisfaction	+/-	(122)
Mind-body therapies	Fibromyalgia*	61	Physical functioning, pain, and low mood	+ for psychological interventions; +/- for biofeedback, mindfulness, movement and relaxation therapies	(123)
	Anxiety in pregnancy§	8	Anxiety	+	(124)
	Chronic pain in older adults†	20	Pain relief and function in adults ≥ 50 yr old with non-malignant pain	+ for OA pain using progressive muscle relaxation & guided imagery; + for pain relief using tai chi, yoga, hypnosis, and progressive muscle relaxation; +/- for others	(25)
Mindfulness	Perioperative effects	26	Pain, postoperative anxiety, pain medication requirement, nausea	+ for anxiety and pain	(121)
	Labour pain	7	Pain, analgesic use, patient satisfaction	+/-	(122)
	Chronic pain	10	Reduction of pain symptoms, improvement of depressive symptoms, coping	+/-	(125)
	Adult pain	24	Pain intensity, analgesic usage	+ for Reiki, correlates with practitioner's experience level	(126)
Tai Chi	Chronic musculoskeletal pain	7	Pain, physical performance, disability, tension, satisfaction with general health	+ for pain and disability in arthritis; +/- for others	(25)
	Rheumatoid arthritis	4	Activities of daily living, tender and swollen joints and patient global overall rating, range of motion	+ for lower extremity range of motion; +/- for all others	(127)
Yoga	Chronic low back pain	10	Pain, back-specific disability, global improvement	+ for short-term & long-term	(128)
	Spinal (back & neck pain)	6	Pain, function	+ for short-term; +/- for long-term	(129)

CAM = complementary and alternative medicine; OA = osteoarthritis. + = positive evidence (low-strong), sufficient research has been performed to support the therapy for the selected indication; +/- = inconclusive, more studies need to be performed before evidence of benefit can be assessed; - = negative evidence (low-strong), sufficient research has been performed to conclude that the therapy should not be supported for the selected indication.*Mind-body therapies included psychological therapies, biofeedback, mindfulness, movement therapies, and relaxation strategies. Energy healing therapies included healing touch (HT), therapeutic touch (TT), and Reiki. §Mind-body therapies included autogenic training, biofeedback, hypnotherapy, imagery, meditation, prayer, auto-suggestion, tai chi, and yoga. †Mind-body therapies included biofeedback, progressive muscle relaxation, meditation, guided imagery, hypnosis, tai chi, *qi gong*, and yoga

such as headaches, anxiety, stress, and hypertension. Biofeedback employs simple monitors, such as electromyography and pulse oximetry, to provide feedback on normally unconsciously regulated bodily functions. The intent of biofeedback is to “teach” patients how they can consciously control parameters such as respiratory rate, temperature, muscle tone, and heart rate.⁷ Hypnotists claim to induce patients into an altered state of consciousness by using a combination of relaxation and intense focus on certain objects or ideas. Practitioners of hypnosis describe hypnosis as an attempt to

modulate attention and preconscious brain processes in order to suggest changes in perception, behaviours or disease states. Actually, cortical activity has been shown to be altered during hypnosis.⁹ The work of Dr. Alan Cyna has provided evidence to suggest the role of communication and the power of suggestive words in altering patients' perception of unpleasant sensations.²¹⁻²³ In meditation, patients strive to suspend their “normal” flow of thoughts for a period of time in an attempt to reduce their stress levels and slow their vital signs. Mindfulness is a form of meditation that encourages the

non-judgmental acceptance of emotions, thoughts, and sensations in the “present moment” without the need for immediate action.²⁴

Energy healing uses objects or human touch with claims of changing the flow of energy through the body. Some examples of energy therapies include laying hands, reiki or healing touch, acupuncture, *qi gong* (tai chi), and magnetic therapy.^{7,9}

Yoga and tai chi combine mind-body, energy, and physical therapies. Both involve combining a set of slow, controlled body movements with mental focus with the purpose of improving energy/blood flow, relaxation, balance, physical strength, and overall health.⁹ Most tai chi studies have focused on its use in musculoskeletal pain, specifically osteoarthritis²⁵⁻²⁷ and fibromyalgia.²⁸ In addition, tai chi has been studied for its use in fall prevention and as an adjunct for rehabilitation in patients with heart failure.²⁹ Limitations of these studies include small sample sizes, large dropout rates, and absence of a double-blind study design.^{25,26,28} In all the studies reviewed, there were no adverse effects from the use of a tai chi exercise program (Table 3). Similar studies show the benefits of yoga for pain relief.³⁰

Herbals, supplements, nutraceuticals & dietary therapies

Herbals, dietary supplements, nutraceuticals, vitamins, functional foods, and diet-based therapies are among the most widely used forms of CAM in the US.^{7,9} According to the most recent US census, they are used by approximately 18% of Americans.¹ A number of studies show the incidence of herbal medication use to be approximately 20-25% among perioperative patients.³¹⁻³⁶ This number may actually be much higher, as many patients do not consider these supplements to be “medications”, which can lead to inadvertent underreporting to physicians.³⁷ Consequently, it is best that physicians specifically ask their patients about the use of herbal and vitamin supplements. Their uses are broad, ranging from self-directed use for health promotion to supervised nutritional supplementation in a hospital setting for critically ill patients or those with digestive disorders (e.g., pancreatitis or inflammatory bowel disease).^{38,39} We refer the reader to more comprehensive reviews of commonly used herbal supplements,³³ vitamin therapy,⁴⁰ and diet⁴¹ and their potential for adverse events.

The term, nutraceutical, is derived from joining the terms nutrition and pharmaceutical. Nutraceuticals can be defined simply as any substance that may be considered a food or part of a food that provides medical and health benefits. The importance of food as medicine varies among cultures. Historically, this concept has received more

attention in India (e.g., Ayurvedic medicine) and China (e.g., TCM); however, evidence of this concept is also present in Western cultures, perhaps with more of an emphasis on symptomatic relief (e.g., chicken soup). Diet and dietary supplements have well-known health benefits for disease prevention (e.g., heart disease, colon cancer, diabetes, vitamin deficiency), and failure to achieve proper nutrition is an often underdiagnosed etiology for chronic disease.

Both pharmaceutical and nutraceutical therapies embody the concept that disease can be mitigated (and good health promoted or restored) through the application, ingestion, inhalation, etc. of an exogenous substance. Vitamins are considered vital nutrients that organisms cannot synthesize. Foods obviously contain vitamins, but they may also contain substances known to specifically influence health or disease. Drugs/pharmaceuticals are defined by the existence of a physiologic effect, and Health Canada defines natural health products as vitamins, minerals, herbs, traditional medicines, probiotics, and other ingestible substances that are considered safe for consideration as a non-prescription product. In the US, nutraceuticals, dietary supplements, herbal remedies, and traditional medicines are all treated separately from food, vitamins, and pharmaceuticals. The main difference between food, vitamins, nutraceuticals, and pharmaceuticals is in the way they are marketed and regulated. Although some patients consult trained herbalists and functional medicine practitioners for insight into therapy, a 1997 survey by Eisenberg *et al.* revealed that 85% of herbal use was patient-directed, and this percentage increased to 95% on the 2002 NHIS survey.³⁷

Many patients participate in special diets (e.g., macrobiotic, Atkins, Zone) for the purpose of weight loss, nutrient supplementation, energy balance, and general wellness.⁴² Some patients with pain conditions that are difficult to treat, e.g., interstitial cystitis, have considered diets where vitamin C and other potential irritants may be eliminated, but these diets should be implemented only under a physician’s supervision.⁴³ Some patients take vitamin doses in excess of the recommended daily allowance in order to treat a specific condition (Table 4) and not as a general health supplement.⁷ Patients may be unaware of the potential side effects and drug interactions that vitamins, nutraceuticals, and dietary therapies can cause. Importantly, medical providers need to include a thorough investigation of their patients’ nutritional and dietary intake and be alert for problems that may arise from excessive use or deficiency.

