Current Scientific Research of Nutraceuticals in Depression & Anxiety

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Overview of Presentation

• Context of Nutraceuticals in Good Mental Health (standardised nutritional and herbal medicines)

• In Major Depression, Bipolar Disorder, Anxiety
  • Kava
  • St John’s wort
  • Adjunctive/Monotherapy Nutraceuticals in Depression
  • Omega 3
  • SAMe

• Concluding Comment
GOOD MENTAL HEALTH

- Good Nutrition
- Adequate Exercise
- Relationship Support
- Mental Hygiene/Psychology
- NUTRIENTS & HERBAL MEDICINES
- Limitation of Vices
- Mindfulness
- Greenspace
- Employment
Clinical Depression: An Evidence-based Integrative Complementary Medicine Treatment Model

Jerome Sarris, PhD, MHSc

ALTERNATIVE THERAPIES, JUL/AUG 2011, VOL. 17, NO. 4

FIGURE 2 The Antidepressant-Lifestyle-Psychological-Social Depression Treatment Model

Abbreviations: SJW, St John’s wort; SAMe, S-adenosyl-methionine; EFA, essential fatty acids.
Kava (Piper methysticum)

- A South Pacific plant
  - Peeled rootstock used decocted with water
  - Drunk as a beverage

- Cultural, religious, medicinal, recreational use

- Commercial use as a medicine in tablet, tincture, tea

Section Foci

Kava chemistry & psychopharmacology

Kava clinical evidence for treating anxiety and depression

Cognition and Genetics

Safety issues & driving

Liver toxicity Issues
Mechanisms of Action

- Inhibition of GABA voltage-dependent sodium/calcium channels
- Enhances ligand binding to GABA-α
- Increases GABA receptor numbers & regulates GABA transmission
- Noradrenaline re-uptake inhibition (pre-frontal cortex)
- Dopamine re-uptake inhibition (nucleus accumbens)
- Reversible MAO-B inhibition
Neurocognitive effects of kava (*Piper methysticum*): a systematic review

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Study design</th>
<th>Key observations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modulation of calcium and sodium channels</td>
<td><em>In vitro</em></td>
<td>Interaction of kavain with voltage-dependent sodium and calcium channels. When applied before anoxia the sodium channel blockers tetrodotoxin and kavain preserved vesicular ATP content, prevented both the veratridine-induced increases of Na⁺ and Ca²⁺.</td>
<td>Gleitz <em>et al.</em> 1996/95 [20, 68]</td>
</tr>
<tr>
<td>Voltage-dependent sodium channel inhibition</td>
<td><em>In vitro</em></td>
<td>Both kavain and methysticin inhibited voltage-dependent Na⁺ channels in acutely dissociated rat CA1 hippocampal neurons leading to a decrease of cellular excitability.</td>
<td>Magura <em>et al.</em> 1997 [69]</td>
</tr>
<tr>
<td>Inhibition of voltage-dependent calcium channels</td>
<td><em>In vitro</em></td>
<td>Kavain interacted with the M3 receptor or the M3 associated G-protein receptor. The actions of kavain did not affect the prostaglandin pathways and nitric oxide mediated relaxation was not observed.</td>
<td>Martin <em>et al.</em> 2000 [70]</td>
</tr>
<tr>
<td>Reduced neuronal re-uptake of dopamine</td>
<td><em>In vivo</em></td>
<td>High doses of kavain and desmethoxyyangonin increased dopamine levels in the nucleus accumbens of rats.</td>
<td>Baum <em>et al.</em> 1998 [71]</td>
</tr>
<tr>
<td>Reduced neuronal re-uptake of noradrenaline</td>
<td><em>In vitro</em></td>
<td>Kavain and methysticin inhibited the uptake of noradrenaline in rat cerebral cortex and hippocampal synaptosomes.</td>
<td>Seitz <em>et al.</em> 1997 [72]</td>
</tr>
<tr>
<td>Enhanced ligand binding to GABA-α receptors</td>
<td><em>In vitro</em></td>
<td>Yangonin, kavain, dihydrokavain, methysticin, and dihydromethysticin enhanced the specific binding of [³H]-bicuculline methochloride (although did not inhibit the specific binding of [³H]-flunitrazepam).</td>
<td>Boonen <em>et al.</em> 1998 [28]</td>
</tr>
<tr>
<td>Enhanced regulation of GABAergic neurotransmission</td>
<td><em>In vitro</em></td>
<td>Kavapyrones enhanced [³H]-muscimol binding in a concentration-dependent manner. Maximum potentiation was observed in the hippocampus, amygdala and medulla oblongata.</td>
<td>Jussofie <em>et al.</em> 1994 [26]</td>
</tr>
</tbody>
</table>
Kava Chemistry

Major Constituents

- Lipophilic resins called “kavalactones” or “kavapyrones”
- 18 in total with 6 major kavalactones
- Chemotypes labelled from 1-6 (Lebot system) e.g. 425631

