Adjuvant use of nutritional and herbal medicines with antidepressants, mood stabilizers and benzodiazepines

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ABSTRACT

Adjuvant use of nutritional and herbal medicines has potential to increase the efficacy of synthetic pharmaceuticals, and perhaps also decrease their side-effects by allowing lower doses to be prescribed. We evaluated current evidence for adjuvant use of nutritional and herbal medicines with antidepressants, mood stabilizers and benzodiazepines; and explored novel future areas of research. The paper also critiques current evidence for co-administration of St. John's wort with synthetic antidepressants. We performed a systematic search of MEDLINE, CINAHL, PsycINFO, The Cochrane database, China National Knowledge Infrastructure and the Chinese Science Citation Database. Search results were supplemented by a review of reference lists and a forward search using the Web of Science. Where possible we calculated effect sizes. Encouraging evidence exists for the use of omega-3 fatty acids, SAMe, folic acid and L-tryptophan adjuvantly with antidepressants to enhance response and improve efficacy. Various nutrients also have emerging evidence as effective adjuncts with antipsychotics and mood stabilizers. While some evidence supports nutritional adjuvancy with various psychopharmacotherapies, adjuvant use of herbal therapies has not been sufficiently studied to warrant standard clinical application. This remains a promising area of research via robust, safety-conscious studies.

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1. Introduction

Adjuvancy strategies of medicines are commonly classified into “augmentation” and “combination” approaches (Fava and Rush, 2006). Prescriptive augmentation in psychiatry involves using psychotropic interventions that are not established mono-therapies in conjunction with pharmaceutical psychotropics, in order to enhance response or limit side-effects. Combination strategies involve using two or more established pharmacological psychotropics for the same purpose. Adjuvancy can be initiated either at the start of the prescription, or later if there is insufficient response to initial treatment. Most clinical trials assessing adjuvancy apply the additional intervention after absent or partial response to the initial prescription. Outcomes that are commonly assessed in adjuvancy studies include enhanced response time and response rate (i.e. >50% reduction on assessment scale used), and improved remission rate (absence of diagnosis or a score below at set level on an assessment measure (Fava and Rush, 2006)). Other outcomes that are less commonly explored include reduction of side-effects (more common in studies using antipsychotics), remission of residual physiological or psychological symptoms, and subjective changes in quality of life.

Surveys have shown that polypharmacy by general practitioners and psychiatrists has increased significantly over recent years (Davids et al., 2006; de la Gandara et al., 2005; Patten and Beck, 2004; Tapp et al., 2003). Polypharmacy combinations commonly involve the use of multiple antidepressants in MDD, antidepressants with benzodiazepines in “anxious” depression, combinations of atypical antipsychotics in psychotic disorders, and mood stabilizers with antipsychotics in bipolar depression. However, such polypharmacy is not always supported by evidence. Those data are briefly reviewed in later sections.

Many open or controlled clinical trials have been conducted using adjuvant applications of nutritional and herbal medicines with antipsychotics for amelioration of side-effects rather and increased efficacy. A major concern in using antipsychotics is tardive dyskinesia, which over 20% of patients experience (Soares-Weiser and Fernandez, 2007). Other side-effects of antipsychotics include weight gain, somnolence, constipation, cardiovascular and metabolic disorders (Haddad and Sharma, 2007; Henderson, 2008).

Traditional Chinese medicine formulas (Rathbone et al., 2005) and Ginkgo biloba (Atmaca et al., 2005; Zhang et al., 2001b) have demonstrated beneficial effects in attenuating either extra-pyramidal side-effects or positive schizophrenic symptoms. An antioxidant and anti-inflammatory mechanism of action is commonly posited as being responsible for attenuation of tardive dyskinesia (Zhang et al., 2001a). Mixed results in respect to amelioration of positive or negative symptoms or tardive dyskinesia have been revealed using omega-3 fatty acids (Berger et al., 2007; Emsley et al., 2006; Fenton et al., 2001; Peet et al., 2001; Vaddadi et al., 1989), and vitamin E (Dorfman-Etrog et al., 2007; Emsley et al., 2006; Fenton et al., 2001; Peet et al., 2001; Vaddadi et al., 1989), and vitamin E (Dorfman-Etrog et al., 2007; Emsley et al., 2006; Fenton et al., 2001; Peet et al., 2001; Vaddadi et al., 1989). A 2001 Cochrane review concluded while vitamin E may not effectively treat tardive dyskinesia, it may have a role in its prevention (Soares and McGrath, 2001). Controlled studies using vitamin B6 have demonstrated beneficial effects on the reduction of extra-pyramidal symptoms (Lerner et al., 2002, 2004, 2007; Miodownik et al., 2003).

Other nutritional and herbal medicines hold potential in adjuvant use with pharmaceutical medicines to increase their efficacy via increased pharmacodynamic synergism (Williamson, 2001). Although this area is controversial because of the potential for pharmacokinetic interactions, beneficial interactions potentially may occur, leading to a reduction in the dos-age of the pharmaceutical medication, or increased efficacy.

