Complementary medicines in mental health

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The use of complementary medicines for mental health problems generates wide public interest. Patients, particularly when suffering from chronic mental health problems such as anxiety and depression, may use complementary medicines for a variety of reasons. Some may feel that a complementary approach is more “integrative” balancing mind and body; others may wish to gain control of their mental health problems. Again others may have been disappointed by conventional treatments.¹ With the ubiquitous availability of knowledge in today's high tech world, patients are increasingly well informed about treatment options. They may even be more knowledgeable about complementary medicines than clinicians whose experience in this area of practice is usually quite limited. Indeed, current professional regulations may make it extremely difficult for doctors to practise complementary medicine. Very rarely conventional treatment options, which a clinician is professionally bound to give preference, cannot be identified. Pharmacological complementary medicines are not subject to the same strict licensing requirements as conventional medicines, and commonly complementary remedies are just registered as food supplements rather than as medicinal substances.²

RANGE OF COMPLEMENTARY MEDICINES

The range of complementary medicines is huge. Pharmacological options include herbal medicines and food supplements. These are further reviewed in this article in regard to the most common psychiatric problems encountered. Countless non-pharmacological options also exist, including acupuncture, transcutaneous electric nerve stimulation (TENS), aromatherapy, homeopathy, yoga, biofeedback, relaxation, meditation, hypnosis, reiki/therapeutic touch and reflexology. However, a review of all treatments would be beyond the scope of this review.

EFFECTIVENESS

Evaluating the effectiveness of complementary medicines can be a daunting task. Perceived effectiveness may originate from anthropological sources describing the use of folk remedies over hundreds and sometimes even thousands of years. Many remedies have percolated this way, but systematically derived clinical evidence often remains limited (table 1). Regarding mental health problems, most of the evidence is available for remedies used for depression, anxiety and insomnia.

The most promising complementary medicines for the treatment of depression are St John's wort (*Hypericum perforatum*)^{3,4} and S-adenosylmethionine (SAME) the latter though being of considerable cost.⁵⁻⁷ N-3 (omega-3) fatty acids also seem to improve depressive symptoms in uni- and bipolar depression, but the evidence is less stringent and conclusive.⁸⁻¹⁰ The four other remedies identified in this category were L-tryptophan/5-hydroxytryptophan, folic acid, inositol and selenium. For these, the evidence was too limited to draw firm conclusions.

In the category of complementary anxiolytics and sedatives, valerian (*Valeriana officinalis*) scored best for the treatment of insomnia¹¹⁻¹³ and kava kava (*Piper methysticum*) best for the treatment of anxiety.¹⁴ However, the evidence concerning valerian is subject to substantial publication bias.¹¹ Kava kava has voluntarily been withdrawn in several countries due to concerns over liver toxicity.¹ The other remedies in this category include passion flower (*Passiflora incarnata*), chamomile (*Matricaria recutita*), lemon balm (*Melissa officinalis*), hops (*Humulus lupulus*), oats (*Avena sativa*), lavender (*Lavendula angustifolia*), star flower (*Borago officinalis*) melatonin or Bach flower remedies. For all those, the evidence was either preliminary, inconclusive or absent.

Complementary treatment options for psychotic disorders are extremely limited. Rauwolfia (*Rauwolfia serpentina*) has been traditionally used, and evidence for its effectiveness emerged around 1950. However, the potential for serious side effects most likely prevented its further systematic clinical application. N-3 fatty

acids have been used as augmentation therapy, but the results remain inconclusive. For the treatment of tardive dyskinesia, two antioxidants, vitamin E and melatonin, have been proposed. Again, their effectiveness has not been demonstrated consistently. N-fatty acids have failed to show any effect so far, and it is unclear whether this route will be explored further.

PROOF OF PRINCIPLE AND PHARMACODYNAMICS

Screening complementary medicines by purported mechanism of action can help to identify the most likely indications (table 1). Thus, all remedies facilitating serotonin neurotransmission may be candidates for the treatment of depression, anxiety disorders and possibly even conditions associated with craving. Substances targeting second messenger systems may stabilise mood. GABAergic substances may alleviate anxiety and promote sleep exerting a generally inhibitory effect. Dopamine-depleting agents or antagonists can be expected to have some antipsychotic properties. Finally, antioxidants are used for the treatment of tardive dyskinesia on the assumption that some neural damage is mediated through oxidative stress.