<table>
<thead>
<tr>
<th>Kavalactones</th>
<th>R¹</th>
<th>R²</th>
<th>C5-C6</th>
<th>C7-C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kavain</td>
<td>H</td>
<td>H</td>
<td>-</td>
<td>=</td>
</tr>
<tr>
<td>Methysticin</td>
<td>OCH₂O</td>
<td></td>
<td>-</td>
<td>=</td>
</tr>
<tr>
<td>Desmethoxyyangonin</td>
<td>OCH₂O</td>
<td></td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Dihydrokavain</td>
<td>H</td>
<td>H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dihydromethysticin</td>
<td>OCH₂O</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yangonin</td>
<td>OCH₃</td>
<td>H</td>
<td>=</td>
<td>=</td>
</tr>
</tbody>
</table>
Kava: Meta-analysis (Pittler & Ernst 2003)

**Analysis 1.1. Comparison | Kava versus placebo for anxiety, Outcome | Improvement (HAMA-score).**

Review: Kava extract versus placebo for treating anxiety

Comparison: Kava versus placebo for anxiety

Outcome: Improvement (HAMA-score)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV(Random,95% CI)</td>
</tr>
<tr>
<td>Connor 2002</td>
<td>17</td>
<td>5.7 (7.6)</td>
<td>18</td>
<td>8.5 (4.2)</td>
<td>- &amp; -</td>
</tr>
<tr>
<td>Geier 2004</td>
<td>25</td>
<td>12.7 (6.7)</td>
<td>25</td>
<td>12.3 (7.3)</td>
<td>- &amp; -</td>
</tr>
<tr>
<td>Knecht 1991</td>
<td>29</td>
<td>12.3 (8.7)</td>
<td>29</td>
<td>3.6 (8.4)</td>
<td>- &amp; -</td>
</tr>
<tr>
<td>Lehrl 2004</td>
<td>34</td>
<td>10.6 (7.3)</td>
<td>23</td>
<td>9.2 (10)</td>
<td>- &amp; -</td>
</tr>
<tr>
<td>Malsch 2001</td>
<td>20</td>
<td>3 (7.5)</td>
<td>20</td>
<td>0.6 (4.6)</td>
<td>- &amp; -</td>
</tr>
<tr>
<td>Volz 1997</td>
<td>52</td>
<td>21 (13)</td>
<td>48</td>
<td>16.2 (14.3)</td>
<td>- &amp; -</td>
</tr>
<tr>
<td>Wamecke 1991</td>
<td>20</td>
<td>25.61 (12.8)</td>
<td>20</td>
<td>7.65 (15.9)</td>
<td>- &amp; -</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>197</td>
<td>183</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 19.89; Chi² = 27.47, df = 6 (P = 0.00012); I² = 78%
Test for overall effect: Z = 1.98 (P = 0.047)
The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of *Piper methysticum*

J. Sarris • D. J. Kavanagh • G. Byrne • K. M. Bone • J. Adams • G. Deed

- **3-week RCT** (n=60)
- **Cross-over study**
- **Kava vs. Placebo** (tablets) (250mg of kavalactones)
- **Adults with generalised anxiety and different levels of depression**

**Participants Included (n= 60)**
- Male = 30  Female = 30

**After 1 week placebo run-in phase (n=41)**
- Placebo drop outs excluded = 14
- Raised LFT enzymes = 3
- Consent Withdrawn = 2

**Participants Randomised to**
- **Group A = 19**
  - **Drop outs after randomisation n= 1** (after Placebo phase)
    - Non-compliance = 1
  - **Participants Completed the Study Group A= 18**
- **Participants Randomised to**
  - **Group B= 22**
  - **Drop outs after randomisation n= 3** (after Kava phase)
    - Minor adverse event = 1
    - Unspecified reason = 1
    - Cold/Flu = 1
  - **Participants Completed the Study Group B= 19**

**Participants Completed the Study Total n=37**
The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of *Piper methysticum*

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**Anxiety Outcome**

**Depression Outcome**

![Graph showing Anxiety Outcome](image1)

![Graph showing Depression Outcome](image2)

Fig. 2 Results on the Hamilton Anxiety Scale (*HAMA*)

Fig. 4 Results on the Montgomery–Asberg Depression Rating Scale (*MADRS*)
Figure 2. Predictive effect of baseline depression to reduction of anxiety

$r = .17, p = 0.32$
An explorative qualitative analysis of participants’ experience of using kava versus placebo in an RCT

Australian Journal of Medical Herbalism 2010 22(1)

Jerome Sarris MHSc PhD
Jon Adams MA PhD
David J Kavanagh MA PhD

<table>
<thead>
<tr>
<th>Major domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of stress and anxiety from kava</td>
</tr>
<tr>
<td>Effects of kava on mood</td>
</tr>
<tr>
<td>Effect of kava on sleep</td>
</tr>
<tr>
<td>Kava’s effect on physical signs of anxiety</td>
</tr>
<tr>
<td>Physiological side effects possibly from kava</td>
</tr>
<tr>
<td>Effect of being on placebo compared with kava</td>
</tr>
</tbody>
</table>

KAVA

- I have been more relaxed in the past week . . and I am able to cope a lot easier. My usual anxiety symptoms have decreased or disappeared (participant 55)
- I have been able to handle stress in a more positive light . . mind has stopped ticking so late in the evening (participant 59)
- Found it easy to accomplish day to day activities without getting worked up. I had a pretty hectic week but didn’t feel too concerned or nervous about anything (participant 18)
- Felt more calm especially in the evening. Not as fearful of the worst happening (participant 52)