Many natural health products studied prospectively and in randomized controlled trials demonstrate safety and efficacy when taken in recommended doses for their intended purpose, but physicians and patients must be wary

Table 4 Select vitamin supplements, indications and anesthetic considerations

	RDA/ DV/ UL†	Indications (evidence)	Anesthetic considerations
Vitamin C (mg)	90/60/ 2,000	Mitigation of cold severity and CPRS (^{130,131}). Also taken for: cancer prevention, cognitive health.	Can cause high blood pressure. Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. Can interfere with blood glucose control (¹³²).
Vitamin D (µg)	15/5/ 100	Bone health (¹³³). Also taken for: asthma, inflammation control, fibromyalgia.	Arterial hardening, constipation, nausea, can cause high blood pressure, interfere with blood glucose levels (¹³⁴).
Vitamin E (mg)	15/10/ 1,000	The evidence for Vitamin E supplementation for cardiovascular disease, liver disease, or to promote cognitive health is not convincing (¹³⁵⁻¹³⁷). Also taken for: general cancer prevention/treatment.	Increases risk of bleeding. Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes (¹³²).
Thiamin (mg)	1.2/1.3/ ND	Nutritional deficits associated with alcoholism or metabolic disorders (¹³⁸). Also taken for: joint problems, diabetic complications.	Can cause low blood pressure and drowsiness. Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. Can interfere with blood glucose control (¹³²).
Niacin (mg)	16/23‡/ 35	Cholesterol lowering agent (¹³⁹). Also taken for erectile dysfunction, osteoarthritis, skin conditions.	Associated with anaphylaxis and arrhythmias. Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. Can interfere with blood glucose control (¹³²).
Vitamin B ₆ (mg)	1.7/1.8/ 100	Nutritional deficits, sideroblastic anemia (¹⁴⁰). Also taken for: attention deficit hyperactive disorder, cognitive health, cardiovascular health, fertility.	Associated with hypotension and arrhythmias. Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. Can interfere with blood glucose control (¹³²).
Folate (µg)	400/ 220/ 1,000	Prevention of neural tube defects (¹⁴¹). Also taken for: cancer prevention, cognitive health.	Associated with hypotension. Can interfere with blood glucose levels (¹⁴²).
Vitamin B ₁₂ (µg)	2.4/2/ ND	Nutritional deficits, specific anemias (¹⁴³). Also taken for: diabetic neuropathy, depression, cognitive health, sleep regulation.	Can cause high blood pressure and rash. Can result in reduced gut absorption of antibiotics, blood pressure medications, H ₂ blockers, oral opioids, and proton pump inhibitors (¹⁴⁴).

†US recommended daily allowance (RDA), Canadian daily values (DV), and tolerable upper limits (UL) per dietary reference intake reports available online via www.nap.edu. ‡Daily value in niacin equivalents. CRPS = complex regional pain syndrome; ND = no data

of the potential risks associated with these products (Table 5). The induction of hepatic enzymes is involved in some of the most serious adverse events related to nutraceuticals.^{44,45}

Patients' use of herbal medications can have twofold significance during the perioperative period. First, these supplements are most often used to treat an underlying condition or as prevention. This should be kept in mind as the medical history is taken. For example, garlic has been marketed to regulate cholesterol levels and maintain normal blood pressure; therefore, it would be prudent to ask the patient about a personal or family history of hypertension and hypercholesterolemia. Second, many of these supplements can have significant side effects or interactions with prescription medications; consequently,

patients may need to discontinue their use prior to surgery (Table 5).

Anesthesiologists must therefore inquire about the potential use of natural health products due to the known effects on arousal/sedation, coagulation, hemodynamics, and metabolism. There is also the potential for pharmacokinetic effects of these supplements on the level of pain medications, antibiotics, or neuromuscular blockers as well as the potential for toxicity at high doses. It is recommended that physicians research the potential consequences of supplemental therapies. Furthermore, physicians in the US and Canada are encouraged to report any suspected adverse events related to their use either to the Federal Drug Administration (i.e., MedWatch) or Health Canada's Adverse Reaction Database (MedEffect™).

Table 5 Select herbals and dietary supplements, indications, and anesthetic considerations

	Common Sources	Indications (evidence)	Anesthetic considerations	Recommendations for perioperative period
Alpha lipoic acid (ALA)	Diet especially red meat, synthetic versions available as pill/pastille.	Diabetic complications especially neuropathy (¹⁴⁵). Also taken for: general cancer prevention and treatment.	Hypoglycemia and arrhythmias are possible (¹³²).	n/a; ALA is an endogenous antioxidant.
Amino acids (e.g., arginine)	Dairy, meat products, pill/pastille, liquids, infusions	Presumably for nutritional deficits. Also taken for muscle gain, diabetic neuropathy, depression, cognitive health, sleep regulation.	Allergic reactions, inflammation, and anaphylaxis are possible. Hyperkalemia, hypoglycemia, hypertension, and heart attack risk (¹⁴⁶).	n/a; endogenous substance. Avoid overdose.
Chamomile	Herbal tea	Anxiolysis (¹⁴⁷). Also taken for reducing sore throat.	Potential to increase sedative effect of anesthetics. Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes (¹³²).	Cease ingestion 7 days prior to surgery (³⁴).
Chondroitin	Pill/pastille	Joint health (¹⁴⁸). Also taken for cardiovascular health and urinary problems.	Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes (¹⁴⁹).	n/a; endogenous substance
Echinacea	Pill/pastille, juice	Cold prevention (¹⁵⁰).	Arrhythmias, allergic reactions, decrease wound healing, leukopenia (¹⁵¹).	Avoid in the perioperative period.
Ephedra / Ma Huang	Energy drinks, pill/pastille, diet tea	Weight-loss, performance enhancement (¹⁵²). Also taken for asthma treatment, CNS stimulatory effects.	Arrhythmias, hypertension, cardiovascular instability, coronary/aortic aneurysm, rhabdomyolysis (¹⁵¹).	Cease ingestion 24 hr prior to surgery (³⁴).
Garlic	Pill/pastille, powder, common food	Cardiovascular health (¹⁵³). Also taken for cold prevention.	Hypotension. Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes (¹³²).	Cease ingestion 7 days prior to surgery (³⁴).
Ginkgo Biloba	Pill/pastille, fleshy seeds are edible	Cognitive health and memory problems (¹⁵⁴). Also taken for stroke recovery, anxiety, and schizophrenia.	Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. Risk of serotonin syndrome (¹³²).	Cease ingestion 36 hr prior to surgery (³⁴).
Ginseng	Pill/pastille, herbal teas, energy drinks	Blood glucose control (¹⁵⁵). Also taken for cardiovascular health, sexual vitality, CNS stimulatory effects.	Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. Can interfere with blood glucose control (¹³²).	Cease ingestion 7 days prior to surgery (³⁴).
Glucosamine	Pill/pastille	Joint health (¹⁴⁸)	Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes (¹⁴⁹).	n/a; endogenous substance
Grapefruit	Common Fruit	There is minimal data on its effects on weight loss and cardiovascular health (¹⁵⁶). Also taken for general antioxidant properties and cancer prevention.	Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. (¹³²)	Avoid large changes in daily consumption in the perioperative period.