Despite an increased practice of synthetic polypharmacy (Preskorn, 2006), co-prescription of herbal medicines is often met with alarm over concerns of potential drug–herb interactions. While caution is indicated in any case where multiple prescriptions have potential for interactions, a differential concern over drug–herb interactions needs further examination. Rigorous study is needed not only to determine the extent of any negative interactions, but also to examine the potential for synergistic benefits.

A previous review by Werneke et al. (2006), explored evidence of herbal and nutritional psychotrophic interventions and touched upon their adjuvant use. Our intention is to provide a comprehensive and critical review of the literature, focusing specifically on the current evidence of adjuvant use of herbal and nutritional medicines with commonly used pharmacotherapies for mood and anxiety disorders. A secondary aim is to provide a perspective on future research and integrative clinical applications of natural and synthetic medicines.

2. Methods

The electronic databases MEDLINE (Pubmed), CINAHL, PsycINFO, Chinese Science Citation Database (via Web of Science) and The Cochrane Library were accessed during late 2008. Pubmed was searched using MeSH, with the terms, “Medicine, Herbal”, “Plants, Medicinal”, “Plant extracts”, “Phytotherapy” and “Drugs, Chinese herbal”, AND “Adjuvant”, “Adjunctive”, “Augmentation”. Searches were conducted on a wide range of individual herbal and nutritional medicines commonly trialed for psychotropic activity (e.g. kava, St. John’s wort, folic acid, omega-3). A forward search of the identified papers was performed using Web of Science cited reference search. We reviewed papers that described controlled, uncontrolled or quasi-experimental human studies. Reasons for exclusion included: a higher level of evidence being available, use of isolated herbal constituents, or inadequate methodological rigor. We reported the effect sizes in all placebo-controlled studies where data was available. We calculated the (d) of the clinical trials by (a) calculating the effect size separately within the active and control group (taking the difference between baseline and post-treatment means, divided by the within-group standard deviation at baseline), and (b) subtracting the effect size of the control group from that of the active group (Morris, 2008).

3. Results

A total of 4345 papers were identified from our search criteria, and 35 clinical trials were judged to be relevant to the review. These studies are reviewed under nutritional and herbal medicine with “Antidepressants”, “Mood Stabilizers” and “Benzodiazepines”. As detailed below, most “Western” adjuvancy studies involved nutritional medicines, while herbal medicine adjuvancy studies were mostly of “Asian” origin, using traditional Chinese or Japanese formulations.

3.1. Depression

3.1.1. Adjuvant use of pharmacotherapies for depression

Only about a third of patients with MDD who are treated by a first-line antidepressant achieve complete remission (Rush et al., 2006), with treatment trials typically focusing on a 50% reduction in symptoms as a positive treatment response. Most adjuvancy studies on antidepressants involve a range of synthetic agents, including other antidepressants (e.g. TCAs or mirtazapine with SSRIs), mood stabilizers (e.g. lithium, carbamazepine, or valproate),...
and noradrenergic or dopaminergic agents (e.g. bupropion, reboxetine, atomoxetine: Berlim et al., 2008; Nelson, 2000). Evidence for pharmacological combinations primarily comprises open, uncontrolled studies, and results are mixed (Fava and Rush, 2006; Trivedi et al., 2006). To date, the most advanced adjuvancy study is the Sequenced Treatment Alternatives to Relieve Depression (STAR D), a multi-site, prospective, randomized, multi-step clinical trial comparing a series of adjunctive or alternative treatments for patients who did not respond to citalopram (Warden et al., 2007). Results confirmed that only a minority of people with MDD achieve remission via initial treatment with an SSRI. Switching, combining or augmenting produced benefits to some initial non-responders, but a third of people with MDD did not achieve complete remission, even after multiple treatment strategies.

As detailed in Table 1, many studies have been conducted using a variety of nutrients adjuvantly with antidepressants (omega-3, S-adenosyl-methionine, folic acid, tryptophan and inositol). Only one herbal medicine mono-therapy study was revealed from our literature review, indicating that this is a relatively uncharted field of research.

3.1.2. Adjuvant use of nutritional and herbal medicines with antidepressants

Omega-3 fatty acids have not yet demonstrated significant results as a mono-therapy for Major Depressive Disorder (Marangell et al., 2003; Parker et al., 2006). However, epidemiological studies have demonstrated that a rise in depressive symptoms is correlated with lower dietary omega-3 fish oil intake (Appleton et al., 2006, 2007; Lin and Su, 2007). Studies have also shown that people with depression tend to have a lower serum level of essential fatty acids (EPA and DHA: Appleton et al., 2006). A recent meta-analysis conducted by Lin and Su (2007), included nine eligible RCTs of sufficient methodological rigor. The results revealed that omega-3 preparations demonstrated a positive standardized mean difference towards a beneficial effect over placebo. Pooling of these results by the authors revealed a moderate effect size ($d = 0.61$). It should be noted that not all studies had positive outcomes and that longer clinical trials using a combination of both EPA/DHA are advised. A Cochrane review that included only one study, commented that beneficial effects may be found for depressive symptoms but not for mania (Montgomery and Richardson, 2008).