PLACEBO

- No noticeable effects on anxiety and stress quite bad, in fact a little worse than usual (participant 1)
- My stress and anxiety stayed elevated, still poor concentration, and motivation, feeling of nervousness in general (participant 18)
- No positive effect occurred. Felt quite fearful and anxious (participant 52)
- Very apprehensive, not a good feeling, free floating anxiety like first week of trial (placebo week). Haven’t felt that restless before (participant 13)
St. John’s wort and Kava in treating major depressive disorder with comorbid anxiety: a randomised double-blind placebo-controlled pilot trial

Jerome Sarris¹*, David J. Kavanagh², Gary Deed¹ and Kerry M. Bone³

HUMAN PSYCHOPHARMACOLOGY

- Ten week study
- Cross-over RCT
- Two wk placebo run-in
- SJW + Kava vs. placebo
- 37 participants with MDD + comorbid anxiety
- Most results not significant
Kava Safety Issues...

- Previous global issues with liver toxicity
- Over 100 cases of liver failure or death (pharmaceutical & traditional extracts)
- Still comparably very safe (2 cases/100 million doses)
Kava hepatotoxicity: pathogenetic aspects and prospective considerations

Rolf Teschke

Table 1. Verified pathogenetic factors of kava hepatotoxicity

<table>
<thead>
<tr>
<th>Pathogenetic factor</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ethnic origin</td>
<td>No</td>
</tr>
<tr>
<td>2. Solvents and solubilizers used for kava extracts</td>
<td>No</td>
</tr>
<tr>
<td>3. Quality of kava cultivar</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Quality of kava plant part</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Adulterations and impurities</td>
<td>No</td>
</tr>
<tr>
<td>6. Hepatic glutathione</td>
<td>No</td>
</tr>
<tr>
<td>7. Cyclooxygenase</td>
<td>No</td>
</tr>
<tr>
<td>8. P-glycoprotein</td>
<td>No</td>
</tr>
<tr>
<td>9. Genetic enzyme deficiencies</td>
<td>No</td>
</tr>
<tr>
<td>10. Comedication, kavalactones overdose and prolonged use</td>
<td>Yes</td>
</tr>
<tr>
<td>11. Alcohol</td>
<td>No</td>
</tr>
<tr>
<td>12. Toxic constituents and metabolites</td>
<td>Yes</td>
</tr>
</tbody>
</table>

May be due to...

- Poor quality kava
- Incorrect plant parts
- Potent inappropriate cultivars
- Co-use with alcohol/medication
- Genetic 2D6 insufficiency
Kava, the anxiolytic herb: back to basics to prevent liver injury?
Rolf Teschke, Jerome Sarris, Xaver Glass & Johannes Schulze

<table>
<thead>
<tr>
<th>Items</th>
<th>Proposals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Quality of kava cultivar</td>
<td>Noble kava cultivar ( \text{(A,B)} )</td>
</tr>
<tr>
<td>2 Minimum of plant maturation</td>
<td>5 years ( \text{(A,B)} )</td>
</tr>
<tr>
<td>3 Kava plant part ( \text{A,B} )</td>
<td>Peeled rhizomes and roots</td>
</tr>
<tr>
<td>4 Solvents used for kava extracts</td>
<td>Water ( \text{(A,B)} )</td>
</tr>
<tr>
<td>5 Solubilizers</td>
<td>None ( \text{(A,B)} )</td>
</tr>
<tr>
<td>6 Adulterations and impurities</td>
<td>Surveillance ( \text{(A,B)} )</td>
</tr>
<tr>
<td>7 Maximum daily dose</td>
<td>To be determined ( \text{(A,B)} )</td>
</tr>
<tr>
<td>8 Maximum duration of use</td>
<td>To be determined ( \text{(A,B)} )</td>
</tr>
<tr>
<td>9 Comedication</td>
<td>Not recommended ( \text{(A,B)} )</td>
</tr>
<tr>
<td>10 Alcohol use</td>
<td>Not recommended ( \text{(A,B)} )</td>
</tr>
<tr>
<td>11 Prescription device</td>
<td>Obligate ( \text{(A)}, ) not feasible ( \text{(B)} )</td>
</tr>
</tbody>
</table>
Kava hepatotoxicity solution: A six-point plan for new kava standardization

Rolf Teschke\textsuperscript{a,*}, Jerome Sarris\textsuperscript{b,c}, Vincent Lebot\textsuperscript{d}

Proposals for future strategies.