Table 5 continued

	Common Sources	Indications (evidence)	Anesthetic considerations	Recommendations for perioperative period
Guarana	Energy drinks, pill/pastille, diet tea	Weight-loss, performance enhancement (¹⁵⁷). Also taken for depression, alertness.	Arrhythmias, hypertension, cardiovascular instability (¹⁵⁸).	Cease ingestion 24 hr prior to surgery (³⁴).
Kava-kava	Herbal tea, pill/pastille	Anxiolysis (¹⁵⁹). Also taken for depression.	Potential to increase sedative effect of anesthetics.	Cease ingestion 24 hr prior to surgery (³⁴).
Melatonin	Pill/pastille	Preoperative anxiety (¹⁶⁰⁻¹⁶²). Also taken for insomnia.	Potential to increase sedative effect of anesthetics	n/a; endogenous substance
Other omega-3 fatty acids (e.g., fish oil, flaxseed oil)	Pill/pastille, also as an oil applied to food	Cognitive (¹⁶²) and cardiovascular health (¹⁶³). Also taken for general antioxidant properties and cancer prevention.	Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. Can interfere with blood glucose control (¹³²).	Avoid large changes in daily consumption in the perioperative period.
Probiotics	Pill/pastille, various cultured foods (e.g., yogurt)	Immune health (^{164,165}). Also taken for allergies, skin disorders, and gastrointestinal symptoms.	Suspected risk of hypotension, interference with gut absorption of antibiotics. Risk to those with immune dysfunction.	Avoid large changes in daily consumption in the perioperative period.
Red yeast rice	Pill/pastille, condiment	Cholesterol lowering agent (¹⁰¹).	Allergic reactions, inflammation, and gastrointestinal disturbances are possible. May interfere with cytochrome P450 enzymes (¹⁶⁶).	Avoid large changes in daily consumption in the perioperative period.
Saw palmetto	Pill/pastille	There is some evidence of Saw Palmetto having mild benefit in urinary symptoms associated with benign prostatic hyperplasia (¹⁶⁷). Also taken for other urinary problems.	Anti-platelet properties. Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes (¹³²).	Cease ingestion 7 days prior to surgery (³⁴).
St. John's Wort	Pill/pastille,	Depression (¹⁶⁸). Also taken for anti-inflammatory properties.	Can interfere with metabolism of blood-thinning drugs, blood pressure medications, opioids, and other drugs via induction of cytochrome P450 enzymes. Risk of serotonin syndrome (⁶⁶).	Cease ingestion 5 days prior to surgery (³⁴).
Valerian Root	Pill/pastille, herbal tea	Insomnia (¹⁶⁹). Also taken for anxiolysis.	Potential to increase sedative effect of anesthetics.	Tapering the dose before surgery can reduce the risk of withdrawal symptoms.
Yerba Mate	Herbal teas, energy drinks	Weight loss (¹⁵⁸). Also taken for CNS stimulatory effects.	Can cause hypertension, cardiovascular instability.	Cease ingestion 24 hr prior to surgery (³⁴).
Yohimbine†	Pill/pastilles energy drinks	Erectile dysfunction (¹⁷⁰). Also taken for sexual vitality, CNS stimulatory effects.	Can cause hypertension, cardiovascular instability.	Cease ingestion 7 days prior to surgery (³⁴).

†Yohimbine hydrochloride is available as a prescription drug in the United States. CNS = central nervous system

Controversies

In general, most of the controversies surrounding CAM are related to a lack of agreement on mechanisms of action and an assumed lack of validity. There is also difficulty in blinding in the investigations of many of the manipulative therapies such as chiropractics, massage, and acupuncture.

Furthermore, medical practitioners are often cautious of the lack of regulatory control for CAM. Nevertheless, there are ways to ensure quality within some of these modalities. For example, Dr. Edzard Ernst has spent much of his career performing evidence-based CAM research in order to ensure critical thinking and prevent the use of potentially harmful therapies that have been put into practice solely on

the basis of belief rather than on sound evidence.^{46,47} A discussion of some controversies within CAM research follows along with examples of ways to help critically evaluate these therapies.

Mechanisms of action

Studies examining inflammatory mediators, pain pathways, positron emission tomography scans, functional magnetic resonance imaging, and a host of possible mechanisms of action have ultimately shown that CAM therapies, including acupuncture, purportedly work through complex and pleiotropic mechanisms that target multiple pathways. This in itself is difficult to accept by those with a rigid desire to identify singular unifying mechanisms. It is just as hard to dissect CAM therapy down to one specific molecule as it is to package pain into one singular experience. Nevertheless, several theories for mechanisms of action have become more widely accepted in the medical literature, specifically for acupuncture and its effects on pain.

The theories surrounding acupuncture's mechanisms are multifactorial, involving various central nervous system pathways that include endogenous opioids and serotonergic and noradrenergic/adrenergic systems.⁴⁸⁻⁵² In the 1980s, Pomeranz *et al.* showed an opioid effect of electroacupuncture that was reversed using naloxone.^{53,54} They also showed acupuncture-induced A-beta and C afferent fibres signalling in the spinal cord, resulting in the release of endogenous opioids (e.g., dynorphin and enkephalin) that can suppress nociception.⁵⁵ The endogenous opioid theory for acupuncture has been tested and reaffirmed over time.⁵⁶⁻⁶²

Validity of data

In addition to the lack of mechanistic understanding for CAM therapies, there is an assumed lack of validity, which may be due to difficulty in designing truly double-blinded randomized controlled trials. Sham controls now exist for studies of acupuncture, e.g., needling at non-acupuncture points, superficial insertion of needles, or non-insertion of needles via attachment to a skin-coloured adhesive bandage. Nevertheless, the idea of blinding is difficult due to the argument that *de qi* - the threshold stimulus on needle insertion that describes the "propagation of sensation along channels" - is required to create neuromodulation and produce a truly effective acupuncture treatment.^{63,64} The patient experiences *de qi* as a soreness or an aching feeling that sometimes radiates in what seems to be the path of a traditional acupuncture meridian. The acupuncturist experiences the feeling of a needle being engaged or "catching a hook".⁶⁵⁻⁶⁷ Other

energy therapies shown to have some benefit in both acute and chronic pain, e.g., repetitive transcranial magnetic stimulation, have also encountered difficulties in developing appropriate sham controls.⁶⁸⁻⁷² Physical modalities, such as chiropractic and massage, are equally difficult to blind, since the subjects under study can clearly discern whether they are truly receiving a massage or spinal manipulation. Furthermore, even a light touch can illicit changes in the limbic system, making it difficult to design a true control for physical modalities.⁷³

Despite controversy over a lack of adequate blinding and potential intellectual biases against acupuncture and other complementary therapies, evidence exists to support these therapies even at the mechanistic level.^{14,74-76} For example, several animal models have shown a therapeutic effect for acupuncture and other CAM therapies. Furthermore, since animals likely do not understand the difference between true vs sham therapies, we can infer that they are not likely to exhibit a placebo response.⁷¹⁻⁸¹ Some argue that acupuncture is no better than placebo since a few human studies showed no significant difference between sham needling and true acupuncture—ignoring the effects of needle insertion itself.⁸² Nevertheless, blinding attempts with non-penetrating shams are possible in humans. For example, one study of acupuncture used needle insertion through adhesive bandages vs the appearance of a needle in a bandage but no true insertion. Study results showed a significantly increased benefit with acupuncture in reducing fatigue, pain, and anxiety in fibromyalgia patients.⁶³ When the patients were surveyed regarding whether they had received true acupuncture, they were unable to discern whether they had received true or sham acupuncture despite the lack of needle penetration. As clinicians, we must judiciously analyze the design of any study, CAM or otherwise, and search for appropriate controls before validating the asserted conclusions.

Over the last four decades, arguments concerning the lack of adequate controls have stressed the potential psychological effects of acupuncture, claiming that any observable benefit is due primarily to placebo responses.⁸³ In contrast, some proponents of CAM embrace the experience as critical for healing and ask whether a placebo effect is really something to be avoided in evaluating therapeutic responses. If the combined psychological and physiological effects from an alternative treatment are beneficial for patients while exposing them to minimal risk, is it possible that this may be the best available treatment? A student of Franz Anton Mesmer, the father of modern hypnotism, once commented, "If Mesmer has no other secret than that he has been able to make the imagination exert an influence upon health, would he not still be a wonder doctor? If

treatment by the use of the imagination is the best treatment, why do we not make use of it?"^{84,85}

Regulation of supplements

Although blinding for herbal therapies and other non-vitamin non-mineral natural products is easy enough in clinical trials, these treatments are already widely used and readily accessible in the consumer marketplace. While much of the world differs in terms of regulatory action, the authors are most familiar with the US and therefore use it as our primary example. The US Food and Drug Administration (FDA) regulates dietary supplements under the Dietary Supplement Health and Education Act (1994). In contrast to regulations for pharmaceuticals, the FDA does not require proof of safety or efficacy; instead, it provides guidance only for manufacturers of ingestible food products that are marketed as reducing the risk of disease. Advertising with specific disease-related claims is prohibited, but manufacturers are encouraged to produce evidence of health benefits. Functional claims of reported benefits are legally required to contain a disclaimer acknowledging that the FDA has not evaluated these claims and that the product "is not intended to diagnose, treat, cure, or prevent any disease". The FDA classifies herbal medications and vitamins as dietary supplements, and under this designation, these supplements can be produced, marketed, and sold without demonstrating either safety or efficacy.