Four adjuvancy trials have been conducted, all with positive clinical outcomes and strong effect sizes. Randomized, double-blind augmentation of 20 mg of fluoxetine with 1 g of EPA over 8 weeks in 60 non-responsive depressed patients demonstrated a significantly better reduction on the Hamilton Depression Rating Scale (HDRS: Hamilton, 1960) than fluoxetine or EPA alone (Jazayeri et al., 2008). The response rate from the combination ($\geq 50\%$ decrease on HDRS) was $81\%$ compared with $56\%$ and $50\%$ for EPA and fluoxetine, respectively. A 4-week controlled study ($n = 20$) using 2 g daily of EPA in patients with non-response to stabilized antidepressants showed similar significant benefits ($d = 2.92$: Nemets et al., 2002). One gram per day of ethyl-eicosapentaenoate was effective as an adjuvant agent in a 12-week study of 70 subjects with non-response to unspecified antidepressants (Peet and Horrobin, 2002). Curiously, the 4 g EPA arm only had a trend towards improvement, and the group receiving 2 g/day did not experience any statistically significant benefits. This may indicate either a curvilinear dose–response effect or insufficient power to detect differential effects. An 8-week study using 6.6 g/day of omega-3 fatty acids adjuvantly in 32 non-responders to antidepressants demonstrated a 13.6 point reduction on the HDRS, compared with 6.4 in the placebo group ($d = 1.85$: Su et al., 2003).

In evaluating effects of omega-3 on depressed mood, it should be noted that there are issues in respect to the type of omega-3 formulation used in research and practice. Studies typically use different formulations containing either eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), a combination of EPA and DHA, or purified ethyl esters. Currently there is not scientific consensus on which preparation is preferential for depressive episodes. Folate deficiency (assessed via low dietary intake or low serum level) has been consistently demonstrated in depressive populations and in poor responders to antidepressants (Morris et al., 2008). Two controlled studies were located in our search. An RCT used 500 g of folic acid or placebo adjuvantly with 20 mg fluoxetine in 127 subjects with HDRS of $\geq 20$ (Coppen and Bailey, 2000). A statistically significant differential reduction after 10 weeks on HDRS occurred only for women on completion of $6.8 \pm 4.1$ in the fluoxetine plus folic acid condition, compared with $11.7 \pm 6.7$ from fluoxetine plus placebo; $d = 0.73$. Over the same period, plasma homocysteine decreased in women 20.6% more in the folate group compared with control. Neither effect occurred in men. A recent RCT involving 27 depressed subjects found that 20 mg of fluoxetine combined with 10 mg of folic acid was more effective in reducing HDRS score compared to augmentation with placebo ($7.43 \pm 1.65$ vs. $11.43 \pm 1.31$, respectively; $p = 0.04$: Resler et al., 2008). A significant reduction of homocysteine was also observed in the folic acid group, compared to placebo. The researchers considered that a mechanism of action may involve a reduced turnover rate of serotonin, and subsequent increased accumulation serotonin in the cells, as the marker 5-Hydroxyindoleacetic acid was significantly lower in lymphocytes of patients receiving folate.

A UK-based RCT with 730 participants ("FolATED") is being currently conducted to assess effects of folic acid augmentation (5 mg/day: Roberts et al., 2007). The study will also evaluate the cost-effectiveness of folic acid augmentation on antidepressant treatment, how genetic polymorphisms relevant to folate metabolism affect antidepressant response, and whether baseline folate status can predict response to antidepressant treatment.

Inositol has been studied as an antidepressant mono-therapy and as an augmenting agent, and has mixed results (Taylor et al., 2004). An early double-blind, controlled 4-week study with 28 participants demonstrated statistically significant antidepressant activity against placebo, using 12 g/day of inositol (Levine et al., 1995). Subsequent double-blind, controlled studies ($n = 27$, and $n = 42$) were conducted using inositol as an augmenting agent with SSRIs (Levine et al., 1999; Nemets et al., 1999). Neither study demonstrated a significant difference between adjuvant use of inositol or placebo.