\textbf{Recommendations}
1. Vanuatu legislation regarding the preferred noble cultivar(s) such as Borogu
2. Additional legislation of peeled rhizome and roots to be used for water based kava extracts
3. Corresponding legislation also in other countries of the South Pacific Islands
4. Regulatory definition of noble cultivar such as Borogu and use of its peeled rhizomes and roots
5. Regulatory standardization of quantitative method for kavalactones in the extract
6. Limitation of kava use to water based extracts
7. Regulatory definition of daily dose and duration of use
8. Mandatory prescription guidance for kava drugs to minimize risks
9. Regulatory surveillance of cultivators, harvesters, farmers, and manufacturers
The acute effects of kava and oxazepam on anxiety, mood, neurocognition; and genetic correlates: a randomized, placebo-controlled, double-blind study

J Sarris\(^1,2,3^*)\, A Scholey\(^2,3\), I Schweitzer\(^1\), C Bousman\(^1\), E LaPorte\(^2,3\), C Ng\(^1\), G Murray\(^4\) and C Stough\(^2,3\)

- 3-Week, Double-Blind, Randomised, Crossover Study
- Acute randomised doses:
  - Kava (180 mg of kavalactones)
  - Oxazepam 30mg
  - Placebo (matching)
- Outcomes
  - STAI, Bond-Lader, STCI
  - COMPASS cog battery
  - Genetic correlates
  - Side effects

1) Baseline STAI, BL, STCI
2) Then randomly assigned to Kava, Oxazepam, Placebo
3) Waited an 1.5 hrs for drugs to take effect
4) COMPASS, Driving
5) STAI, BL, STCI
6) Safety screen
Results for participants with mild-moderate anxiety (n=22) subjected to moderate cognitive demand on the primary outcome of STAI-S revealed:

- A significant interaction between treatments ($p=0.046$, partial $\eta^2 = 0.14$)

- Participants experienced greater anxiety when given placebo compared to oxazepam having a reduction of 2.6 points on STAI-S ($p=0.035$)*

- Placebo anxiety went up by 1.8 points on STAI-S (trend $p=0.08$)

- Kava anxiety stayed flat (NS) potentially mitigating the anxiogenic effects of the cognitive demand

* $p = 0.035$
No significant Group X Time treatment interaction was found on mood outcomes for Kava

Alertness was significantly reduced in the oxazepam on Bond-Lader VAS \((p<0.001)\)

No significant reduction for alertness was found in the Kava or placebo conditions
Overall, kava had no negative effect on cognition.

However no definitive positive effect was found for attention, memory, vigilance, reaction-time.

On mood and anxiety outcomes of participants administered kava, the NET rs3785157-T allele (\( \rho = -0.48, \ p=0.01 \)) was associated with declines in Bond-Lader “content” subscale scores.

NET rs2242446-T allele (\( \rho = 0.60, \ p<0.01 \)) associated with an increase in STCI-S “seriousness” subscale score.

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### Table 1. Genetic polymorphisms analyzed

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA transporters (SLC6A1)</td>
<td>rs956053, rs2697153, rs2930152,</td>
</tr>
<tr>
<td></td>
<td>rs1710879, rs2601126</td>
</tr>
<tr>
<td>GABA receptors (GABR)</td>
<td>rs2229940, rs279858, rs279871</td>
</tr>
<tr>
<td>Noradrenaline transporters</td>
<td>rs3785157, rs11568324, rs998424,</td>
</tr>
<tr>
<td>(NET, SLC6A2)</td>
<td>rs2242447, rs28386840, rs2242446</td>
</tr>
<tr>
<td>Catechol-O-methyltransferase</td>
<td>rs737865, rs4680(Val158Met)</td>
</tr>
<tr>
<td>(COMT)</td>
<td></td>
</tr>
<tr>
<td>Brain derived neurotrophic</td>
<td>rs7124442, rs6265(Val66Met)</td>
</tr>
<tr>
<td>factor (BDNF)</td>
<td>Promoter region variable number</td>
</tr>
<tr>
<td></td>
<td>tandem repeat</td>
</tr>
<tr>
<td>Serotonin transporter (SLC6A4)</td>
<td>1 to 70 alleles</td>
</tr>
<tr>
<td>Cytochrome P450 2D6 (CYP2D6)</td>
<td>rs2740574</td>
</tr>
<tr>
<td>Cytochrome P450 3A4 (CYP3A41b)</td>
<td></td>
</tr>
</tbody>
</table>
Liver function tests revealed no significant change on all parameters (e.g. GGT, ALP, AST, bilirubin) between baseline and after kava or oxazepam use ($p$’s $>0.05$)

Reported adverse effects noted at the conclusion of each session found no significant differences between treatments.

Marked fatigue occurred in 12/22 (kava), 10/22 (oxazepam), 10/22 (placebo); while after oxazepam treatment 3/22 experienced headaches, dizziness 5/22; placebo group experienced headaches 4/22 and dizziness 2/22
Kava and Driving?

• One study has assessed the potential effects of kava on driving

• Herberg (1991) conducted an RCT which investigated the effects of 300mg of kava daily over 15 days on driving ability

• Participants were subjected to a battery of tests including measures of concentration, vigilance, optical orientation, motor co-ordination and reaction time under stress

• Results showed that kava had no effect on measures of driving performance

Don’t Kava Drink-Drive...
Kava and Driving: Acute RCT
(Sarris et al. 2012)

Methods

- Driving simulator (AusEd™) was used by 22 adults aged between 18-65

- After being randomly administered an acute medicinal dose of kava (180mg of kavalactones), oxazepam (30mg), and placebo

- One week apart in a cross-over design trial
Kava and Driving Acute RCT: Results

- No impairing effects on driving outcomes were found after kava compared to placebo.