As psychiatric disorders can rarely be explained by one specified pathophysiological mechanism, complementary remedies are unlikely to outperform conventional medicines unless they target a previously unidentified mechanism of action. Complementary medicines must be highly specific to match the effect of conventional medicines. In clinical medicine, though, effectiveness is not an absolute measure but needs to be traded off against potentially adverse effects. Obviously, when different agents are combined in one remedy, it may become extremely difficult to attribute a specific effect to a particular component. For instance, valerian preparations are commonly offered in combination with hops. This issue is further complicated when non-standardised remedies are used or when standardisation is based on an ingredient known not to be effective. St John's wort is the best-known example, being customarily standardised on hypericin, which is known to contribute little to its mechanism of action. Currently, the most likely effective ingredient seems to be hyperperforin.^{3,4}

ADVERSE EVENTS

Adverse events and potentially significant drug interactions can be derived from the

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Table 1 Evidence for pharmacological complementary medicines

Remedy	Effectiveness at RCT/meta-analysis (META) level in placebo (PLB) or equivalence (EQU) studies	Receptor targets/mechanism of action	Selected safety concerns
<i>Affective disorders</i>			
St John's wort	META PLB (n = 26): marginally effective in major depression	5HT	CYP 3A4 and p-glycoprotein induction may lead to significant pharmacological interactions, serotonergic side effects including serotonin syndrome and induction of mania possible
	META EQU (n = 14): effective (3)	GABA	
	META PLB (n = 18): trend towards reduction in effect size in meta-analysis, effect size inversely associated with sample size (4)	MAO inhibition	
S-Adenosyl-methionine (SAMe)	META PLB (n = 6) EQU (n = 7) and RCTs EQU (n = 2): effective in major depression (5,6,7)	Facilitates monoamine synthesis (5HT, NA, DA)	Serotonergic side effects as above
n-3 fatty acids	RCT: no effect on mild to moderate depression (8)	Modification of 2nd messenger systems	Toxicity possible if combined with other vitamin A preparations
	META PLB (n = 10): improves depressive symptoms in patients with clearly defined depression or bipolar affective disorder. Results heterogenous and subject to publication bias. Role of EPA and DHA requires further evaluation. High-dose EPA more effective? (9)		
	META PLB (n = 8) improves depression in patients with bipolar or unipolar depression either as augmentation or monotherapy. Ceiling effect of 1 g for EPA? (10)		
L-Tryptophan, 5-hydroxy-tryptophan	Preliminary	5HT	Serotonergic side effects as above
Folic acid	Preliminary re augmentation strategy	Precursor to SAMe	Association with eosinophilic myalgic syndrome remains unclear
Inositol	Inconclusive re treatment or augmentation strategy	Modification of 2nd messenger systems	Caution in patients with cancer Induction of mania?
Selenium	None available	Antioxidant ↑ T4→T3 conversion	Carbamazepine, valproate and lithium ↓ inositol Narrow therapeutic index
<i>Anxiety and related disorders and insomnia</i>			
Valerian	META PLB (n = 6) and RCTs EQU (n = 2): improves insomnia (11–13)	GABA	Liver toxicity may depend on extract (valepotriates)
	Anxiety: insufficient evidence available		
Passion flower	Preliminary for reduction in anxiety	GABA	Some extracts contain cyanogenic components
Chamomile	None available	GABA	
Kava kava	META PLB (n = 7): effective in the reduction in anxiety (14)	GABA	Significant liver toxicity possible (may be extract-dependent)
		DA antagonist	
Star flower/borage	None available	Unclear	May ↓ seizure threshold, potentially liver toxic
Lemon balm	None available	GABA?	
Hops	No single-component trials available	Cholinergic?	
Oats	None available	Unclear	
Lavender	None available	5HT? (a source of tryptophan)	
		Unclear, also purported to have antidepressive and pain-reducing properties	
Melatonin (N-acetyl-S-methoxy tryptamine)	Inconclusive	Regulates circadian rhythm	
		GABA	
Bach flower remedies	Not effective	Unclear	
<i>Psychosis and schizophrenia</i>			
Rauwolfia	Evidence dating back to 1950s/60s. No current evidence available.	Facilitates degradation of monoamines	Depression, cardiac effects
n-3 fatty acids	Inconclusive	Cf above	Cf above
Tardive dyskinesia			
Vitamin E	Inconclusive	Antioxidant	May ↑ all-cause mortality
Melatonin	Inconclusive	Antioxidant	
n-3 fatty acids	Not effective	Cf above	Cf above

Updated and collated from references 1 and 2.