S-Adenosyl-methionine (SAMe) has been studied for antidepressant activity for several decades. Most studies involve parenteral or intramuscular injections of SAMe which subsequently crosses the blood–brain barrier (Williams et al., 2005). SAMe has consistently demonstrated an antidepressant mechanism of activity, and comparable effects to synthetic antidepressants (Papakostas et al., 2005). Several adjuvancy studies were found. A 6-week open label study using 800–1600 mg/day of SAMe with 30 non-responders to stabilized prescription of SSRI or venlafaxine was conducted by Alpert et al. (2004). Intention-to-treat analysis revealed that adjuvant use of SAMe significantly reduced depression from baseline to week 6 on HDRS ($17 \pm 4.2$ to $10.0 \pm 6.6$). Intramuscular administered SAMe (200 mg/day) demonstrated a significant increase in the onset of response of imipramine (150 mg/day: Berlanga et al., 1992). A significant effect became apparent by day 4 and remained until day 12, after which there was no difference between groups. Due to concerns over development of hypomania or mania, SAMe should be used cautiously in patients with a history of mania. Another caveat is cost. Therapeutic dosage of oral SAMe may require up to 1600 mg, which costs approximately US$8/day.

Monoamine precursors are necessary for synthesis of serotonin, dopamine and norepinephrine (Hood et al., 2005; Roiser et al., 2005). L-tryptophan has been studied extensively as an antidepressant.
<table>
<thead>
<tr>
<th>Herbal/nutritional medicine</th>
<th>Clinical evidence</th>
<th>Precautions</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Omega-3</td>
<td>Four studies have demonstrated positive results after 2 or more weeks of omega-3 (1–6.6 g/day) with SSRIs, TCAs, MAOIs (Jazayeri et al., 2008; Nemets et al., 2002; Peet and Horrobin, 2002)</td>
<td>High dosage may ↓ INR (caution with warfarin)</td>
<td>A potentially beneficial antidepressant effect may occur, especially in subjects with low EFA serum status. May also be beneficial in subjects with comorbid cardiovascular disease (which has increased risk in depression)</td>
</tr>
<tr>
<td></td>
<td>High dosage may also alter triglyceride levels</td>
<td></td>
<td>Typical dose: 3–9 g/day of omega-3 or 1–2 g/day EPA plus 1–2 g of DHA</td>
</tr>
<tr>
<td>S-Adenosyl-methionine (SAMe)</td>
<td>Intramuscular and oral augmentation of SAMe with antidepressants has demonstrated ↑ response and remission rates (Berlanga et al., 1992). May enhance response in antidepressant non-responders (Alpert et al., 2004)</td>
<td>May interact with serotonergic antidepressants; caution in bipolar patients to avoid switching to mania</td>
<td>Expense may restrict applicability. Parenteral administration may be more efficacious than oral administration</td>
</tr>
<tr>
<td></td>
<td>High dosage may cause adverse reactions, e.g. GIT complaints, nausea or serotonin syndrome (Byerley et al., 1987)</td>
<td></td>
<td>Typical dose: 400–1600 mg/day</td>
</tr>
<tr>
<td>L-tryptophan</td>
<td>L-tryptophan augmentation with MAOIs, SSRIs and some TCAs is effective in increasing the antidepressant response: phenezine sulphate (Glassman and Platman, 1969), fluoxetine (Levitan et al., 2000), clomipramine (Nardini et al., 1983; Walinder et al., 1976). No difference occurred compared to placebo with other tricyclics (Shaw et al., 1975)</td>
<td>May be of use in subjects taking antidepressants, in tryptophan deficiency, or in depression caused by serotonergic pathway dysregulation</td>
<td>Typical dose: 200 mg–2 g/day</td>
</tr>
<tr>
<td>Inositol</td>
<td>Controlled studies have demonstrated inositol augmentation with SSRIs does not improve depression in SRI treatment failures (Levine et al., 1999; Nemets et al., 1999)</td>
<td>None noted</td>
<td>Inositol augmentation is currently not recommended</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Antidepressant augmentation with folic acid may increase response rate increases and efficacy (Coppen and Bailey, 2000; Resler et al., 2008). Subjects with lower folate levels are more likely to have a delayed response by average 1.5 weeks (Papakostas et al., 2005)</td>
<td>Caution should be observed in pernicious anaemia (addition of B12 required); ↓ doses may cause agitation and anxiety</td>
<td>May increase response to antidepressants, perhaps especially in cases of folate deficiency, but further trials are required. May be more efficacious in females than males</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Typical dose: 400 µg–2 g/day</td>
</tr>
<tr>
<td>Lavender (Lavendula angustifolia)</td>
<td>4-week RCT (n = 45) 60 drops 1:5 lavender vs. 100 mg imipramine. Lavender + imipramine was more effective than imipramine alone in reducing depression (Akhoundzadeh et al., 2003)</td>
<td>The only side-effect from lavender use was a slight statistical increase in the occurrence of mild headaches</td>
<td>Larger studies are needed to confirm beneficial synergistic pharmacodynamic activity</td>
</tr>
<tr>
<td>Traditional Chinese medicine formulas</td>
<td>Results of two studies using Xiao Yao and San Pu Xin Nao herbal formulas with amitriptyline and fluoxetine showed significantly ↓ adverse reactions and ↓ remission rates</td>
<td>None noted</td>
<td>Traditional Chinese herbal formulas may reduce side-effects and increase compliance to antidepressants, but there is currently no evidence of added antidepressant benefit. Further studies are needed</td>
</tr>
</tbody>
</table>

