

## Complementary medicines in psychiatry

### Review of effectiveness and safety

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**Background** The use of complementary medicines in those with mental health problems is well documented. However, their effectiveness is often not established and they may be less harmless than commonly assumed.

**Aims** To review the complementary medicines routinely encountered in psychiatric practice, their effectiveness, potential adverse effects and interactions.

**Method** Electronic and manual literature search on the effectiveness and safety of psychotropic complementary medicines.

**Results** Potentially useful substances include ginkgo and hydergine as cognitive enhancers, passion flower and valerian as sedatives, St John's wort and s-adenosylmethionine as antidepressants, and selenium and folate to complement antidepressants. The evidence is less conclusive for the use of omega-3 fatty acids as augmentation treatment in schizophrenia, melatonin for tardive dyskinesia and l8-methoxyconaridine, an ibogaine derivative, for the treatment of cocaine and heroin addiction.

**Conclusions** Systematic clinical trials are needed to test promising substances. Meanwhile, those wishing to take psychotropic complementary medicines require appropriate advice.

**Declaration of interest** None.

Complementary medicines are either used as an alternative or in addition to conventional medicine (Zimmerman & Thompson, 2002). Their use by those with chronic disorders such as cancers, with their associated physical and psychological problems, is well documented (Eisenberg *et al*, 1993; Ernst & Cassileth, 1999). In psychiatric patients, estimates of their use range from 8 to 57%, with the most frequent use being in depression and anxiety. A population-based study from the USA found that 9% of respondents had anxiety attacks, 57% of whom used complementary medicines; 7% of respondents reported severe depression, with 54% of these using complementary medicines (Kessler *et al*, 2001). Another survey from the USA reported mental disorders in 14% of respondents, 21% of whom used complementary medicines (Unutzer *et al*, 2000). Usage was highest (32%) in respondents with panic disorder. In studies restricted to those with psychiatric disorders, usage ranged from 13 to 54% (Knaudt *et al*, 2001; Wang *et al*, 2001; Alderman & Kieper, 2003; Matthews *et al*, 2003). Complementary medicines are also used by those seen by liaison psychiatrists and a recent study of cancer patients showed that 25% took substances with psychoactive properties (Werneke *et al*, 2004a).

Complementary medicines can be grouped into herbal remedies, food supplements, including vitamin preparations, and other organic and inorganic substances, including omega-3 fatty acids. Some people take food supplements and vitamin preparations in high doses, often outside the safety margins recommended by the Food Standards Agency (Food Standards Agency, 2003). People with mental health problems may take complementary medicines to treat anxiety and depression or to counter side-effects of conventional treatments, for example tardive dyskinesia and weight gain. Some seek a more holistic approach to treatment, others hope that complementary

medicines have fewer or no side-effects, and many with chronic anxiety and depression understandably feel disillusioned by the apparent ineffectiveness of conventional treatment. The aim of this review is to acquaint psychiatrists with the complementary medicines routinely encountered in clinical practice, to review the evidence base for their purported effectiveness and to discuss potential adverse effects and interactions.

### METHOD

We searched the Medline and Cochrane databases for evidence of the effectiveness of complementary medicines for the treatment of psychiatric conditions. We divided the substances into different categories: cognitive enhancers, sedatives and anxiolytics, antidepressants, antipsychotics and remedies for movement disorders, and anti-addictives. Search terms included the identified substances in each category *and* EFFECTIVENESS *or* SIDE-EFFECTS *or* ADVERSE DRUG REACTION *or* INTERACTION. All recovered papers were reviewed for further relevant references. All evidence was collated and ranked as available. We also accessed web-based resources, such as the Natural Medicines Comprehensive Database (<http://www.naturaldatabase.com>), and for monographs, such as the *PDR (Physicians' Desk Reference for Herbal Medicines; Medical Economics, 2000)* for further information on the identified substances. Where available, we used reviews summarising the proposed mechanism of action and effectiveness, since presenting all the evidence in detail was beyond the scope of this paper. Whenever possible, we gave priority to meta-analyses, systematic reviews and double-blind randomised controlled trials (RCTs), but we also included other evidence such as open trials and case reports when the findings were relevant to our review. Where standardised comparative measures such as the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967) were available for meta-analyses, we reported the relevant risk ratios. Owing to the heterogeneity of the data, no attempt at meta-analysis of other trials was made. We included only studies applicable to general adult psychiatry and psychiatry of older adults. Other special patient groups and healthy volunteers were excluded, as were studies on a combination of substances with evidence available for the single substance (Fig. 1).