The popular use of dietary supplements with different regulations and a potential for medication interactions, side effects, and adverse events has become an area of concern for many physicians. It is known that commonly ingested supplements (e.g., fish oil, flax seed oil, garlic, ginger, ginkgo, chamomile, and others) can affect coagulation (Table 4). Theoretically, this could result in some degree of cardioprotection, but it can also lead to easy bruising and bleeding.³³ Perhaps most importantly, many of these supplements can interfere with the metabolism of other perioperative medications through the cytochrome P450 system, notably the popular "antidepressant" herb *Hypericum perforatum* (St. John's Wort).⁸⁶ Some estimates show that more than 70% of prescription medications are susceptible to these interactions. This can lead to decreased bioavailability and therefore subtherapeutic doses of prescription medications co-administered with St. John's Wort.⁸⁶ Furthermore, when individuals purchase supplements, there is an unknown quantity of effective ingredient and variable or unknown dosing due to variability among manufacturers.⁸⁷

In the US, Canada, and Europe, additional controversy also exists over the availability, marketing, and use of nutraceuticals.⁸⁸ Until 2004, when the Natural Health

Products Regulations (NHPR) in Canada took effect, the provisions of the Food and Drugs Act made strict distinctions between substances, requiring classification as either food or drug. This dichotomy forced nutraceutical manufacturers to either make no health claims about their product or undergo the more stringent regulations for drugs. Since then, over 55,000 applications for natural health product licenses have been granted with recommended health uses. The passage of the NHPR was intended to focus on the safety, marketing, and manufacturing of substances sold over the counter without a prescription. Despite these changes, some may consider the required paperwork onerous and limiting to innovation, and controversy persists.^{89,90}

In the US, most natural health products and nutraceuticals are regulated as dietary supplements, as there is no legal meaning to the terms nutraceutical, functional food, or natural health products. In North America, a delicate balance has yet to be struck between consumer health protection from an unregulated market and stifling new product development. Nevertheless, many manufacturers appear to favour stricter regulation of clinical claims, chemical purity, and good manufacturing practices in order to inspire greater confidence in the industry; in collaboration with the NIH Office of Dietary Supplements, the Dietary Supplement Laboratory Quality Assurance Program was launched.⁹¹

Regulation of providers

Another area of contention results from the viewpoint that CAM practitioners are held to a lesser standard of care than that of conventional medicine practitioners. Nevertheless, while malpractice claims against massage therapists, chiropractors, and acupuncturists occur less often than claims against traditional practitioners and often involve less serious injuries, CAM practitioners are still subject to the ethical and legal implications of their practice.⁹² Indeed, there are risks related to these interventions, e.g., chiropractic manipulation may be associated with significant risks, including arterial dissection leading to stroke (approximate incidence = 0.005%), epidural hematoma, disc herniation, and myelopathy.⁹³⁻⁹⁷ Some have argued that these adverse events are not causally related but rather only associations and that the benefits of chiropractic manipulation may still outweigh the risks.^{98,99} The most common side effects of acupuncture are syncope and nausea, with the most common serious risks being pneumothorax and infection.^{100,101}

Before integrating CAM as part of their practice, physicians must critically evaluate the literature for the physiological mechanisms in the setting of their training. This is necessary to reduce the risk of misdiagnosis,

treatment failure, and misrepresentation.⁸⁵ Over a decade ago, The Federation of State Medical Boards issued Model Guidelines for the Use of Complementary and Alternative Therapies in Medical Practice.¹⁰² Accordingly, prior to licensing a practitioner, many state boards now require CAM practitioners to provide a copy of the informed consent form they intend to use. One way to ensure quality of care is to refer patients only to those individuals who have the appropriate certification and licensure for their practice—whether acupuncture, chiropractic, massage, or other integrative medicine techniques.

Conclusions: practical information for anesthesiologists and pain physicians

Anesthesia providers will most commonly be exposed to CAM in two scenarios: 1) in the care of a perioperative patient already employing CAM, and 2) as an adjunct in the management of acute or chronic pain. In the perioperative setting, patients should always be questioned regarding their use of CAM in order to develop an appropriate anesthetic plan. For patients interested in using CAM as an alternative to conventional pharmacotherapy for pain, a multimodal approach should be developed to address the pain, including nutritional, physical, energy, and mind-body therapies.

While some manipulation and procedural therapies carry the potential for adverse reactions, the rates of serious adverse events, though not negligible, are relatively low compared with conventional medical therapies.^{93,94,100,101,103} When the risk to benefit ratio is low, then it may be appropriate to continue with a therapy. On the other hand, when evidence exists to show that the cost or risk of a particular therapy is greater than the evidence for benefit, it is the physician's responsibility to advise the patient against further use of that treatment.

Although physical exercise should generally be encouraged, some patients may be unable to tolerate even the gentle low-impact movements of tai chi and some forms of yoga. These individuals may benefit from other mindfulness exercises, including cognitive behavioural therapy, biofeedback, meditation, and hypnosis. Art therapy and music therapy may also help these patients to desensitize wind-up of the central nervous system. Movement and breathing to self-selected music has been shown to improve global function, sleep, and pain in some syndromes.^{85,104,105} Again, these therapies are relatively low-risk and underutilized by both physicians and patients in the treatment of the psychological and physical aspects of chronic pain.

Low-risk therapies, such as guided imagery and mindful meditation (including prayer), can almost always be

considered, since these may aid in self-management of pain and anxiety. Similarly, in the perioperative setting, while it is not necessary to have formal training in hypnosis, communicating with patients in a soothing and reassuring manner can bring about beneficial results.²¹⁻²³ Other CAM therapies for pain may also offer surprising benefit at minimal risk to those patients who are amenable. These therapies should probably be tried prior to initiation of opioid therapy or more invasive procedures for chronic pain.

The appropriate certification and credentials should be obtained for potentially harmful procedural therapies such as acupuncture, chiropractic treatment, ultrasound, and magnetic stimulation. Physicians should encourage their patients to inquire about CAM practitioners' credentials in order to ensure they have completed the appropriate training. For example, acupuncturists and chiropractic practitioners can obtain licensure and board certification in their respective practices to assure that baseline standards of care are met. The Academic Consortium for Complementary and Alternative Health Care (ACCAHC)^A attempts to maintain a list of accrediting agencies and testing and certification organizations for the various licensed CAM professions.¹⁰⁶ Although no licensure is required for other less invasive therapies, such as biofeedback or hypnosis, appropriate certification can be obtained. Theoretically, referral to individuals with such credentials may decrease the risk of adverse events and improve quality of care.

Physicians should always question patients regarding their use of nutraceutical and herbal supplements and be aware of potential pharmaceutical interactions. While nutraceuticals, herbals, and dietary supplements can be difficult to assess for efficacy and quality control, evidence-based resources do exist. A branch of the US NIH, The National Center for Complementary and Alternative Medicine (NCCAM), provides fact sheets about commonly used herbs on their website (<https://nccih.nih.gov/health/herbsataglance.htm>). The NCCAM also provides current information on acupuncture and other commonly used modalities. Physicians may, if their knowledge base allows, make recommendations on supplements. Nevertheless, it may be advisable to collect a file of articles regarding the literature and evidence supporting the use of such therapies prior to their initiation. Due to the potential for polypharmacy in chronic pain patients, it may be inadvisable to add supplements unless simultaneously tapering a separate prescription medication. Large variations in the active ingredients (and the resulting dose) may be present;³¹ as a result, clinicians should ask patients to bring in the actual bottles so they can determine the

^A The ACCAHC website can be found at <http://accahc.org/>.

quantity (and possibly the quality) of what is being ingested. To assess for quality control, the NIH maintains a database of products by main ingredients and brand (<http://www.dsld.nlm.nih.gov/dsld/>). Another potential resource for clinicians is the Natural Medicines Comprehensive Database (<http://naturaldatabase.therapeuticresearch.com/>).