* When prescribing nutritional and herbal medicines adjuvantly with pharmacotherapies, clinicians should be aware that many natural products vary in formulation design and chemical composition. Standardized results are unlikely to uniformly occur where a deficit of quality (manufacturing, storage, and standardization of active chemicals) is apparent. Caution in dosage is therefore required.
sant (Byerley et al., 1987). Although there are several positive studies, a rigorous systematic review and meta-analysis by Shaw et al. (2002) concluded that due to small sample sizes, poor outcome measures and publication bias, there were insufficient data to inform clinical practice. Eight controlled adjuvancy studies were located. L-tryptophan (or its biological intermediary, 5-hydroxytryptophan) augmentation was found to be effective in increasing the antidepressant response with phenezine sulphate (Glassman and Platman, 1969), clomipramine (Nardini et al., 1983; Walinder et al., 1976), tranlycpramine (Coppen et al., 1963) and fluoxetine (Levit et al., 2000). However, other clinical studies using tricyclics discovered no additional benefit compared with placebo (Ayuso Gutierrez et al., 1973; Shaw et al., 1975; Thomson et al., 1982).

Many of the older studies were of weak methodological design, and additional rigorous studies are needed to confirm these results. Amino acids (ω-phenylalanine and t-tyrosine, precursors to dopamine and norepinephrine), may provide augmenting antidepressant activity however no studies were located assessing this.

Lavender (Lavendula angustifolia) is currently the only herbal mono-therapy examined as an adjunct with other antidepressant pharmacotherapy. A 4-week RCT using a combination of lavender tincture (1:5 60 drops/day) and imipramine (100 mg/day) in 45 people with diagnosed MDD, was significantly more effective than imipramine alone on HDRS, indicating a synergistic effect (Akhandzadeh et al., 2003). Two small studies testing traditional oriental formulas Xiaoyao (Yang et al., 2007) and Sanpu Ximao (Zhang et al., 2006) adjuvantly with amitriptyline and fluoxetine, respectively, demonstrated no significant increase in antidepressant activity. Adverse reactions were however reduced in both combination groups, and relapse rates were also lower.

3.2. Bipolar disorder

3.2.1. Adjuvant use of pharmacotherapies for bipolar disorder

Mood stabilizers including lithium and valproic acid and antipsychotics are commonly used as first-line agents to treat the presentation of the manic phase in Bipolar I Disorder (Miklowitz and Johnson, 2006). Statistics vary regarding the effectiveness of lithium in treating acute mania, with previous accounts of an effect rate of 60–80% perhaps being overestimated (Miklowitz and Quiroz, 2003). Mixed or negative results occurred in controlled studies using gabapentin or lamotrigine with mood stabilizers, although the small samples in these studies prohibit firm conclusions. Our review of research on treatment or prevention of BD depression revealed few studies with robust methodology. No consistent benefit in antidepressant augmentation was apparent, while evidence indicated that tricyclic antidepressants such as imipramine may also increase switching between depressive and manic states.

The most comprehensive study of combination treatments in BD I/II is the Sequenced Treatment Enhancement Program for Bipolar Depression (STEP-BD: Sachs et al., 2003). This complex naturalistic quasi-controlled program involving 4370 participants explored the outcomes on depression and mania, involving standard care vs. various controlled interventions (e.g. mood stabilizers in concert with bupropion, paroxetine, lamotrigine or inositol; and psychological treatments). No beneficial adjuvant effects on depression were observed from bupropion or paroxetine over those from mood stabilizers alone. Surprisingly, a trend occurred in favor of the antidepressants over placebo in reducing the incidences of hypomania and mania (Thase, 2007). Results for adjunctive psychological intervention were more positive than adjunctive pharmacotherapy. The study highlighted the difficulty in managing BD effectively, as demonstrated by poor compliance and response to treatments.

Due to the intensity of neurochemical involvement and potentially harmful effects on mortality and morbidity in BD, standard pharmaceutical interventions continue to be the required first-line treatment. Complementary medicines currently lack evidence in addressing acute mania, and cannot be recommended as a first-line intervention. They may however have a potential role in augmenting the action of mood stabilizers or atypical antipsychotics, reducing side-effects, and in improving compliance. Treatment adherence is a major problem of treating BD, with up to 60% of patients discontinuing treatment within the first year of prescription (Miklowitz and Johnson, 2006). The use of specific adjuvant nutritional or herbal medicines may allow for smaller doses of mood stabilizers required. This could potentially ameliorate typical side-effects, increasing adherence and overall outcomes. Papers on the adjuvant use of herbal medicines and nutritional supplements with mood stabilizers are summarized in Table 2.