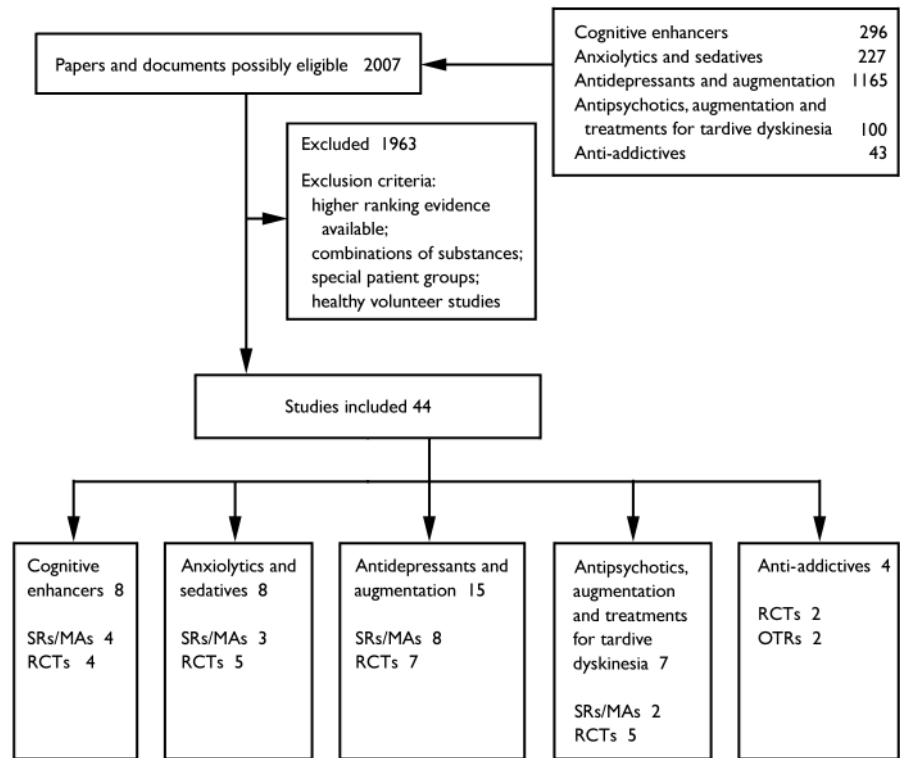
**RESULTS**

Two thousand and seven studies were identified for the 20 remedies under review for the five categories of mental health problems. The literature ranged from case reports and narrative reviews to systematic reviews including meta-analyses. For four categories, the evidence with regard to efficacy could be limited to RCTs, systematic reviews and meta-analyses. For anti-addictive substances we also considered open trials, since there was very little evidence available (Fig. 1).

**Cognitive enhancers**

Cognitive enhancers are either used in the treatment of dementia to enhance mental performance or to prevent cognitive decline in healthy people. This can be achieved by increasing choline availability in the brain, e.g. by inhibiting acetylcholinesterase. Alternative non-cholinergic neuroprotective strategies have been postulated; these include antioxidants scavenging free radicals, thereby reducing neurotoxicity, and anticoagulants increasing cerebral blood flow (Spinella, 2001). Suggested herbal cognitive enhancers include ginkgo, ginseng, hydergine, which is an ergot (*Claviceps purpurea*) derivative, and solanaceous plants, including potatoes, tomatoes and aubergines (Table 1).

Although in some individuals with Alzheimer's disease ginkgo biloba has been reported to improve cognitive performance (Birks *et al*, 2002; Kanowski & Hoerr, 2003), another trial did not show any benefit in elderly people with Alzheimer's disease of vascular type or age-associated cognitive impairment (van Dongen *et al*, 2003). Whether the effect in those with Alzheimer's disease is equivalent to that of synthetic cholinesterase inhibitors is debatable (Itil *et al*, 1998; Wettstein, 2000; Schreiter-Gasser & Gasser, 2001). Hydergine was reported to lead to significant improvement of cognitive impairment in dementia, but most studies were performed before standardised dementia criteria were agreed (Olin *et al*, 2001). The results for panax ginseng and vitamin E were inconclusive (Sano *et al*, 1997; Vogeler *et al*, 1999). Solanaceous plants may exercise strong cholinergic effects by inhibiting not only acetyl- but also butyrylcholinesterase. However, no clinical studies have been conducted to determine their effects on cognition. They may augment cocaine toxicity via the same mechanism (Krasowski *et al*, 1997).



**Fig. 1** Selection of efficacy studies. SRs, systematic reviews; MAs, meta-analyses; RCTs, randomised controlled trials; OTRs, open trials.

**Anxiolytics and sedatives**

Anxiolytics and sedatives essentially have the same underlying mechanisms of action. The stronger the agent the greater the sedative effect, leading to coma in extreme cases. Four mechanisms of action have been implicated (Spinella, 2001): (a) binding to gamma-aminobutyric acid (GABA) receptors leading to hyperpolarisation of the cell membrane through increased influx of chlorine anions; (b) inhibition of excitatory amino acids, thereby also impairing the ability to form new memories; (c) sodium channel blockade, decreasing depolarisation of the cell membrane; and (d) calcium channel blockade, decreasing the release of neurotransmitters into the synaptic cleft. Most complementary medicines prescribed for anxiolysis/sedation (e.g. kava kava, valerian, passion flower and chamomile) are GABAergic, though for some such as hops the mechanism of action remains unknown. As expected, all remedies can lead to drowsiness when taken in high doses and can potentiate the effect of synthetic sedatives (Table 2).

The most researched substance is kava kava (*Piper methysticum*), which originated from Polynesia and was traditionally used for religious rituals (Chevallier, 1996).

Kava has an anxiolytic effect that has been established in several RCTs (Pittler & Ernst, 2003). Kava has been associated with several cases of liver toxicity (Natural Medicines Database, 2004a), which has led to its voluntary withdrawal from the UK market. Valerian (*Valeriana officinalis* or *Valeriana edulis*) is a sedative believed to have been known to Galen and Dioscorides, which has maintained its importance throughout the centuries (Spinella, 2001). In 1845, Coffin described it as 'an excellent sedative...predisposing the mind to quietness and the body to sleep'. Valerian may have comparable efficacy to oxazepam (Dorn, 2000; Ziegler *et al*, 2002). However, a systematic review on the effectiveness of valerian in insomnia produced inconclusive results (Stevinson & Ernst, 2000).