For those who wish to incorporate integrative medicine into their own practice or refer patients to quality CAM practitioners, formal training is available and can lead to certification, licensing, and credentialing in some fields, e.g., acupuncture, chiropractic treatment, massage therapy, and naturopathic medicine. Whether or not anesthesiologists and pain management physicians choose in-depth training, they should stay abreast of available therapies in order to counsel patients regarding potential risks, benefits, and pharmaceutical interactions.

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References

1. U.S. Census Bureau. Health and Nutrition. Statistical Abstract of the United States: 2012. Available from URL: <https://www.census.gov/prod/2011pubs/12statab/health.pdf> (accessed August 2015).
2. Leach MJ. Profile of the complementary and alternative medicine workforce across Australia, New Zealand, Canada, United States and United Kingdom. *Complement Ther Med* 2013; 21: 364-78.
3. Moore JE. Chronic low back pain and psychosocial issues. *Phys Med Rehabil Clin N Am* 2010; 21: 801-15.
4. Rubinstein SM, Terwee CB, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for acute low-back pain. *Cochrane Database Syst Rev* 2012; 9: CD008880.
5. Lenssinck ML, Damen L, Verhagen AP, Berger MY, Passchier J, Koes BW. The effectiveness of physiotherapy and manipulation in patients with tension-type headache: a systematic review. *Pain* 2004; 112: 381-8.
6. Posadzki P, Watson LK, Alotaibi A, Ernst E. Prevalence of use of complementary and alternative medicine (CAM) by patients/consumers in the UK: systematic review of surveys. *Clin Med* 2013; 13: 126-31.
7. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report* 2008; 10: 1-23.
8. Deare JC, Zheng Z, Xue CC, et al. Acupuncture for treating fibromyalgia. *Cochrane Database Syst Rev* 2013; 5: CD007070.
9. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States. *Adv Data* 2002; 2004: 1-19.
10. Anonymous. NIH Consensus Conference. Acupuncture. *JAMA* 1998; 280: 1518-24.
11. Kotani N, Hashimoto H, Sato Y, et al. Preoperative intradermal acupuncture reduces postoperative pain, nausea and vomiting, analgesic requirement, and sympathoadrenal responses. *Anesthesiology* 2001; 95: 349-56.
12. Manheimer E, Cheng K, Linde K, et al. Acupuncture for peripheral joint osteoarthritis. *Cochrane Database Syst Rev* 2010; 1: CD001977.
13. Melchart D, Linde K, Fischer P, et al. Acupuncture for idiopathic headache. *Cochrane Database Syst Rev* 2001; 1: CD001218.
14. Zhang R, Lao L, Ren K, Berman BM. Mechanisms of acupuncture-electroacupuncture on persistent pain. *Anesthesiology* 2014; 120: 482-503.
15. Smith CA, Collins CT, Crowther CA, Levett KM. Acupuncture or acupressure for pain management in labour. *Cochrane Database Syst Rev* 2011; 7: CD009232.
16. Yoo HG, Yoo WH. Images in clinical medicine. Acupuncture with gold thread for osteoarthritis of the knee. *N Engl J Med* 2013; 369: e37.
17. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for tension-type headache. *Cochrane Database Syst Rev* 2009; 1: CD007587.
18. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for migraine prophylaxis. *Cochrane Database Syst Rev* 2009; 1: CD001218.
19. Trinh KV, Graham N, Gross AR, et al. Acupuncture for neck disorders. *Cochrane Database Syst Rev* 2006; 3: CD004870.
20. Lee MS, Ernst E. Acupuncture for pain: an overview of Cochrane reviews. *Chin J Integr Med* 2011; 17: 187-9.
21. Dutt-Gupta J, Bown T, Cyna AM. Effect of communication on pain during intravenous cannulation: a randomized controlled trial. *Br J Anaesth* 2007; 99: 871-5.
22. Zoanetti DC, Cyna AM. Distorting the perception of smell during gaseous induction. *Paediatr Anaesth* 2005; 15: 1148; author reply 1149.
23. Cyna AM, Andrew MI, Tan SG, Smith AF. *Handbook of Communication in Anaesthesia & Critical Care: A Practical Guide to Exploring the Art*: Oxford University Press; 2011.
24. Zgierska A, Rabago D, Chawla N, Kushner K, Koehler R, Marlatt A. Mindfulness meditation for substance use disorders: a systematic review. *Subst Abuse* 2009; 30: 266-94.
25. Hall A, Maher C, Latimer J, Ferreira M. The effectiveness of Tai Chi for chronic musculoskeletal pain conditions: a systematic review and meta-analysis. *Arthritis Rheum* 2009; 61: 717-24.
26. Wang C, Schmid CH, Hibberd PL, et al. Tai Chi is effective in treating knee osteoarthritis: a randomized controlled trial. *Arthritis Rheum* 2009; 61: 1545-53.
27. Morone NE, Greco CM. Mind-body interventions for chronic pain in older adults: a structured review. *Pain Med* 2007; 8: 359-75.
28. Wang C, Schmid CH, Rones R, et al. A randomized trial of tai chi for fibromyalgia. *N Engl J Med* 2010; 363: 743-54.
29. Yeh GY, Wood MJ, Lorell BH, et al. Effects of tai chi mind-body movement therapy on functional status and exercise capacity in patients with chronic heart failure: a randomized controlled trial. *Am J Med* 2004; 117: 541-8.
30. Ward L, Stebbings S, Cherkin D, Baxter GD. Yoga for functional ability, pain and psychosocial outcomes in musculoskeletal conditions: a systematic review and meta-analysis. *Musculoskeletal Care* 2013; 11: 203-17.
31. Bent S. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. *J Gen Intern Med* 2008; 23: 854-9.
32. King AR, Russett FS, Generali JA, Grauer DW. Evaluation and implications of natural product use in preoperative patients: a retrospective review. *BMC Complement Altern Med* 2009; 9: 38.