### Table 2
<table>
<thead>
<tr>
<th>Herbal/nutritional medicine</th>
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<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Omega-3</td>
<td>Augmentation with pre-prescribed mood stabilizers. Limited evidence in benefitting BD depression. Ineffective in preventing or improving treatment of mania (Chiu et al., 2005; Frangou et al., 2006; Krock et al., 2006) An RCT using folic acid (200 µg) with lithium demonstrated minor benefit</td>
<td>High dosage may</td>
<td>Appears safe and is more beneficial in addressing depression than mania. More studies are required using EPA/DHA combinations</td>
</tr>
<tr>
<td>Folic acid</td>
<td>None noted</td>
<td>None noted</td>
<td>Further studies using a higher dose of folate acid may be of benefit</td>
</tr>
<tr>
<td>Inositol</td>
<td>None noted</td>
<td>None noted</td>
<td>As with MDD, inositol may have little or no benefit in augmenting antidepressant or mood stabilizing effects with lithium or valproate. A larger study is required</td>
</tr>
<tr>
<td>Traditional Chinese medicine formula</td>
<td>Combination with carbamazepine increased response and efficacy on depression outcomes. A statistically significant reduction in fatigue and dizziness also occurred</td>
<td>This formulation reduces serum level of carbamazepine. Heavy metals and plant substitutions have occurred in some Chinese herbal medicines</td>
<td>Positive results of this research on the reduction of depression and side-effects, encourages further exploration of adjuvant use herbal medicines with mood stabilizers</td>
</tr>
</tbody>
</table>

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3.2.2. Adjuvant use of nutritional and herbal medicines with mood stabilizers

Omega-3 fatty acids have been studied as a mono-therapy and as an adjuvant intervention in bipolar depression. An RCT involving 44 participants using a combination of EPA and DHA (9.6 g/day) as a mono-therapy revealed positive results on depression outcomes in terms of response and remission on HDRS ($d = 1.15$; Stoll et al., 1999). No significant effect on mania outcomes occurred. In terms of adjuvant use of omega-3 in treating BD, three studies were located. A 12 week, 3-arm controlled study involving 75 participants using 1 g or 2 g of EPA adjuvantly with unrestricted psychotropic medications revealed a small but significantly greater reduction on the HDRS from either dose, compared with placebo (1 g: $d = 0.90$, 2 g: $d = 0.50$; Frangou et al., 2006). However, no significant effect for mania was achieved on the Young Mania Rating Scale (YMRS: Young et al., 1978). A larger study ($n = 385$) using 6 g of EPA adjuvantly with at least one mood stabilizer in patients with rapidly cycling bipolar disorder found no effect compared to placebo on reducing mania on YMRS (Keck et al., 2006). A small RCT with 15 participants, using 4.4 g of EPA and 6.6 g of DHA/day adjuvantly with 20 mg/day of valproate also revealed no effect compared to placebo on reducing mania (Chiu et al., 2005). Current evidence appears to weakly support omega-3 preparations adjuvantly in the depressive phase of bipolar. Omega-3 in the manic phase appears to possess no clinical effect in attenuating mania.

Coppen et al. (1986) conducted a RCT using adjuvant folic acid (200 μg) over a period of a year in 75 patients stabilized on lithium. They found a small but significant reduction on the Beck Depression Inventory (Beck et al., 1961) in the folic acid group, but not in the placebo group. A comparison of the active and placebo groups converts to a $d$ of 0.22. It should be noted that the folic acid dose was very low (200 μg), and that higher doses 500–1000 μg may yield a different response.

A pilot RCT was conducted, involving twenty-four participants with DSM-IV bipolar depression (bipolar I = 21; bipolar II = 3) randomly assigned in addition to stable neuroleptic prescription with 12 g of inositol or d-glucose as placebo for 6 weeks (Chengappa et al., 2000). The results revealed a non-significant response between the groups on HDRS, Montgomery–Asberg Depression Rating Scale (MADRS: Montgomery and Asberg, 1979) and Clinical Global Impression scales (CGI: Guy and Bonato, 1970). A small 6-week RCT involving 17 participants using inositol or placebo adjuvantly in currently depressed bipolar patients with stabilized levels of lithium or valproate revealed mixed results (Eden Evins et al., 2006). Although no differential reduction occurred in HDRS or YMRS scores, four out of nine people achieved remission (≥50% reduction on HDRS) in the inositol group compared with none out of eight in the placebo group. This is consistent with the results of the STEP-BD inositol adjuvancy arm, where there was only a 17% increase in remission rates (Thase, 2007).