CYP, cytochrome P 450; DA, dopamine; GABA, gamma-aminobutyric acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EQU, equivalence studies; 5HT, 5-hydroxytryptophan (serotonin); MAO, monoaminooxidase; META, meta-analysis; n-3 fatty acids, omega-3 fatty acids; PLB, placebo controlled studies; RCT, randomised controlled trial.

pharmacodynamic and pharmacokinetic properties of a remedy. The method of extraction is a potential further determinant of adverse events. Thus, it comes as no surprise that all serotonergic remedies may potentially increase the risk of (hypo-) manic episodes in predisposed individuals just like conventional serotonergic medicines (table 1). Equally, they could increase the risk of serotonin syndrome if combined with other serotonergic agents. Likewise, all sedatives acting on the GABAergic system may potentiate sedation if combined with conventional sedatives. Knowledge of pharmacokinetic properties can be used to predict drug interactions. For instance, many complementary medicines interfere with the hepatic cytochrome enzyme (CYP) system. It is not always clear, though, whether interactions found in vitro translate into clinically significant effects. Prescribers are advised always to check the latest evidence, since the knowledge base is evolving rapidly. The most commonly cited clinically significant interaction is the induction of CYP 3A4 by St John's wort. In consequence, the efficacy of many drugs including oral contraceptives, ketokonazole and ciclosporin may be compromised.¹⁵ Advice regarding St John's wort can be modelled on carbamazepine, another potent CYP 3A4 inducer. Finally, the extraction method can determine whether a remedy becomes potentially toxic. Ethanol extraction can be used to eliminate potentially toxic volatile substances such as the valepotriates in some valeriana species.² However, ethanol extraction may also be harmful in certain circumstances. For example, commercially available kava kava extracted in ethanol or acetone is associated with a high risk of liver toxicity, most likely due to depletion of liver-protective glutathione in these extracts.¹⁶

TRADITIONAL CHINESE MEDICINE AND AYURVEDA

From a Western medical standpoint, Traditional Chinese medicine (TCM) and Ayurveda are frequently defined as complementary medicines. However, this seems to be presumptuous, since both systems have evolved over thousands of years and are used widely and independently in many parts of the world. Whereas the Western medical system is essentially disease-oriented, TCM and Ayurveda are symptom-orientated. This allows the interpretation of the presenting problems in light of the patient's individual context.^{17 18} Thus, whilst the Western medical system largely retains the lead in the treatment of acute diseases

including acute exacerbations of chronic conditions, TCM and Ayurveda may at times be better equipped to deal with chronic conditions. They may be particularly relevant when patients have to learn to come to terms with their condition over a long period of time.¹⁸ It has to be borne in mind, though, that grouping of certain symptoms may lead to illness formulations and syndromes quite different from the Western diagnostic conventions.^{17 18}

Both TCM and Ayurveda use combination therapies rather than relying on one single agent to tackle a specific disease. TCM particularly applies formulae combining different substances which are finely balanced with respect to synergistic effects and toxicity-limiting properties.¹⁷ Unfortunately, the highly individualised approach coupled with a preference for substance combinations can make it extremely difficult to derive reproducible results which can be replicated and pooled in meta-analysis. Drug safety can also be of concern if dosages are unknown or substances are added to the formula to counteract the toxicity of another ingredient. Finding the right formula requires considerable experience and extensive study. Consequently, this approach does not yield itself easily to mass-replication. More recently, however, whole industries have developed dedicated at identifying and testing promising individual agents, thereby trying to integrate TCM and Ayurvedic medicine with the Western medical approach.¹⁹

CAN COMPLEMENTARY MEDICINE EVER BE EVIDENCE-BASED?

Theoretically, there is no reason why complementary medicines cannot be evaluated in the same way as conventional medicines. However, as outlined above, due to the variability of remedy formulations and dosing schemes, combination treatments as well as different diagnostic approaches studies in this area are usually highly heterogeneous. In consequence, meta-analyses may not compare like with like. For instance, variability of extracts, standardisation and dosing are still rarely considered in systematic reviews. Combining trials based on different extracts may not be scientifically valid. Most studies are quite small compared with trials of conventional drugs, and publication bias may become a significant problem in meta-analysis. Remedies unfolding effects through defined mechanisms of action also found in several synthetic disease-specific drugs may have an advantage over remedies