- Oxazepam group as having significantly slower breaking reaction time compared to placebo \( (p=0.002) \) and kava \( (p=0.003) \).

- Kava group had significantly less lapses of concentration compared to oxazepam \( (p=0.033) \).

- No significant differences were found between groups for steering deviation, speed deviation, and number of crashes.

- Not modified by driving experience.
Kava and Driving: Acute RCT

* Significantly slower reaction time (between groups $p<0.001$); oxazepam group vs. placebo ($p=0.002$); oxazepam vs. kava ($p=0.003$)
The KALM Study

- 8 week RCT \((n=75)\)
- Participants with GAD and no depression
- Kava \((120\text{mg kavalactones})\) versus placebo \((\text{titrated to } 240\text{mg in non-response})\)
- Outcomes: anxiety scales, quality of life, sexual function, liver function
- Genetic polymorphisms: GABA & noradrenalin transporters
Kava in the Treatment of GAD: Results
A Double-Blind, Randomized, Placebo-Controlled Study
Sarris J, Stough C, Bousman CA... Schweitzer I

CURRENTLY IN SUBMISSION
‘Omic’ Genetic Technologies for Herbal Medicines in Psychiatry

Jerome Sarris,¹,²* Chee Hong Ng¹ and Isaac Schweitzer¹
¹Professorial Unit, The Melbourne Clinic, Department of Psychiatry, University of Melbourne, Australia
²Swinburne University of Technology, Centre for Human Psychopharmacology, Melbourne, Australia

The field of genetics, which includes the use of ‘omic’ technologies, is an evolving area of science that has emerging application in phytotherapy. Omic studies include pharmacogenomics, proteomics and metabolomics. Herbal medicines, as monotherapies, or complex formulations such as traditional Chinese herbal prescriptions, may benefit from omic studies, and this new field may be termed ‘herbomics’. Applying herbomics in the field of psychiatry may provide answers about which herbal interventions may be effective for individuals, which genetic processes are triggered, and the subsequent neurochemical pathways of activity. The use of proteomic technology can explore the differing epigenetic effects on neurochemical gene expression between individual herbs, isolated constituents and complex formulae. The possibilities of side effects or insufficient response to the herb can also be assessed via pharmacogenomic analysis of polymorphisms of cytochrome P450 liver enzymes or P-glycoprotein. While another novel application of omic technology is for the validation of the concept of synergy in individual herbal extracts and prescriptive formulations. Chronic administration of psychotropic herbal medicines may discover important effects on chromatin remodelling via modification of histone and DNA methylation. This paper focuses on the emerging field of herbomics, and is to our knowledge the first publication to explore this in the area of psychiatry. Copyright © 2011 John Wiley & Sons, Ltd.
Reduction of Anxiety on HAMA in the Kava Group: GABA Transporter Genotype

CURRENTLY IN SUBMISSION
St John’s wort (*Hypericum perforatum*)

• *Hypericum perforatum* is a plant medicine with established efficacy in treating MDD (>40 clinical trials)

- Modulation of monoamine transmission via Na+ channel
- Nonselective inhibition of re-uptake of serotonin, dopamine, norepinephrine
- Decreased degradation of neurochemicals
- Increased binding/sensitivity/density to 5-HT1AB
- Dopaminergic activity (prefrontal cortex)
- Inhibited neuronal release of glutamate
- Neuroendocrine modulation
- Anti-depressant and anxiolytic activity in animal models

Precautions

- Potential drug interactions
- Switching in Bipolar Disorder
- Serotonin Syndrome

(Butterweck 2003, Sarris and Kavanagh 2009)
### Table 2. St. John’s Wort (SJW) Reviews and Meta-analyses of Randomized Clinical Trials Using the Hamilton Rating Scale for Depression (HAM-D) as the Outcome Measure

<table>
<thead>
<tr>
<th>Study</th>
<th>n of trials</th>
<th>SJW</th>
<th>Comparison</th>
<th>RR (95% CI)</th>
<th>Mean response&lt;sup&gt;a&lt;/sup&gt;</th>
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<td></td>
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<td>Comparison</td>
</tr>
<tr>
<td><strong>SJW versus placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linde et al. (2008)</td>
<td>9 larger</td>
<td>1129</td>
<td>915</td>
<td>1.28 (1.10–1.49)</td>
<td>56.7%</td>
</tr>
<tr>
<td></td>
<td>9 smaller</td>
<td>506</td>
<td>514</td>
<td>1.87 (1.22–2.87)</td>
<td>46.8%</td>
</tr>
<tr>
<td>Röder et al. (2004)</td>
<td>18</td>
<td>1086</td>
<td>1043</td>
<td>1.52 (1.28–1.75)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>53.3%</td>
</tr>
<tr>
<td>Werneke et al. (2004)</td>
<td>18</td>
<td>*</td>
<td>*</td>
<td>1.73 (1.40–2.14)</td>
<td>*</td>
</tr>
<tr>
<td>Whiskey et al. (2001)</td>
<td>14</td>
<td>690</td>
<td>646</td>
<td>1.98 (1.49–2.62)</td>
<td>56.5%</td>
</tr>
<tr>
<td><strong>SJW versus synthetic antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Linde et al. (2008)</td>
<td>12 SSRIs</td>
<td>905</td>
<td>889</td>
<td>1.00 (0.90–1.15)</td>
<td>52.0%</td>
</tr>
<tr>
<td></td>
<td>5 Tri/tetracycl</td>
<td>508</td>
<td>508</td>
<td>1.02 (0.90–1.15)</td>
<td>48.6%</td>
</tr>
<tr>
<td>Röder et al. (2004)</td>
<td>15</td>
<td>1117</td>
<td>1114</td>
<td>1.04 (0.93–1.78)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>53.2%</td>
</tr>
<tr>
<td>Whiskey et al. (2001)</td>
<td>9</td>
<td>694</td>
<td>700</td>
<td>1.00 (0.90–1.11)</td>
<td>60.8%</td>
</tr>
</tbody>
</table>
St John’s wort (Hypericum perforatum)