The only located study that examined herbal medicine being used adjuvantly with mood stabilizers involved the traditional Chinese medicine formulation Jia-Wei-Xiao-Yao-San (Free and Easy Wanderer Plus: Zhang et al., 2005). A 12-week double-blind, randomized, controlled study involving 124 bipolar (depressed) and 111 bipolar (manic) participants was conducted. Response, efficacy and side-effects were assessed using carbamazepine mono-therapy (CBZ), or carbamazepine adjuvantly with Free and Easy Wanderer Plus (CBZ + FEWP) or placebo. Results showed a significantly increased response rate on HDRS, MADRS and CGI from CBZ + FEWP, compared with placebo or CBZ alone (84.8%, 63.8% and 34.8%, respectively). The combination also significantly reduced depression scores against placebo and carbamazepine at weeks 8 and 12. Effect sizes on the HDRS at week 12 using intention-to-treat and completers analysis were $d = 0.90$ and $d = 1.80$, respectively. No significant effects were found on the mania outcome measures at endpoint between carbamazepine mono-therapy and the combination. Interestingly, compared with carbamazepine, patients receiving CBZ + FEWP had a lower incidence of dizziness (18.2% vs. 7.9%) and fatigue (9.1% vs. 1.1%). A follow-up study ($n = 188$) continued treatment of CBZ and CBZ + FEWP to 26 weeks. Results revealed no significantly greater improvement at the endpoint, indicating that adjuvant FEWP administration may enhance initial response and reduce some side-effects in the short term, but that this benefit is not maintained over time.

3.3. Anxiety disorders

3.3.1. Adjuvant use of pharmacotherapies for anxiety

Adjuvancy strategies to treat anxiety disorders are commonly focused on integrating psychological interventions or benzodiazepines with antidepressants (Dunlop and Davis, 2008; Tyrer and Baldwin, 2006). Benzodiazepines are commonly prescribed for a range of anxiety disorders, or to attenuate anxious symptomatology occurring as a side effect from commencement of antidepressants (Dunlop and Davis, 2008). Aside from psychological intervention, common adjuvant psychotropic interventions with benzodiazepines include β-blockers (e.g. propranolol) to address somatic anxious symptoms, and sedating antipsychotics (e.g. olanzapine or risperidone: Rickels and Rynn, 2002). We located no augmentation studies using nutritional or herbal medicines with benzodiazepines.

Although benzodiazepines are effective anxiolytics, concerns over dependence and tolerance caution their long-term use (Rickels and Rynn, 2002). Use of nutritional or herbal medicines in conjunction with benzodiazepines may also therefore focus on their reduction or withdrawal, whereby they are given during dose reduction, or as a substitute at benzodiazepine cessation. Because the former involves adjuvant use, this application of nutritional or herbal medicines is included here.

3.3.2. Adjuvant use of nutritional and herbal medicines with benzodiazepines

One study using kava (Piper methysticum) in benzodiazepine withdrawal was identified in the search. A 5-week RCT was conducted using a standardized kava extract (WS® 1490) on 40 subjects with chronic anxiety and a long history of benzodiazepine use (Malisch and Kieser, 2001). Subjects were tapered off their benzodiazepines over the first 2 weeks, while the kava was titrated from 50 mg up to 300 mg by the end of week one. Kava produced a statistically significant drop of 7.5 point decrease over placebo at week 5 in anxiety on the Hamilton anxiety scale (Hamilton, 1959), and a positive result on the Benfindlichkeits–Skala subjective well-being scale (CIPS, 1996). Importantly, aside from some subjects experiencing withdrawal symptoms, no negative reactions (e.g. increased sedation) occurred during the first week of adjuvant kava use. Furthermore, only five subjects in the kava group displayed adverse symptoms from benzodiazepine withdrawal compared with 10 in the placebo group. During a follow-up study, 9 out of 14 subjects who were switched from kava to placebo experienced re-occurrence of anxiety. Practitioners considering adjuvant use of kava should however be aware that kava was withdrawn in 2002 from Europe, UK and Canadian markets over concerns over potential hepatotoxicity.

3.4. Novel adjuvant therapeutic uses of herbal medicines

Our review revealed that few clinical trials to date have studied co-administered herbal preparations with pharmaceuticals. One unexplored area of potential benefit to sufferers of BD, MDD, or anxiety disorders is the use of herbal medicines to reduce side-effects from psychopharmacotherapies, thereby subsequently
improving compliance. A major problem with many synthetic pharmaceutical antidepressants, is that compliance is often poor, with fewer than 50% of patients continuing with their prescribed medication after 3 months (Ellen et al., 2007). An illustration of this attrition occurred in the STAR*D project, with approximately 1 in 4 patients at stage 1 (citalopram) discontinuing before remission was achieved (Warden et al., 2007). An example of the potential of herbal medicines to reduce side-effects and improve compliance with synthetic psychotropics is detailed in a Cochrane database systematic review of Chinese herbal medicine (CHM) preparations for schizophrenia (Rathbone et al., 2005). Compared with those given only antipsychotics, significantly fewer patients withdrew from treatment in the CHM plus antipsychotic groups than from the antipsychotic mono-therapy groups. Subjects also displayed fewer side-effects such as constipation. The authors of the Cochrane review concluded that CHM when combined with antipsychotic drugs may be of benefit in treating schizophrenia. As discussed previously, a similar amelioration of side-effects (dizziness and fatigue) occurred in a bipolar disorder study using CHM with carbamazepine (Zhang et al., 2005).