Passion flower (*Passiflora incarnata*) contains chrysin, a partial agonist to benzodiazepine receptors. One study comparing passion flower with oxazepam found both to be equally effective (Akhondzadeh *et al*, 2001a); more trials are needed to confirm the effect. No data are available on chamomile and hops. Chamomile (*Chamaemelum nobile* or *Matricaria recutita*) contains apigenin which binds to benzodiazepine receptors (Viola *et al*, 1995). The mechanism of action for hops

**Table 1** Cognitive enhancers

Substance	Postulated mechanism of action	Effectiveness	Side-effects	Potential drug interactions
Ginkgo	Antioxidant: destroying free radicals implicated in cell damage (Oken <i>et al.</i> , 1998; Tabet <i>et al.</i> , 2000); ↑ cerebral blood flow through platelet activation factor inhibition and nitric oxide pathways (Macleanman <i>et al.</i> , 2002; Ahlemeyer & Krieglstein, 2003); cholinergic effects (Tang <i>et al.</i> , 2002)	Possible improvement of cognitive function, activities of daily living and mood in those with Alzheimer's disease or other cognitive decline, but recent results inconsistent (Birks <i>et al.</i> , 2002; Kanowski & Hoerr, 2003; van Dongen <i>et al.</i> , 2003)	↑ Bleeding time. Case reports of intracerebral haemorrhage (Matthews, 1998; Benjamin <i>et al.</i> , 2001); possibly adverse effects on male and female fertility (Ondrizek <i>et al.</i> , 1999)	Antithrombolytic agents (Medical Economics, 2000)
Panax ginseng	Interference with platelet aggregation and coagulation (Medical Economics, 2000); neuroprotection through nicotinic activity (Lewis <i>et al.</i> , 1999), antioxidant effects (Lee <i>et al.</i> , 1998)	Improvement of mental arithmetic and abstraction; age-delaying properties unproven (Vogeler <i>et al.</i> , 1999); one recent trial reporting marginal improvement in Mini-Mental State Examination and improvement in memory tests (Tian <i>et al.</i> , 2003)	Insomnia, mania, hyper- and hypotension, ↑ vaginal bleeding (Medical Economics, 2000)	Insulin and oral hyperglycaemics, anti-thrombolytic agents, MAOIs (phenelzine), loop diuretics (Medical Economics, 2000)
Hydergine (ergoloid)	↑ Cholinergic activity (Le Poncin-Lafitte <i>et al.</i> , 1985); reversal of age-related decline of choline acetyltransferase (Dravid, 1983) and muscarinic receptors (Armenta <i>et al.</i> , 1989); modulation of all monoaminergic neurotransmitter systems (Markstein, 1985)	Behavioural but no cognitive improvement with combination of vitamin E with selegiline; possibly delay of residential care using vitamin E (Sano <i>et al.</i> , 1997)	Cholinergic and monoaminergic side-effects possible; risk of psychotic recurrence	Serotonergic antidepressants, cholinesterase inhibitors
Vitamin E	Antioxidant (Tabet <i>et al.</i> , 2000)	Significant improvement in dementia patients; hydergine was more effective at higher doses and in younger patients (Olin <i>et al.</i> , 2001)	High doses: ↑ risk of bleeding due to antagonism of vitamin K-dependent clotting factors (Liede <i>et al.</i> , 1998)	Anticoagulants including aspirin, clopidogrel, warfarin (Corrigan, 1982; Liede <i>et al.</i> , 1998) and herbal anticoagulants such as ginkgo, garlic and ginseng; possible prevention of nitrate tolerance (Watanabe <i>et al.</i> , 1997); possible ↑ effect of sildenafil and related phosphodiesterase-5 inhibitors
Solanaceous plants	Inhibit acetylcholinesterase and butyrylcholinesterase (Krasowski <i>et al.</i> , 1997)	No study available	Cholinergic poisoning through dietary intake possible (Krasowski <i>et al.</i> , 1997)	Prolonged action of pancuronium, other myorelaxants and cocaine through ↑ inhibition of butyrylcholinesterase (Krasowski <i>et al.</i> , 1997)

MAOIs, monoamine oxidase inhibitors.

(*Humulus lupulus*) remains unclear. Bach flower remedies are a combination of 38 flowers and seem to have no effect (Ernst, 2002). Melatonin extracted from the pineal gland may improve sleep in those with delayed sleep phase disorder, but no benefit has been shown in the treatment of primary sleep disorder (MacMahon *et al*, 2005). It may also improve initial sleep quality in older adults with insomnia (Olde Rikkert & Rigaud, 2001), but its role as a treatment for insomnia in those with Alzheimer's disease remains disputed (Cardinali *et al*, 2002; Singer *et al*, 2003).

### Antidepressants and augmentation therapy

All known synthetic antidepressants act via the enhancement of serotonergic and noradrenergic neurotransmission. Most complementary antidepressants are thought to work through the same pathways (Tables 3 and 4). The mechanism of action for selenium is not clear but does seem to be different. Its antioxidant qualities may reduce nerve cell damage (Benton, 2002), and it is also known to facilitate conversion from thyroxine (T4) to thyronine (T3); T3 substitution is one possible means of augmentation of antidepressants in conventional psychiatry. There are no clinical studies but low selenium levels have been associated with depression, anxiety and hostility (Hawkes & Hornbostel, 1996), and high dietary intake or supplementation has been associated with mood improvement. The apparent therapeutic effect may be dose-dependent (Benton & Cook, 1991; Benton, 2002). Like lithium, there may be a narrow therapeutic index. A recent report by the Food Standards Agency (2003) reduced the recommended limits of safe daily intake. Trials may be most promising in those with a low baseline selenium level.