Hypericum Clinical Trial Study Group 2002

8-week 3-arm RCT (n=344)

SJW vs. sertraline vs. placebo
St John’s Wort (*Hypericum perforatum*) versus Sertraline and Placebo in Major Depressive Disorder: Continuation Data from a 26-Week RCT

Pharmacopsychiatry 2012; 45: 1–4

J. Sarris\(^1,2\), M. Fava\(^3\), I. Schweitzer\(^1\), D. Mischoulon\(^3\)

Continuation Phase: Weeks 10-26

<table>
<thead>
<tr>
<th>Treatment (n)</th>
<th>Wk 10</th>
<th>Wk 14</th>
<th>Wk 18</th>
<th>Wk 22</th>
<th>Wk 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>49</td>
<td>43</td>
<td>39</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>SJW</td>
<td>35</td>
<td>33</td>
<td>27</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Placebo</td>
<td>40</td>
<td>37</td>
<td>32</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>
Conditional Probability of Response or Non-Response of Placebo, Sertraline or St John’s wort in Major Depressive Disorder

Jerome Sarris PhD, MHSc /***, Andrew A Nierenberg, MD***, Maurizio Fava, MD***, Isaac Schweitzer MD*, Jonathan E Alpert, MD***, PhD, Jerrold F Rosenbaum, MD***, Nadia Iovieno, MD***, Jennifer Covino, MPA***, David Mischoulon, MD, PhD***

➤ CURRENTLY IN SUBMISSION
Clinical Recommendations

• Quality issue: Use standardised products made via GMP

• Using lower ‘hyperforin’ SJW extracts (e.g. Ze 117) to minimise induction of PgP and CYP 3A detoxification pathways

• Caution in Bipolar Disorder

• May have a role in being introduced in people withdrawing from antidepressants when at the lower end of downward titration (SJW can be gradually titrated up)
• Current evidence only supports SAMe as a monotherapy

• Evidence for Omega-3 fatty acid is mixed

• No supportive evidence for Folic acid or Inositol

• Limited evidence for Tryptophan

• The rest is adjunctive/adjuvant evidence...
Review

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

Jerome Sarris a, *, David J. Kavanagh b, Gerard Byrne a

a School of Medicine, University of Queensland, Queensland, Australia
b Institute of Health and Biomedical Innovation and School of Psychology and Counselling, Queensland University of Technology, Queensland, Australia

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Kava
St. John’s wort

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 5-hydroxytryptophan 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.
Adjuvant use of nutritional and herbal medicine with antidepressants.

<table>
<thead>
<tr>
<th>Herbal/nutritional medicine</th>
<th>Clinical evidence</th>
</tr>
</thead>
<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>
</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>
</tr>
<tr>
<td>Lavender (Lavandula 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 (Akhondzadeh et al., 2003)</td>
</tr>
<tr>
<td>Provenance</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</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>
</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 on average 1.5 weeks (Papakostas et al., 2005)</td>
</tr>
<tr>
<td>Inositol</td>
<td>Controlled studies have demonstrated inositol augmentation with SSRIs does not improve depression in SSRI treatment failures (Levine et al., 1999; Nemets et al., 1999)</td>
</tr>
</tbody>
</table>
Review Article

Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials


Objective: Studies using augmentation of pharmacotherapies with nutraceuticals in bipolar disorder (BD) have been conducted and preliminary evidence in many cases appears positive. To date, however, no specialized systematic review of this area has been conducted. We present the first systematic review of clinical trials using nutrient-based nutraceuticals in combination with standard pharmacotherapies to treat BD. A subsequent aim of this report was to discuss posited underlying mechanisms of action.