33. Kaye AD, Kucera I, Sabar R. Perioperative anesthesia clinical considerations of alternative medicines. *Anesthesiol Clin North America* 2004; 22: 125-39.
34. Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. *JAMA* 2001; 286: 208-16.
35. Tsen LC, Segal S, Pothier M, Bader AM. Alternative medicine use in presurgical patients. *Anesthesiology* 2000; 93: 148-51.
36. Adusumilli PS, Ben-Porat L, Pereira M, Roesler D, Leitman IM. The prevalence and predictors of herbal medicine use in surgical patients. *J Am Coll Surg* 2004; 198: 583-90.
37. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998; 280: 1569-75.
38. Afghani E, Sinha A, Singh VK. An overview of the diagnosis and management of nutrition in chronic pancreatitis. *Nutr Clin Pract* 2014; 29: 295-311.
39. Bost RB, Tjan DH, van Zanten AR. Timing of (supplemental) parenteral nutrition in critically ill patients: a systematic review. *Ann Intensive Care* 2014; 4: 31.
40. Weitzel LR, Mayles WJ, Sandoval PA, Wischmeyer PE. Effects of pharmacognutrients on cellular dysfunction and the microcirculation in critical illness. *Curr Opin Anaesthesiol* 2009; 22: 177-83.
41. Heys SD, Ogston KN. Peri-operative nutritional support: controversies and debates. *Int J Surg Investig* 2000; 2: 107-15.
42. Neal R. Report by David M. Eisenberg, M.D., on complementary and alternative medicine in the United States: overview and patterns of use. *J Altern Complement Med* 2001; 7(Suppl 1): S19-21.
43. Friedlander JI, Shorter B, Moldwin RM. Diet and its role in interstitial cystitis/bladder pain syndrome (IC/BPS) and comorbid conditions. *BJU Int* 2012; 109: 1584-91.
44. Di Lorenzo C, Ceschi A, Kupferschmidt H, et al. Adverse effects of plant food supplements and botanical preparations: a systematic review with critical evaluation of causality. *Br J Clin Pharmacol* 2015; 79: 578-92.
45. Estes JD, Stolpman D, Olyaei A, et al. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. *Arch Surg* 2003; 138: 852-8.
46. Ernst E. How nurses can be misled about complementary and alternative medicine. *J Adv Nurs* 2015; 71: 235-6.
47. Ernst E. Thirteen follies and fallacies about alternative medicine. *EMBO Rep* 2013; 14: 1025-6.
48. Kim HW, Kwon YB, Han HJ, Yang IS, Beitz AJ, Lee JH. Antinociceptive mechanisms associated with diluted bee venom acupuncture (apipuncture) in the rat formalin test: involvement of descending adrenergic and serotonergic pathways. *Pharmacol Res* 2005; 51: 183-8.
49. Park H, Yoo D, Kwon S, et al. Acupuncture stimulation at HT7 alleviates depression-induced behavioral changes via regulation of the serotonin system in the prefrontal cortex of maternally-separated rat pups. *J Physiol Sci* 2012; 62: 351-7.
50. Yonehara N. Influence of serotonin receptor antagonists on substance P and serotonin release evoked by tooth pulp stimulation with electro-acupuncture in the trigeminal nucleus caudalis of the rabbit. *Neurosci Res* 2001; 40: 45-51.
51. Li SJ, Tang J, Han JS. The implication of central serotonin in electro-acupuncture tolerance in the rat. *Sci Sin B* 1982; 25: 620-9.
52. Mao W, Ghia JN, Scott DS, Duncan GH, Gregg JM. High versus low intensity acupuncture analgesia for treatment of chronic pain: effects on platelet serotonin. *Pain* 1980; 8: 331-42.
53. Cheng RS, Pomeranz B. A combined treatment with D-amino acids and electroacupuncture produces a greater analgesia than either treatment alone; naloxone reverses these effects. *Pain* 1980; 8: 231-6.
54. Pomeranz B, Chiu D. Naloxone blockade of acupuncture analgesia: endorphin implicated. *Life Sci* 1976; 19: 1757-62.
55. Pomeranz B, Bibic L. Electroacupuncture suppresses a nociceptive reflex: naltrexone prevents but does not reverse this effect. *Brain Res* 1988; 452: 227-31.
56. Wang XJ, Wang LL. A mechanism of endogenous opioid peptides for rapid onset of acupuncture effect in treatment of depression (Chinese). *Zhong Xi Yi Jie He Xue Bao* 2010; 8: 1014-7.
57. Kim SK, Moon HJ, Na HS, et al. The analgesic effects of automatically controlled rotating acupuncture in rats: mediation by endogenous opioid system. *J Physiol Sci* 2006; 56: 259-62.
58. Sher L. The role of the endogenous opioid system in the effects of acupuncture on mood, behavior, learning, and memory. *Med Hypotheses* 1998; 50: 475-8.
59. Zhou L, Jiang JW, Wu GC, Cao XD. Changes of endogenous opioid peptides content in RPGL during acupuncture analgesia (Chinese). *Sheng Li Xue Bao* 1993; 45: 36-43.
60. He LF. Involvement of endogenous opioid peptides in acupuncture analgesia. *Pain* 1987; 31: 99-121.
61. Pomeranz B. Do endorphins mediate acupuncture analgesia? *Adv Biochem Psychopharmacol* 1978; 18: 351-9.
62. Pomeranz B, Cheng R, Law P. Acupuncture reduces electrophysiological and behavioral responses to noxious stimuli: pituitary is implicated. *Exp Neurol* 1977; 54: 172-8.
63. Martin DP, Sletten CD, Williams BA, Berger IH. Improvement in fibromyalgia symptoms with acupuncture: results of a randomized controlled trial. *Mayo Clin Proc* 2006; 81: 749-57.
64. Tian DS, Xiong J, Pan Q, et al. De qi, a threshold of the stimulus intensity, elicits the specific response of acupoints and intrinsic change of human brain to acupuncture. *Evid Based Complement Alternat Med* 2014; 2014: 914878.
65. Zhu SP, Luo L, Zhang L, et al. Acupuncture de-qi: from characterization to underlying mechanism. *Evid Based Complement Alternat Med* 2013; 2013: 518784.
66. Yang Y, Wang LP, Zhang L, et al. Factors contributing to de qi in acupuncture randomized clinical trials. *Evid Based Complement Alternat Med* 2013; 2013: 329392.
67. Sun J, Zhu Y, Yang Y, et al. What is the de-qi-related pattern of BOLD responses? A review of acupuncture studies in fMRI. *Evid Based Complement Alternat Med* 2013; 2013: 297839.
68. Kozel FA, George MS, Simpson KN. Decision analysis of the cost-effectiveness of repetitive transcranial magnetic stimulation versus electroconvulsive therapy for treatment of nonpsychotic severe depression. *CNS Spectr* 2004; 9: 476-82.
69. Khedr EM, Kotb HI, Mostafa MG, et al. Repetitive transcranial magnetic stimulation in neuropathic pain secondary to malignancy: a randomized clinical trial. *Eur J Pain* 2014; 19: 519-27.
70. Hasan M, Whiteley J, Bresnahan R, et al. Somatosensory change and pain relief induced by repetitive transcranial magnetic stimulation in patients with central poststroke pain. *Neuromodulation* 2014; 17: 731-6.
71. Tamura Y, Okabe S, Ohnishi T, et al. Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. *Pain* 2004; 107: 107-15.
72. Rollnik JD, Wustefeld S, Dauper J, et al. Repetitive transcranial magnetic stimulation for the treatment of chronic pain - a pilot study. *Eur Neurol* 2002; 48: 6-10.
73. Lund I, Lundeberg T. Are minimal, superficial or sham acupuncture procedures acceptable as inert placebo controls? *Acupunct Med* 2006; 24: 13-5.
74. Funke K, Benali A. Modulation of cortical inhibition by rTMS - findings obtained from animal models. *J Physiol* 2011; 589(Pt 18): 4423-35.