Our review of the literature revealed that the only mono-preparations of HMs trialed adjuvantly with psychotropics are L. angustifolia and G. biloba. As detailed above, these results were positive, encouraging further research into other HMs. Two psychotherapies that may provide novel adjuvant application with synthetic antidepressants for enhancing efficacy in the treatment of MDD are golden root (Rhodiola rosea), and saffron (Crocus sativus). Preliminary studies of moderate methodological rigor using R. rosea have demonstrated potential antidepressant, anti-fatigue and anxiolytic activity (Bystritsky et al., 2008; Darbinyan et al., 2007; Kelly, 2001; Shevtsov et al., 2003). Before however adjuvancy studies are pursued, more substantive evidence of R. rosea as a thymoleptic mono-therapy is required. In two studies with small samples, the petals and stamen from C. sativus have demonstrated placebo significant antidepressant activity (Akhondzadeh et al., 2005; Moshiri et al., 2006), and in three trials have displayed equivalent efficacy to imipramine (Akhondzadeh et al., 2004), and fluoxetine (Akhondzadeh et al., 2007; Noorbala et al., 2005). Additional studies by different research groups and with larger samples are needed to validate these findings. Regardless, the evidence currently encourages research into adjuvant use of saffron with antidepressants.

A curious deficiency uncovered in our review of the literature was the absence of adjuvancy studies using St. John’s wort (Hypericum perforatum; SJW). A potential reason for the lack of trials exploring co-prescription of SJW with antidepressants, may be a concern over pharmacodynamic antagonism causing serotonin syndrome and/or switching to hypomania or mania (Finfgeld, 2004). However, evidence to support such a concern is weak and is currently based only on unsubstantiated case reports (Knuppel and Linde, 2004; Rodriguez-Landa and Contreras, 2003; Schulz, 2006). The case studies typically also have concomitant use of other medications and/or recreational drugs, and a background of cyclothymia (Nierenberg et al., 1999; Raja and Azzoni, 2006; Schneck, 1998). In several cases, a clear temporal association appeared to exist between SJW use and induction of hypomania or mania, so caution is warranted in people with a personal or family history of bipolar depression. Several case reports of serotonin syndrome have been documented by drug surveillance agencies (Knuppel and Linde, 2004). Currently however, it is not clear whether it is a dose-dependent phenomenon or what its mechanisms may be, and in particular, whether an interaction with antidepressants causing hyperserotonergism actually occurs. We note that concerns over serotonin syndrome do not appear to be inhibiting research or off-label prescription of multiple synthetic antidepressants (Davids et al., 2006; de la Gandara et al., 2005; Pat-
sense suggests that a “one-size fits all” approach often adopted in clinical trials may have less success than tailored prescriptions treating the cause/s of the individual’s depression; although this contention requires further evidence. The difficulty both clinicians and researchers face is how to provide evidence-based adjuvant strategies when a paucity of data exists on clear prescriptive protocols (Antonijevic, 2006). Research needs to be advanced in identifying which treatments combinations (synthetic or natural) are more beneficial for which manifestations of MDD.

In the case of nutritional adjuvancy, a beneficial effect may more likely occur when specific deficiencies or neurological dysregulations are apparent. For example, a patient who does not eat any omega-3 containing foods may potentially benefit more from adjuvant omega-3 prescription than a patient who regularly eats deep sea fish. Common deficiencies affecting mental health outcomes may involve amino acids (e.g. tryptophan, phenylalanine, tyrosine), which provide the precursors to neurochemicals (Byerley et al., 1987); B vitamins in particular B6, B12 and folate, which are involved in methylating pathways (Morris et al., 2008; Papakostas et al., 2005); and omega-3, which encourages neuronal communication (Appleton et al., 2006; Lin and Su, 2007).

In conclusion, while some positive evidence supports nutritional adjuvancy with various psychopharmacotherapies, adjuvant use of herbal therapies has not been sufficiently studied to warrant standard clinical application. This remains a promising area of research via robust, safety-conscious studies.

Conflict of interest

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References


Antonijevic IA. Depressive disorders – is it time to endorse different strategies when a paucity of data exists on clear prescriptive protocols? Psychother Psychosomatics 2006;75:139–53.


CIPS. Internationale skalen fur die Psychiatrie. Gottingen: Beltz; 1996.


Schulz V. Safety of St. John’s wort extract compared to synthetic antidepressants. Psychopharmacology 2006;163:199–204.


Shaw K, Turner J, Del Mar C. Folic acid and 5-hydroxytryptophan for schizophrenia. Cochrane Database Systematic Reviews 2002 [CD003198].


Soares K, McGrath J. Vitamin E for neuroleptic-induced tardive dyskinesia. Cochrane Database Systematic Reviews 2001(4) [CD000209].