The most robust clinical data are available for St John's wort (*Hypericum perforatum*). These have been extensively reviewed in meta-analyses (Linde *et al*, 1996; Williams *et al*, 2000; Whiskey *et al*, 2001; Roder *et al*, 2004; Werneke *et al*, 2004b; Linde *et al*, 2005; Table 3) which have found a decrease in effect size over time when tested against placebo. The more recent meta-analyses mostly suggest that the effectiveness of St John's wort is limited to mild depression, and more homogenous studies targeting patients with mild depression are required (Roder *et al*, 2004; Werneke *et al*, 2004b; Linde *et al*, 2005).

However, four of these meta-analyses have demonstrated equivalence to standard antidepressants (Linde *et al*, 1996; Whiskey *et al*, 2001; Roder *et al*, 2004; Linde *et al*, 2005). One recent trial using high doses (up to 1800 mg) of St John's wort reported equivalence to paroxetine in those with moderate or severe depression (Szegedi *et al*, 2005). Hyperforin, which inhibits the reuptake of monoamines, is thought to be the most likely active component (Chatterjee *et al*, 1998; Müller *et al*, 1998). Thus, the use of extracts with maximum hyperforin content should be examined more systematically (Werneke *et al*, 2004b).

Folate and S-adenosylmethionine are in the same biochemical pathway, with folate being required to synthesise methionine, the direct precursor of S-adenosylmethionine, from homocysteine. S-adenosylmethionine facilitates many methylation reactions required for the synthesis of many neurotransmitters (Bottiglieri *et al*, 2000; Morris *et al*, 2003). Thus, those with high levels of homocysteine may be more likely to become depressed, or possibly less likely to respond to antidepressant treatment. Interestingly, hypothyroidism can lead to an increase in homocysteine levels (Roberts & Ladenson, 2004) and this may contribute to the associated depression. In clinical studies, folate has been reported to be effective only when added to antidepressant therapy (Taylor *et al*, 2004).

Parenteral S-adenosylmethionine has been reported to be superior to placebo (Bressa, 1994), and equivalence to imipramine has been demonstrated in two RCTs (Delle Chiaie *et al*, 2002; Pancheri *et al*, 2002). The onset of action may be more rapid (Fava *et al*, 1995). Oral S-adenosylmethionine may require doses four times as high as the parenteral formulation (Delle Chiaie *et al*, 2002). Finally, omega-3 fatty acids are known to stabilise membranes and to facilitate monoaminergic, serotonergic and cholinergic neurotransmission (Haag, 2003) but their antidepressant effect has not been convincingly demonstrated in clinical studies (Marangell *et al*, 2003; Su *et al*, 2003). Omega-3 fatty acids are possibly effective when added to lithium in the treatment of bipolar affective disorder (Bowden, 2001; Table 4).

### Antipsychotics, augmentation and treatment of tardive dyskinesia

Only two complementary medicines have been suggested for the treatment of

psychosis. *Rauwolfia* (*Rauwolfia serpentina*) extracts were traditionally used before synthetic antipsychotics became widely available, several alkaloid derivatives, including reserpine, being introduced in the 1950s (Malamud *et al*, 1957). *Rauwolfia* originates from India and was mentioned in Ayurvedic medicine around 700 BC (Chevallier, 1996). It blocks vesicular storage of monoamines, allowing them to be more easily degraded by monoamine oxidases in the cytoplasm. As a consequence, the amount of neurotransmitter available on depolarisation of the cell membrane is reduced (Spinella, 2001), which may lead to a reduction in dopamine and the resolution of psychotic symptoms. However, serotonin and noradrenaline will also be less available, which explains why reserpine readily precipitates depression. An alternative strategy is the augmentation of antipsychotic treatment with omega-3 fatty acids, but the results of clinical trials remain inconclusive (Joy *et al*, 2003; Table 5).

Attempts have been made to treat tardive dyskinesia with vitamin E. This treatment strategy relies on the assumption that tardive dyskinesia not only results from dopamine receptor supersensitivity but is also related to the oxidative tissue damage of antipsychotic drugs (Shamir *et al*, 2001; Lohr *et al*, 2003). Meta-analysis of ten small trials has indicated that vitamin E protects against deterioration of tardive dyskinesia (Soares & McGrath, 2001); one recent trial has reported improvement (Zhang *et al*, 2004). A far more powerful antioxidant than vitamin E is melatonin, which attenuates the dopaminergic activity in the striatum as well as the release of dopamine from the hypothalamus (Shamir *et al*, 2001; Lohr *et al*, 2003). However, as with omega-3 fatty acids, clinical trials have been inconclusive (Shamir *et al*, 2000, 2001), and larger trials are required to test its therapeutic effectiveness (Table 5).