Methods: PubMed, CINAHL, Web of Science, and Cochrane Library databases, and grey literature were searched during mid-2010 for human clinical trials in English using nutraceuticals such as omega-3, N-acetyl cysteine (NAC), inositol, and vitamins and minerals, in combination with pharmacotherapies to treat bipolar mania and bipolar depression. A review of the results including an effect size analysis (Cohen’s d) was subsequently conducted.
Clinical trials (n = 203)

Eliminated: not relevant, not a human study, no bipolar disorder outcome measure

Relevant human studies (n = 25)

Eliminated:
Wozniak et al. 2007 (61): not adjunctive
Marangell et al. 2003 (62): not adjunctive
Simmons 2003 (63): case studies
Stoll et al. 1996 (64): small sample
Heiden et al. 1999 (65): small sample
Chouinard et al. 1990 (17): small sample
Cohen et al. 1982 (66): small sample

Studies meeting inclusion criteria (n = 18)

Omega-3:
Gracious et al. 2010 (26)
Clayton et al. 2009 (24)
Hirashima et al. 2004 (32)
Frangou et al. 2006 (29)
Frangou et al. 2007 (31)
Keck et al. 2006 (33)
Osher et al. 2005 (25)
Chiu et al. 2005 (23)
Stoll et al. 1999 (28)

Others:
Behzadi et al. 2009 (49)
Berk et al. 2008 (22)
Chengappa et al. 2000 (42)
Evins et al. 2006 (43)
Kaplan et al. 2001 (8)
Scamà et al. 2003 (11)
Chouinard et al. 1985 (39)
Giannini et al. 2000 (44)
Coppen et al. 1986 (47)

Initial search (n= 1,710)
RESULTS

- Bipolar Depression
  - N-acetyl cysteine ($d=1.04$)
  - Chelated mineral/vitamin ($d=1.70$)

- Mania
  - L-Tryptophan ($d=1.47$)
  - Magnesium ($d=1.44$)
  - Folic acid ($d=0.40$)
  - Chelated mineral/vitamin ($d=0.83$)
  - Branch-chain amino acids ($d=1.60$)

- Bipolar Disorder outcomes may be potentially improved with nutraceuticals
- Adjunctively with conventional medication
- Caution is needed interpreting large effects
- Studies have not been replicated...
Omega-3 fatty acids

Thymoleptic effect:
- Reuptake inhibition of serotonin & dopamine
- Modulation of secondary messengers
- Enhanced cell membrane fluidity
- Anti-inflammatory effects

Mood stabilisation:
- Modulation of cell-signalling pathways via effects such as T₂ reduction (increasing cell membrane fluidity)
- Select cytokine modulation and arachidonic acid inhibition, and phosphoinositide (PI)-protein kinase C antagonism

(Sarris, Mischoulon, Schweitzer 2011)
Forest plot examining the effect of the type of \( \omega-3 \) LC-PUFA supplementation employed on the reduction in depressive symptoms.

**Group**  **Study [reference]**  **Statistics for each study**  **Relative weight**

**Mainly**  
- *DHA*  
  - Grenyer et al. 2007 [47]: Std diff = 0.170, Lower limit = -0.262, Upper limit = 0.601
  - Rees et al. 2008 [51]: Std diff = -0.352, Lower limit = -1.127, Upper limit = 0.423
  - Rogers et al. 2008 [52]: Std diff = -0.022, Lower limit = -0.288, Upper limit = 0.243
  - Silvers et al. 2005 [53]: Std diff = 0.611, Lower limit = 0.153, Upper limit = 1.069
  - Overall effect size: Std diff = 0.141, Lower limit = -0.195, Upper limit = 0.477

**Mainly**  
- *EPA*  
  - Behan et al. 1990 [44]: Std diff = -0.761, Lower limit = -1.287, Upper limit = -0.236
  - da Silva et al. 2008 \( \omega-3 \) [42]: Std diff = -1.175, Lower limit = -2.359, Upper limit = 0.099
  - da Silva et al. 2008 \( \omega-3 \) + AD [42]: Std diff = -1.621, Lower limit = -2.769, Upper limit = -0.472
  - Fontani et al. 2005 [68]: Std diff = -0.226, Lower limit = -0.710, Upper limit = 0.258
  - Freeman et al. 2008 [57]: Std diff = 0.507, Lower limit = -0.012, Upper limit = 1.026
  - Hallahan et al. 2007 [41]: Std diff = -0.954, Lower limit = -1.677, Upper limit = -0.232
  - Hirashima et al. 2004 [69]: Std diff = 0.151, Lower limit = -0.715, Upper limit = 1.016
  - Lucas et al. 2009 [58]: Std diff = -0.083, Lower limit = -0.441, Upper limit = 0.275
  - Nemets et al. 2006 [43]: Std diff = -1.353, Lower limit = -2.361, Upper limit = -0.345
  - Stoll et al. 1999 [38]: Std diff = -1.016, Lower limit = -1.778, Upper limit = -0.254
  - Su et al. 2003 [39]: Std diff = -2.067, Lower limit = -3.105, Upper limit = -1.029
  - Su et al. 2008 [40]: Std diff = -0.877, Lower limit = -1.592, Upper limit = -0.162
  - van de Rest et al. 2008 0.4g [59]: Std diff = 0.089, Lower limit = -0.184, Upper limit = 0.363
  - van de Rest et al. 2008 1.8g [59]: Std diff = 0.021, Lower limit = -0.255, Upper limit = 0.297
  - Warren et al. 1999 [55]: Std diff = 0.490, Lower limit = -0.073, Upper limit = 1.053
  - Overall effect size: Std diff = -0.446, Lower limit = -0.753, Upper limit = -0.138