75. Platz T, Rothwell JC. Brain stimulation and brain repair—rTMS: from animal experiment to clinical trials—what do we know? *Restor Neurol Neurosci* 2010; 28: 387-98.
76. Lisanby SH, Belmaker RH. Animal models of the mechanisms of action of repetitive transcranial magnetic stimulation (RTMS): comparisons with electroconvulsive shock (ECS). *Depress Anxiety* 2000; 12: 178-87.
77. Ryu HK, Baek YH, Park YC, Seo BK. Current studies of acupuncture in cancer-induced bone pain animal models. *Evid Based Complement Alternat Med* 2014; 2014: 191347.
78. Mo YP, Yao HJ, Song HT, Xu AP, Tang YS, Li ZG. Progress of animal research on electro-acupuncture treatment for depression(Δ). *Chin Med Sci J* 2014; 29: 43-7.
79. Satalangka C, Wattanathorn J, Muchimapura S, Thukham-Mee W, Wannanon P, Tong-un T. Laser acupuncture improves memory impairment in an animal model of Alzheimer's disease. *J Acupunct Meridian Stud* 2013; 6: 247-51.
80. Oh JH, Bai SJ, Cho ZH, et al. Pain-relieving effects of acupuncture and electroacupuncture in an animal model of arthritic pain. *Int J Neurosci* 2006; 116: 1139-56.
81. Kwon YB, Kang MS, Kim HW, et al. Antinociceptive effects of bee venom acupuncture (apipuncture) in rodent animal models: a comparative study of acupoint versus non-acupoint stimulation. *Acupunct Electrother Res* 2001; 26: 59-68.
82. Colquhoun D, Novella SP. Acupuncture is theatrical placebo. *Anesth Analg* 2013; 116: 1360-3.
83. Toomey TC, Ghia JN, Mao W, Gregg JM. Acupuncture and chronic pain mechanisms: the moderating effects of affect, personality, and stress on response to treatment. *Pain* 1977; 3: 137-45.
84. Goldsmith M. Franz Anton Mesmer: A History of Mesmerism. Garden City, NY: Doubleday, Doran, and Company, Inc.; 1934 .
85. Weintraub MI, Mamiani R, Micozzi MS. Complementary and Integrative Medicine in Pain Management. New York, NY: Springer Publishing Company, LLC; 2008 .
86. Gurley BJ, Fifer EK, Gardner Z. Pharmacokinetic herb-drug interactions (part 2): drug interactions involving popular botanical dietary supplements and their clinical relevance. *Planta Med* 2012; 78: 1490-514.
87. Trucksess MW, Whitaker TB, Weaver CM, et al. Sampling and analytical variability associated with the determination of total aflatoxins and ochratoxin A in powdered ginger sold as a dietary supplement in capsules. *J Agric Food Chem* 2009; 57: 321-5.
88. Coppens P, da Silva MF, Pettman S. European regulations on nutraceuticals, dietary supplements and functional foods: a framework based on safety. *Toxicology* 2006; 221: 59-74.
89. Lexchin J. Canada's patented medicine notice of compliance regulations: balancing the scales or tipping them? *BMC Health Serv Res* 2011; 11: 64.
90. Laeque H, Boon H, Kachan N, Cohen JC, D'Cruz J. The Canadian Natural Health Products (NHP) regulations: industry compliance motivations. *Evid Based Complement Alternat Med* 2007; 4: 257-62.
91. Phillips MM, Rimmer CA, Wood LJ, et al. Dietary supplement laboratory quality assurance program: the first five exercises. *J AOAC Int* 2011; 94: 803-14.
92. Studdert DM, Eisenberg DM, Miller FH, Curto DA, Kaptchuk TJ, Brennan TA. Medical malpractice implications of alternative medicine. *JAMA* 1998; 280: 1610-5.
93. Gouveia LO, Castanho P, Ferreira JJ. Safety of chiropractic interventions: a systematic review. *Spine (Phila Pa 1976)* 2009; 34: E405-13.
94. Cassidy JD, Boyle E, Cote P, et al. Risk of vertebrobasilar stroke and chiropractic care: results of a population-based case-control and case-crossover study. *J Manipulative Physiol Ther* 2009; 32(2 Suppl): S201-8.
95. Jeret JS, Bluth M. Stroke following chiropractic manipulation. Report of 3 cases and review of the literature. *Cerebrovasc Dis* 2002; 13: 210-3.
96. Tuchin P. Chiropractic and stroke: association or causation? *Int J Clin Pract* 2013; 67: 825-33.
97. Rothwell DM, Bondy SJ, Williams JI. Chiropractic manipulation and stroke: a population-based case-control study. *Stroke* 2001; 32: 1054-60.
98. Rubinstein SM. Adverse events following chiropractic care for subjects with neck or low-back pain: do the benefits outweigh the risks? *J Manipulative Physiol Ther* 2008; 31: 461-4.
99. Rubinstein SM, Leboeuf-Yde C, Knol DL, de Koekkoek TE, Pfeifle CE, van Tulder MW. The benefits outweigh the risks for patients undergoing chiropractic care for neck pain: a prospective, multicenter, cohort study. *J Manipulative Physiol Ther* 2007; 30: 408-18.
100. Ernst E, Lee MS, Choi TY. Acupuncture: does it alleviate pain and are there serious risks? A review of reviews. *Pain* 2011; 152: 755-64.
101. Chung A, Bui L, Mills E. Adverse effects of acupuncture. Which are clinically significant? *Can Fam Physician* 2003; 49: 985-9.
102. Institute of Medicine (US) Committee on the Use of Complementary and Alternative Medicine by the American Public. Complementary and Alternative Medicine in the United States. Washington (DC): National Academies Press (US); 2005. Available from URL: <http://www.ncbi.nlm.nih.gov/books/NBK83798/> (accessed August 2015).
103. Posadzki P, Ernst E. Spinal manipulation: an update of a systematic review of systematic reviews. *N Z Med J* 2011; 124: 55-71.
104. Garza-Villarreal EA, Wilson AD, Vase L, et al. Music reduces pain and increases functional mobility in fibromyalgia. *Front Psychol* 2014; 5: 90.
105. Picard LM, Bartel LR, Gordon AS, Cepo D, Wu Q, Pink LR. Music as a sleep aid in fibromyalgia. *Pain Res Manag* 2014; 19: 97-101.
106. ACCAHC – Academic Consortium for Complimentary and Alternative Health Care. Clinicians' & Educators' Desk Reference on the Licensed Complementary & Alternative Healthcare Professions, 2 ed. Seattle, WA: ACCAHC; 2013: 265.
107. Kwon YD, Pittler MH, Ernst E. Acupuncture for peripheral joint osteoarthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2006; 45: 1331-7.
108. Lee A, Fan LT. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2009; 2: CD003281.
109. Pennick V, Liddle SD. Interventions for preventing and treating pelvic and back pain in pregnancy. *Cochrane Database Syst Rev* 2013; 8: CD001139.
110. Furlan AD, van Tulder MW, Cherkin DC, et al. Acupuncture and dry-needling for low back pain. *Cochrane Database Syst Rev* 2005; 1: CD001351.
111. Green S, Buchbinder R, Hetrick S. Acupuncture for shoulder pain. *Cochrane Database Syst Rev* 2005; 2: CD005319.
112. Casimiro L, Barnsley L, Brosseau L, et al. Acupuncture and electroacupuncture for the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev* 2005; 4: CD003788.
113. Smith CA, Hay PP, Macpherson H. Acupuncture for depression. *Cochrane Database Syst Rev* 2010; 1: CD004046.
114. Gross A, Miller J, D'Sylva J, et al. Manipulation or mobilisation for neck pain. *Cochrane Database Syst Rev* 2010; 1: CD004249.
115. Walker BF, French SD, Grant W, Green S. Combined chiropractic interventions for low-back pain. *Cochrane Database Syst Rev* 2010; 4: CD005427.
116. Lee SH, Kim JY, Yeo S, Kim SH, Lim S. Meta-analysis of massage therapy on cancer pain. *Integr Cancer Ther* 2015; 14: 297-304.