### Anti-addictives

Although there are many addictive plants, few have been identified as having the potential to counter addiction (Table 6). Such may be ibogaine, which is derived from the West African shrub *Tabernanthe iboga*. It has hallucinogenic properties and is traditionally used in religious ceremonies and initiation rites, but has also been claimed to counter nicotine, cocaine and opiate addiction, via blockade of dopamine release in the nucleus accumbens (and the dopamine response in general) in chronic

**Table 2** Anxiolytics and sedatives

Substance	Postulated mechanism of action	Effectiveness	Side-effects	Potential drug interactions
Valerian	GABAergic effects (Houghton, 1999)	Inconclusive evidence. May improve sleep latency and slow wave sleep (Stevinson & Ernst, 2000); no more effective than placebo in patients with acute sleep problems (Diaper & Hindmarch, 2004); comparable efficacy to oxazepam in patients with non-organic insomnia (Dorn, 2000; Ziegler <i>et al.</i> , 2002)	Cognitive impairment and drowsiness; case reports of hepatotoxicity (Klepser & Klepser, 1999)	↑ Effect of sedatives, CYP4A inhibitor (see Table 3)
Passion flower	Partial agonist to benzodiazepine receptors (Wolfman <i>et al.</i> , 1994)	Comparable efficacy to oxazepam in treatment of general anxiety disorder (Akhoondzadeh <i>et al.</i> , 2001a)	Case report of severe nausea, vomiting, drowsiness, prolonged QTc and episodes of non-sustained ventricular tachycardia (Fisher <i>et al.</i> , 2000); may contain cyanogenic glycosides (Jaroszewski <i>et al.</i> , 2002)	Anticoagulants, ↑ effect of sedatives, CYP3A4 inhibitor (see Table 3)
Kava	GABAergic effects (Jusoff <i>et al.</i> , 1994; Dinh <i>et al.</i> , 2001), D <sub>2</sub> antagonist (Schelosky <i>et al.</i> , 1995)	Meta-analysis of nine studies showed significant reduction of HRSA score compared with placebo (weighted mean difference=5.0, 95 CI 1.1–8.8; P=0.01) (Pittler & Ernst, 2003); one trial report of equivalence to buspirone and opipramole (Boerner <i>et al.</i> , 2003); one trial report of improvement of sleep in patients with anxiety disorder (Lehrl, 2004)	At least 68 cases of liver toxicity (NMCD, 2004a); one case report of movement disorder (Meseguer <i>et al.</i> , 2002)	CYP1A2, 2C9, 2C19, 2D6, 3A4 and 4A9/11 inhibition (Mathews <i>et al.</i> , 2002)
Chamomile	Binds to benzodiazepine receptors (Viola <i>et al.</i> , 1995)	No study available	Contains coumarins: increase of bleeding time	Anticoagulants, ↑ effect of sedatives, CYP3A4 inhibitor (see Table 3)
Hops	Possibly oestrogenic mechanism (Medical Economics, 2000)	Comparable efficacy of a hops–valerian preparation to bromazepam in the treatment of sleep disturbance (Schmitz & Jackel, 1998); no studies on hops alone available	None reported	↑ Effect of sedatives
Bach flower remedies	38 herbs with postulated differential effects, 5 herbs in rescue remedies	Not effective (Ernst, 2002)	Unclear	Unclear
Melatonin (N-acetyl-5-methoxy-tryptamine)	Regulation of the body's circadian rhythm, endocrine secretions and sleep pattern; ↑ GABA binding (Munoz-Hoyos <i>et al.</i> , 1998)	Possibly effective in delayed sleep phase disorder; no clear-cut effect in primary insomnia (MacMahon <i>et al.</i> , 2005); inconclusive evidence for effectiveness as insomnia treatment in Alzheimer's disease (Cardinali <i>et al.</i> , 2002; Singer <i>et al.</i> , 2003); may improve initial sleep quality in older adults with insomnia (Olde Rikkert & Rigaud, 2001)	Daytime sleepiness (Herxheimer & Petrie, 2003); ↑ depressive mood (Carman <i>et al.</i> , 1976)	Anticoagulants, ↑ effect of sedatives (Herxheimer & Petrie, 2003)

GABA, gamma-aminobutyric acid; CYP3A4, cytochrome P3A4; HRSA, Hamilton Rating Scale for Anxiety; NMCD, Natural Medicines Comprehensive Database.

**Table 3** Antidepressants and augmentation: St John's wort

Postulated mechanism of action	Effectiveness <sup>1</sup>	Side-effects	Potential drug interactions
MAOI inhibition and GABAergic activity (Cott, 1997), monoamine reuptake (Perovic & Müller, 1995; Neary & Bu, 1999), upregulation of 5HT <sub>1A</sub> and 5HT <sub>2A</sub> receptors (Teufel-Mayer & Gleitz, 1997); modulation of cytokine production (Thiele et al, 1994)	Six meta-analyses v. placebo using HRSD scores with trend toward reduced effect size Linde et al, 1996: OR=2.67 (1.78–4.01); Williams et al, 2000: RR=1.9 (1.2–2.8); Whiskey et al, 2001: RR=1.98 (1.49–2.62); Werneke et al, 2004b: RR=1.73 (1.40–2.14); Roder et al, 2004: RR=1.51 (1.28–1.75) <sup>2</sup> ; Linde et al, 2005: major depression – RR=2.06 (1.65–2.59) (smaller trials), 1.15 (1.02–1.29) (larger trials), not restricted to major depression – RR=6.13 (3.63–10.38) (smaller trials), 1.71 (1.40–2.09) (larger trials), Linde et al, 2005: all studies, <sup>3</sup> RR=1.71 (1.40–2.09) Four meta-analyses v. standard antidepressants Linde et al, 1996: OR=1.10 (0.93–1.31) compared with TCAs or maprotiline; Whiskey et al, 2001: RR=1.00 (0.93–1.09) compared with TCAs, maprotiline or SSRIs; Roder et al, 2004: RR=0.96 (0.85–1.08) compared with TCAs, maprotiline or SSRIs and RR=0.85 (0.75–0.97) in mild or moderate depression; Linde et al, 2005: RR=1.01 (0.93–1.10) for all trials, RR=1.03 (0.93–1.14) compared with TCAs or maprotiline, RR=0.98 (0.85–1.12) compared with SSRIs RCT, Szegedi et al, 2005: RR=1.18 (0.98–1.42) compared with paroxetine <sup>4</sup>	Similar to SSRIs, photosensitivity (Whiskey et al, 2001)	Serotonergic antidepressants: CYP3A4, IA2 and 2C9 induction: HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, anti-warfarin, cyclosporin, oral contraceptives, anti-convulsants, digoxin and theophylline (Committee on Safety of Medicines & Medicines Control Agency, 2000)