relying on more ubiquitous mechanisms of action at a more basic molecular level. This may explain why it has been possible to identify St John's wort as an effective antidepressant, even though there is still some uncertainty about the pharmacologically active ingredient. Recently, an intriguing situation has arisen with the emerging scepticism about the effectiveness of SSRIs.²⁰ If SSRIs were judged not to be effective, it would become difficult to conclude that St John's wort was effective citing the corresponding equivalence studies. The evidence from meta-analyses of studies comparing St John's wort to placebo is indeed weaker than the data from equivalence studies.^{3 4} Possibly, some of these difficulties are due to the use of current diagnostic criteria rather than the substances under study. Such concerns about the validity and usefulness of the current classification systems have given rise to the current development of DSM V.

FROM BENCH TO BEDSIDE: THE PATIENT'S PERSPECTIVE

Whereas the evidence-based approach basically represents a public health perspective, patients will naturally take an individual approach. Clinicians discussing the advantages and disadvantages of complementary medicines must apply a statistically derived knowledge base to a patient's individual experience. Obviously it is not possible to discuss treatments of any kind in absolute terms; one can only derive likelihoods. Since it is not possible to infer from summary statistics to an individual, a patient—against all odds—may derive benefit or harm from a treatment, even if the majority of patients do not. The decision to embark on a certain treatment ultimately needs to be explored in terms of opportunity costs. If individuals use remedies as an alternative to established care options, they may run a risk that their condition deteriorates. Patients who have become disillusioned with their conventional therapies due to either a lack of effect or harmful side effects may not easily appreciate that they could be worse off abandoning such treatment. Clinicians will need to be aware of side effects or interactions associated with complementary medicines, identify potential health risks and discuss these with patients. Ethically, and indeed medicolegally, uncritical encouragement of potentially harmful use should be avoided. Conversely, overcautious discouragement is equally undesirable.

Box 1 Useful websites

- ▶ Department of Health: Complementary and Alternative Medicine: <http://www.dh.gov.uk/en/PublicHealth/Healthimprovement/Complementaryandalternativemedicine/index.htm>
- ▶ National Centre for Complementary Alternative Medicines/National Institute of Health: <http://nccam.nih.gov>
- ▶ Natural Medicines Comprehensive Database: <http://www.naturaldatabase.com>
- ▶ Royal College of Psychiatrists: Mental Health Information: Therapies: Complementary and Alternative Medicines 1 & 2: <http://www.rcpsych.ac.uk/mentalhealthinformation/treatments.aspx>
- ▶ RX List: Alternative medicine: <http://www.rxlist.com/script/main/art.asp?articlekey=78831>

SUMMARY: 10 QUESTIONS TO ASK WHEN READING A STUDY ON COMPLEMENTARY MEDICINES

Reading a study on complementary medicines may pose a challenge if unfamiliar with the topic. Here are some simple questions to ask yourself when you read a paper:

1. Which medical system is the study concerned with: Western medical, TCM or Ayurveda?
2. Are one or several interventions studied?
3. Concerning pharmacological interventions, what kind of agent is studied: one single substance or several substances combined?
4. Is the active ingredient of the substance under study known?
5. Which type of extract is used: alcoholic or aqueous?
6. Is the extract used standardised? If yes, against which ingredient? Is this ingredient the purportedly active substance?
7. How is the dose of the agent defined? On which ingredient is the dose based?
8. Which indication is there that a dose is in a therapeutic range, that is not too high and not low?
9. Is the sample size of the study sufficient to be able to identify an effect? Has a power calculation been conducted?

10. Have significant adverse effects been reported? Is the study sufficiently powered to do so? If not, is the potential for serious adverse effects and clinically significant drug interactions discussed in light of what is known about the remedy under study?

Competing interests: None.

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Web matters

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For even the most Luddite among you, it must now be clear that there is more to the Internet than email. The World Wide Web has become not only one of the best

available resources for health information but also a virtual couch for E-therapy. The total number of Internet users in the world has grown beyond a record number of 1.4 billion in 2008 and the usage of the Internet has seen a growth of over 300% in just 8 years from 2000.¹

Public and private health care agencies, academic institutions, voluntary organisations and members of the public are increasingly making health information available on their websites in many languages and a wide range of users across the world are accessing this information. Medical dictionaries and glossaries are also accessible through the Internet to help users understand medical terms with relative ease. Survey results of Pew Internet and American Life Project, carried out in 2004, have shown that eight out of

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