117. Yuan SL, Matsutani LA, Marques AP. Effectiveness of different styles of massage therapy in fibromyalgia: a systematic review and meta-analysis. *Man Ther* 2015; 20: 257-64.
118. Patel KC, Gross A, Graham N, et al. Massage for mechanical neck disorders. *Cochrane Database Syst Rev* 2012; 9: CD004871.
119. Loew LM, Brosseau L, Tugwell P, et al. Deep transverse friction massage for treating lateral elbow or lateral knee tendinitis. *Cochrane Database Syst Rev* 2014; 11: CD003528.
120. Bowker E, Dorstyn D. Hypnotherapy for disability-related pain: a meta-analysis. *J Health Psychol* 2014. DOI:10.1177/1359105314530452.
121. Kekecs Z, Nagy T, Varga K. The effectiveness of suggestive techniques in reducing postoperative side effects: a meta-analysis of randomized controlled trials. *Anesth Analg* 2014; 119: 1407-19.
122. Madden K, Middleton P, Cyna AM, Matthewson M, Jones L. Hypnosis for pain management during labour and childbirth. *Cochrane Database Syst Rev* 2012; 11: CD009356.
123. Theadom A, Cropley M, Smith HE, Feigin VL, McPherson K. Mind and body therapy for fibromyalgia. *Cochrane Database Syst Rev* 2015; 4: CD001980.
124. Marc I, Toureche N, Ernst E, et al. Mind-body interventions during pregnancy for preventing or treating women's anxiety. *Cochrane Database Syst Rev* 2011; 7: CD007559.
125. Chiesa A, Serretti A. Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *J Altern Complement Med* 2011; 17: 83-93.
126. So PS, Jiang Y, Qin Y. Touch therapies for pain relief in adults. *Cochrane Database Syst Rev* 2008; 4: CD006535.
127. Han A, Robinson V, Judd M, Taixiang W, Wells G, Tugwell P. Tai chi for treating rheumatoid arthritis. *Cochrane Database Syst Rev* 2004; 3: CD004849.
128. Cramer H, Lauche R, Haller H, Dobos G. A systematic review and meta-analysis of yoga for low back pain. *Clin J Pain* 2013; 29: 450-60.
129. Crow EM, Jeannot E, Trehwela A. Effectiveness of Iyengar yoga in treating spinal (back and neck) pain: a systematic review. *Int J Yoga* 2015; 8: 3-14.
130. Hemila H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev* 2013; 1: CD000980.
131. Chen S, Roffey DM, Dion CA, Arab A, Wai EK. Effect of perioperative vitamin C supplementation on postoperative pain and the incidence of chronic regional pain syndrome: a systematic review and meta-analysis. *Clin J Pain* 2015. DOI:10.1097/AJP.0000000000000218.
132. Abe A, Kaye AD, Gritsenko K, Urman RD, Kaye AM. Perioperative analgesia and the effects of dietary supplements. *Best Pract Res Clin Anaesthesiol* 2014; 28: 183-9.
133. Witteveen JE, van Thiel S, Romijn JA, Hamdy NA. Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. *Eur J Endocrinol* 2013; 168: R45-53.
134. Avenell A, MacLennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J Clin Endocrinol Metab* 2012; 97: 614-22.
135. Myung SK, Ju W, Cho B, et al. Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2013; 346: f10.
136. Clarke MW, Burnett JR, Croft KD. Vitamin E in human health and disease. *Crit Rev Clin Lab Sci* 2008; 45: 417-50.
137. Farina N, Isaac MG, Clark AR, Rusted J, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database Syst Rev* 2012; 11: CD002854.
138. Kumar N. Neurologic presentations of nutritional deficiencies. *Neurol Clin* 2010; 28: 107-70.
139. Duggal JK, Singh M, Attri N, et al. Effect of niacin therapy on cardiovascular outcomes in patients with coronary artery disease. *J Cardiovasc Pharmacol Ther* 2010; 15: 158-66.
140. Clayton PT. B6-responsive disorders: a model of vitamin dependency. *J Inherit Metab Dis* 2006; 29: 317-26.
141. Wolff T, Witkop CT, Miller T, Syed SB. Folic acid supplementation for the prevention of neural tube defects: an update of the evidence for the US Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US). Report No.: 09-05132-EF-1 Rockville (MD) 2009.
142. Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007; 297: 2351-9.
143. Banka S, Ryan K, Thomson W, Newman WG. Pernicious anemia - genetic insights. *Autoimmun Rev* 2011; 10: 455-9.
144. Herberg S, Kesse-Guyot E, Druesne-Pecollo N, et al. Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a postintervention follow-up in the SU.VI.MAX Study. *Int J Cancer* 2010; 127: 1875-81.
145. Ziegler D, Low PA, Litchy WJ, et al. Efficacy and safety of antioxidant treatment with alpha-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. *Diabetes Care* 2011; 34: 2054-60.
146. Schulman SP, Becker LC, Kass DA, et al. L-arginine therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA* 2006; 295: 58-64.
147. Amsterdam JD, Li Y, Soeller I, Rockwell K, Mao JJ, Shults J. A randomized, double-blind, placebo-controlled trial of oral *Matricaria recutita* (chamomile) extract therapy for generalized anxiety disorder. *J Clin Psychopharmacol* 2009; 29: 378-82.
148. Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev* 2015; 1: CD005614.
149. Knudsen JF, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: case report and review of the literature and MedWatch database. *Pharmacotherapy* 2008; 28: 540-8.
150. Karsch-Volk M, Barrett B, Kiefer D, Bauer R, Ardjomand-Woelkart K, Linde K. Echinacea for preventing and treating the common cold. *Cochrane Database Syst Rev* 2014; 2: CD000530.
151. Ciocon JO, Ciocon DG, Galindo DJ. Dietary supplements in primary care. *Botanicals can affect surgical outcomes and follow-up. Geriatrics* 2004; 59: 20-4.
152. Gurley BJ, Steelman SC, Thomas SL. Multi-ingredient, caffeine-containing dietary supplements: history, safety, and efficacy. *Clin Ther* 2015; 37: 275-301.
153. Wang HP, Yang J, Qin LQ, Yang XJ. Effect of garlic on blood pressure: a meta-analysis. *J Clin Hypertens (Greenwich)* 2015; 17: 223-31.
154. Tan MS, Yu JT, Tan CC, et al. Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: a systematic review and meta-analysis. *J Alzheimers Dis* 2015; 43: 589-603.
155. Shishtar E, Stevenpiper JL, Djedovic V, et al. The effect of ginseng (the genus *panax*) on glycemic control: a systematic review and meta-analysis of randomized controlled clinical trials. *PLoS One* 2014; 9: e107391.
156. Onakpoya I, O'Sullivan J, Heneghan C, Thompson M. The effect of grapefruits (citrus paradisi) on body weight and cardiovascular risk factors: a systematic review and meta-analysis of randomized clinical trials. *Crit Rev Food Sci Nutr* 2015. DOI:10.1080/10408398.2014.901292.

157. *Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL.* An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial. *Int J Obes Relat Metab Disord* 2001; 25: 316-24.
158. *Pittler MH, Schmidt K, Ernst E.* Adverse events of herbal food supplements for body weight reduction: systematic review. *Obes Rev* 2005; 6: 93-111.
159. *Sarris J, Stough C, Bousman CA, et al.* Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. *J Clin Psychopharmacol* 2013; 33: 643-8.
160. *Hansen MV, Halladin NL, Rosenberg J, Gogenur I, Moller AM.* Melatonin for pre- and postoperative anxiety in adults. *Cochrane Database Syst Rev* 2015; 4: CD009861.
161. *Naguib M, Samarkandi AH.* The comparative dose-response effects of melatonin and midazolam for premedication of adult patients: a double-blinded, placebo-controlled study. *Anesth Analg* 2000; 91: 473-9.
162. *Sydenham E, Dangour AD, Lim WS.* Omega 3 fatty acid for the prevention of cognitive decline and dementia. *Cochrane Database Syst Rev* 2012; 6: CD005379.
163. *Hooper L, Thompson RL, Harrison RA, et al.* Omega 3 fatty acids for prevention and treatment of cardiovascular disease. *Cochrane Database Syst Rev* 2004; 4: CD003177.
164. *Hao Q, Dong BR, Wu T.* Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev* 2015; 2: CD006895.
165. *Huang J, Frohlich J, Ignaszewski AP.* The impact of dietary changes and dietary supplements on lipid profile. *Can J Cardiol* 2011; 27: 488-505.
166. *Chen CH, Uang YS, Wang ST, Yang JC, Lin CJ.* Interaction between red yeast rice and CYP450 enzymes/P-glycoprotein and its implication for the clinical pharmacokinetics of lovastatin. *Evid Based Complement Alternat Med* 2012; 2012: 127043.
167. *Wilt T, Ishani A, Mac Donald R.* *Serenoa repens* for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2002; 3: CD001423.
168. *Linde K, Berner MM, Kriston L.* St John's wort for major depression. *Cochrane Database Syst Rev* 2008; 4: CD000448.
169. *Bent S, Padula A, Moore D, Patterson M, Mehling W.* Valerian for sleep: a systematic review and meta-analysis. *Am J Med* 2006; 119: 1005-12.
170. *Vogt HJ, Brandl P, Kockott G, et al.* Double-blind, placebo-controlled safety and efficacy trial with yohimbine hydrochloride in the treatment of nonorganic erectile dysfunction. *Int J Impot Res* 1997; 9: 155-61.