1. 95% CI in parentheses.

2. Calculated by changing the baseline to enable comparison with the other meta-analyses: original RR=0.66 (0.57–0.88).

3. Calculated from all studies (random effect size) and not included in original paper; subgroup analysis reports fixed effect size.

4. Calculated from the reported figures of treatment responses, not included in original paper.

MAOI, monoamine oxidase inhibitors; GABA, gamma-aminobutyric acid; 5HT, 5-hydroxytryptamine; HRSD, Hamilton Rating Scale for Depression; OR, odds ratio; RR, risk ratio; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; RCT, randomised controlled trial; CYP3A4, cytochrome P3A4.

**Table 4** Antidepressants and augmentation: supplements

Substance	Postulated mechanism of action	Effectiveness	Side-effects	Potential drug interactions
Selenium	Antioxidant; brain had a preferential affinity for selenium (Benton, 2002). Selenium facilitates the conversion of T4 into T3 (Sher, 2001)	No study available	Acute toxicity: nausea causes vomiting, nail changes, irritability and weight loss; chronic toxicity: resembles arsenic toxicity (Werneke, 2003)	Potential ↓ effect of simvastatin/niacin combination used with a selenium/beta-carotene/vitamins C and E supplement (Brown <i>et al</i> , 2001). Other statins may also be affected (NMCD, 2004c)
Folic acid	Cofactor in neurotransmitter synthesis; methylation homocysteine to methionine, the immediate precursor of S-adenosyl-methionine (Bottiglieri <i>et al</i> , 2000; Morris <i>et al</i> , 2003)	Two pooled studies using HRSD and addition of folic acid to antidepressants RR=0.47 (0.24–0.92); effect possibly dose-dependent; folic acid alone not effective (Taylor <i>et al</i> , 2004)	Caution in pernicious anaemia: not to be given without vitamin B <sub>12</sub> ; large doses can lead to agitation, insomnia, confusion and increased seizure frequency	↓ Effect of methotrexate, primidone, phenobarbital and pyrimethamine (NMCD, 2004d)
S-adenosyl-methionine	As above	Parenteral S-adenosylmethionine superior to placebo (Bressa, 1994); comparable efficacy to imipramine in two RCTs (Delle Chiaie <i>et al</i> , 2002; Pancheri <i>et al</i> , 2002); oral S-adenosyl-methionine requires high dose (1600 mg; Delle Chiaie <i>et al</i> , 2002)	Induction of mania in patients with bipolar affective disorder (Friedel <i>et al</i> , 1989; Mischoulon & Fava, 2002); significantly better tolerated than TCAs (Delle Chiaie <i>et al</i> , 2002; Mischoulon & Fava, 2002; Pancheri <i>et al</i> , 2002); more rapid onset of effect (Fava <i>et al</i> , 1995)	Serotonergic antidepressants
Omega-3 fatty acids	Influences catecholaminergic, serotonergic and cholinergic neurotransmission, modulation of signal transmission mechanisms in neuronal membranes, modulation of prostaglandins and ion channels (Haag, 2003)	Results of two small trials with short end-points inconclusive (Marangell <i>et al</i> , 2003; Su <i>et al</i> , 2003); successful augmentation of antidepressant treatment reported (Nemets <i>et al</i> , 2002); ↑ of remission period when added to lithium in bipolar affective disorder (Stoll <i>et al</i> , 1999)	↑ INR with high or changing doses (Fugh-Bergman, 2000)	↑ Effect of warfarin, aspirin and non-steroidal anti-inflammatory drugs (Fugh-Bergman, 2000); serotonergic antidepressants?

T4, thyroxine; T3, thyronine; HRSD, Hamilton Rating Scale for Depression; RR, risk ratio; RCTs, randomised controlled trials; TCA, tricyclic antidepressants; INR, international normalised ratio; NMCD, Natural Medicines Comprehensive Database.

**Table 5** Antipsychotics, augmentation and treatment of tardive dyskinesia

Substance	Postulated mechanism of action	Effectiveness	Side-effects	Potential drug interactions
Rauwolfia (includes reserpine)	↓ Dopamine availability: blocks vesicular storage of monoamines, which can then be degraded by monoamine oxidases (Spinella, 2001)	More effective than placebo in patients with chronic schizophrenia with regard to general mental state and behavioural disturbance (Malamud <i>et al.</i> , 1957); adjunctive treatment to antipsychotics (Wolkowitz, 1993)	Depression, seizures, extrapyramidal reactions, blood pressure changes and heart rate (NMCD, 2004e)	↑ Effect of antipsychotics and barbiturates, severe bradycardia with digitalis glycosides, ↓ effect of levodopa, hypertension in combination with sympathomimetics (Medical Economics, 2000)
Omega-3 fatty acids	See Table 4	Meta-analysis of five small studies inconclusive; the use of omega-3 fatty acids remains experimental until larger trials are conducted (Joy <i>et al.</i> , 2003)	See Table 4	See Table 4
Melatonin	Antioxidant, also attenuates dopaminergic activity in the striatum and dopamine release from the hypothalamus (Lohr <i>et al.</i> , 2003; Shamir <i>et al.</i> , 2001)	Two small RCTs led to inconclusive results; duration of tardive dyskinesia and melatonin dosage may influence treatment outcome (Shamir <i>et al.</i> , 2000, 2001)	See Table 2	See Table 2
Vitamin E	Antioxidant	Meta-analysis of ten small trials of uncertain quality indicate that vitamin E protects against deterioration of tardive dyskinesia but there is no evidence that vitamin E improves symptoms (Soares & McGrath, 2001). One recent trial reports significant improvement of abnormal involuntary movements (Zhang <i>et al.</i> , 2004)	See Table 1	See Table 1

RCTs, randomised controlled trials; NMCD, Natural Medicines Comprehensive Database.



**Table 6** Anti-addictives

Substance	Postulated mechanism of action	Effectiveness	Side effects	Potential drug interactions
Ibogaine and its derivative 18-MC for nicotine, cocaine and opiate addiction	Blocks sensitised dopamine response to chronic morphine and cocaine administration (Maisonneuve & Glick, 2003); may alter morphine induced dopamine release in nucleus accumbens (Maisonneuve & Glick, 2003); binds to the cocaine site of the serotonin transporter (Staley <i>et al.</i> , 1996); 18-MC binds to the NMDA receptor (Mash <i>et al.</i> , 1995) See Table 2	One small open trial only: tested in seven with opiate misuse: three remained abstinent at 14 weeks (Sheppard, 1994); otherwise evidence limited to case studies (Spinella, 2001) 18-MC only tested in animal experiments; ↓ morphine, cocaine and alcohol intake in rats (Rezvani <i>et al.</i> , 1997; Glick <i>et al.</i> , 2000)	Cholinesterase inhibitor: can lead to cholinergic toxicity (NMCD, 2004f); bradycardia (Maisonneuve & Glick, 2003); ibogaine but not 18-MC: significant cerebellar toxicity (Maisonneuve & Glick, 2003)	Cholinergic and anticholinergic drugs (NMCD, 2004f)
Valerian for benzodiazepine addiction	See Table 2	May improve sleep in patients withdrawing from benzodiazepines (Poyares <i>et al.</i> , 2002); no controlled trials available	See Table 2	See Table 2
Passion flower for cannabis, benzodiazepine, nicotine and opiate addiction	Cannabis: unclear, benzoflavones may decrease tolerance and withdrawal symptoms (Dhawan <i>et al.</i> , 2002a); opiates: use of anxiolytic effect, see Table 2	Opiates: effective as adjuvant therapy to clonidine demonstrated in one small RCT (Akhondzadeh <i>et al.</i> , 2001b)	See Table 2	See Table 2
St John's wort for alcohol addiction	Not fully understood, and possibly related to reducing serotonin, dopamine, noradrenaline and GABA reuptake (Rezvani <i>et al.</i> , 1999, 2003)	↓ Alcohol craving demonstrated in animal experiments only (De Vry <i>et al.</i> , 1999; Rezvani <i>et al.</i> , 1999; Overstreet <i>et al.</i> , 2003a,b); effect may be dose-dependent	See Table 3	See Table 3
Kudzu for alcohol addiction	Ingredient puerarin, counteracts the anxiogenic effects associated with alcohol withdrawal; may also have flumazenil-like properties (Overstreet <i>et al.</i> , 2003b)	Only one small trial in humans available showing no difference to placebo (Shebek & Rindone, 2000)	None reported (NMCD, 2004g)	Theoretically with anticoagulants, aspirin, cardiovascular agents and hypoglycaemic drugs (NMCD, 2004g)

18-MC, 18-methoxycoronaridine; NMDA, N-methyl-D-aspartate; GABA, gamma-aminobutyric acid; RCT, randomised controlled trial; NMCD, Natural Medicines Comprehensive Database.

cocaine and opiate users (Maisonneuve & Glick, 2003). Ibogaine also binds to the cocaine site of the serotonin transporter (Staley *et al*, 1996), but its therapeutic value is limited as it is highly neurotoxic and can cause irreversible cerebellar damage (Maisonneuve & Glick, 2003); as a result, further clinical studies have been abandoned. A synthetic derivative 18-methoxycoronaridine has similar reported effects but no cerebellar toxicity or specific effects on the serotonin transporter (Maisonneuve & Glick, 2003). To date 18-methoxycoronaridine has only been tested in animal experiments where it has been shown to reduce cocaine, morphine and alcohol intake in rats (Rezvani *et al*, 1997; Glick *et al*, 2000).

Passion flower has also been used to ameliorate the effects of opiate, cannabis, benzodiazepine and nicotine addiction, but clinical data are limited (Dhawan *et al*, 2002a,b, 2003; Akhondzadeh *et al*, 2001b). Likewise, valerian has been tried in benzodiazepine withdrawal (Poyares *et al*, 2002) and St John's wort has been used for the treatment of alcohol dependence (De Vry *et al*, 1999; Rezvani *et al*, 1999; Overstreet *et al*, 2003b), but effectiveness has not been established. Kudzu, Japanese arrowroot (*Pueraria lobata*), has traditionally been used for the treatment of alcoholic hangover. The active ingredient, puerarin, counteracts the anxiogenic effects associated with alcohol withdrawal (Overstreet *et al*, 2003a). Kudzu also contains two potent, reversible inhibitors of human alcohol dehydrogenase isozymes (Keung, 1993), but an effect has only been demonstrated *in vitro* (Lin & Li, 1998). One small trial among those with chronic alcohol misuse has not shown any difference from placebo (Shebek & Rindone, 2000). Further trials are required to test its genuine therapeutic potential, perhaps using more standardised formulations of the active ingredient.

## DISCUSSION

Our review demonstrates that the evidence base for the use of psychotropic complementary medicines is extremely limited. The best evidence is available for St John's wort and kava kava, both of which are used extensively in various cultures. However, trials of St John's wort need improved definition of inclusion criteria (Werneke *et al*, 2004b), and kava kava has been withdrawn due to concerns about hepatotoxicity. Further

RCTs are required to assess other promising agents such as selenium and S-adenosylmethionine for the treatment of depression, ideally in individuals showing the corresponding deficiencies at baseline. This may lead to new therapeutic approaches for treatment-resistant depression. Valerian and passion flower should be tested as anxiolytics and sedatives; their potential value in the treatment of addiction also requires further clarification. The role of omega-3 fatty acids as an adjunct to antipsychotics and melatonin as a treatment or prophylactic agent for tardive dyskinesia remain ambiguous, both requiring trials with sound methodology.

We have outlined only a limited range of complementary medicines used for the treatment of common psychiatric problems. Clearly there are many more remedies that may be taken to improve general health or to counter the side-effects of conventional treatments. Clinicians need to be aware of and enquire about such forms of self-medication, since all remedies may interact with prescribed medication or have associated side-effects in their own right. For instance, patients may take phyto-oestrogens, such as black cohosh (*Actaea racemosa*), wild yam (*Dioscorea composita*) or dong quai (*Angelica sinensis*) to counter sexual side-effects, and this might pose a problem in patients with oestrogen receptor-positive breast cancer (Werneke *et al*, 2004a). For the same reason, patients may also try evening primrose oil (*Oenothera biennis*), which could decrease the effect of sodium valproate (Miller, 1989). Kelp (*Laminaria digitata* or *Fucus vesiculosus*) may be taken to counter weight gain, but can contain substantial amounts of iodine and can interfere with treatment for thyroid function disorders. Iodine taken together with lithium may have additive hypothyroid effects (Natural Medicines Comprehensive Database, 2004b).

Given the complex pattern of potential interactions, clinicians should not be afraid to discuss complementary medicines with their patients. Although some patients may choose to use complementary medicines as alternatives to conventional treatment, many may decide to use them in addition to prescribed medications. Complementary medicines have – rightly or wrongly – a very positive 'natural' reputation among significant sections of the population, and therefore can be popular with

those from a wide variety of cultural backgrounds. This may lead to higher acceptance and adherence compared with conventional drugs, making it important to be 'willing and prepared to work in partnership with patients' beliefs and preferences – provided their actions are safe' (Brugha *et al*, 2004). Also, we do not know whether the agreed use of complementary medicines could in itself improve insight and subsequently lead to greater adherence to conventional treatment regimens. This emphasises the importance of further research on complementary medicines focusing on promising agents such as passion flower, valerian and S-adenosylmethionine, which appear to be obvious candidates for further RCTs. In addition, it might be important to consider patients' attitudes and preferences in future studies, possibly targeting those demanding complementary medicines.

Finally, clinicians need to be aware of side-effects associated with complementary medicines and any interactions with other treatments. They should be able to identify hazards, advising patients accordingly and avoiding uncritical encouragement of potentially harmful use. Ignorance in this area, given the independent usage of complementary medicines, may lead to criticism and possibly litigation (Cohen & Eisenberg, 2002). Equally, patients should be encouraged to disclose information about complementary medicines to healthcare professionals. These discussions need to be conducted sensitively in order to avoid alienating patients who may feel that they have not been taken seriously or have been criticised for using complementary medicines. Such discussions can be complex and may demand more time than is available in routine clinics. Service models need to be designed to meet this challenge, with consideration being given to specialist clinics providing regular updated advice to both clinicians and patients.

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## CLINICAL IMPLICATIONS

■ Depending on the inclusion criteria chosen, between 8 and 57% of psychiatric patients (most commonly those with depression and anxiety) use complementary medicines.

■ Clinicians must be prepared to discuss the use of complementary medicine with patients who prefer a holistic approach to treatment.

■ Clinicians need to be aware of side-effects associated with complementary medicines and their interactions with conventional treatments.

## LIMITATIONS

■ The evidence base for the use of psychotropic complementary medicines is extremely limited and randomised controlled trials of promising agents are urgently needed.

■ Often, the active ingredient in herbal formulations has not been identified, which leads to problems with standardisation of extracts and dose recommendations.

■ Discussions of complementary medicine use may demand more time than is available in routine clinics.

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