(Martins 2009)
Adjunctive Low-Dose Docosahexaenoic Acid (DHA) on Mood and Cognitive Outcomes in Major Depression: A Naturalistic Open-Label Pilot Trial

METHODS:

- An 8-week open-label trial of adjunctive DHA (260mg or 520mg), in 28 patients (aged 18-65) with diagnosed MDD and a Hamilton Depression Rating Scale (HAM-D) score > 17

- Primary outcomes of mood, and cognition were measured. Background antidepressant and psychological treatment had been stable for at least 4 weeks prior to study entry

- Participants were required to agree to not eat more than one serving of oily fish a week or take additional complimentary medicine

- Participants were excluded if they had any concurrent or past psychiatric disorder other than mood disorders, a current substance use disorder or neurological disorder or suicidality

- The DHA and antidepressant medication dose remained fixed

(Smith, Sarris…Schweitzer 2012 in submission)
Adjunctive Low-Dose Docosahexaenoic Acid (DHA) on Mood and Cognitive Outcomes in Major Depression: *A Naturalistic Open-Label Pilot Trial*

CURRENTLY IN SUBMISSION- Sorry!
Studies using augmentation omega-3 in BD have been conducted and evidence indicates a positive effect.

Often not significant. Due to small sample sizes?

Meta-analytic pooling of the studies may be beneficial.

PubMed, CINAHL, Web of Science and Cochrane Library databases were searched during mid 2010:

- RCTs four weeks or longer
- Omega-3 in combination with pharmacotherapies or treatment as usual to treat BD depression and mania
| Study                  | Dose                                                                 | Design                          | Duration (wk) | Patients (n) | Mean Age (y) | Clinical Characteristics                                                                 | Comedication              | Outcomesa                           | Resultsb                           | Quality Analysis |
|-----------------------|----------------------------------------------------------------------|---------------------------------|---------------|--------------|--------------|------------------------------------------------------------------------------------------|---------------------------|-------------------------------------|------------------------------------|----------------|----------------|
| **Flaxseed oil**      |                                                                      |                                 |               |              |              |                                                                                          |                          |                                     |                                    |                |                |
| Gracious et al, 201019 | Flaxseed oil capsules titrated to maximum of alpha-linolenic acid 6.6 g vs placebo | Randomized, DB, PC              | 16            | 51           | 13           | DSM-IV bipolar I/II YMRS score ≥ 4 (children and adolescents)                            | Stable psychotropic medication | CDRS-R                             | No significant differences between groups occurred Fewer dropouts with flaxseed oil than placebo | 9               |                |
| **EPA**               |                                                                      |                                 |               |              |              |                                                                                          |                          |                                     |                                    |                |                |
| Frangou et al, 200731  | EPA 2 g/d or liquid paraffin placebo capsules                        | Randomized, DB, PC              | 12            | 14           | 42           | DSM-IV bipolar I HDRS-17 score > 10 (women)                                               | Stable lithium            | HDRS                                | No statistically significant differences were found between the groups on HDRS | 7.5             |                |
| Frangou et al, 200623,4 | EPA 1 or 2 g/d vs placebo capsules                                  | Randomized, DB, PC              | 12            | 75           | 47           | DSM-IV bipolar I/II HDRS-17 score > 10                                                   | Stable psychotropic medication > 8 wk | HDRS-17 YMRS | A significant reduction of 1 g and 2 g EPA vs placebo on HDRS, but not on YMRS | 9.5             |                |
| Keck et al, 200632,e  | EPA 6 g/d or placebo capsules                                       | Randomized, B, PC               | 16            | 121          | 44           | DSM-IV bipolar I/II or bipolar NOS (current MDD or rapid cycling)                        | A stable therapeutic dose of a mood stabilizer | IDS-C YMRS | No significant difference between EPA or placebo on any outcome                  | 8               |                |
| **EPA/DHA**           |                                                                      |                                 |               |              |              |                                                                                          |                          |                                     |                                    |                |                |
| Chiu et al, 200520     | EPA 4.4 g and DHA 2.4 g/d or olive oil placebo capsules              | Randomized, DB, PC              | 4             | 15 (14t)     | NA           | DSM-IV bipolar I (acute mania)                                                          | Valproate (fixed dose 20 mg/kg/d) | YMRS                              | Reductions in both groups on YMRS from baseline, but no difference between groups | 6               |                |
| Stoll et al, 199933    | EPA 6.2 g and DHA 3.4 g/d vs placebo capsules                        | Randomized, DB, PC              | 16            | 44 (30t)     | 43           | DSM-IV screening for mania and depression                                                | Medication treatment as usual | HDRS YMRS | Omega-3 group significantly reduced HDRS scores over placebo, but not on YMRS | 9.5             |                |
### Figure 2. Meta-Analysis: Omega-3 Versus Control in Bipolar Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Standard Difference in Means</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>P Value</th>
<th>Standard Difference in Means and 95% CI</th>
<th>Relative Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gracious et al, 2010&lt;sup&gt;19&lt;/sup&gt;</td>
<td>0.058</td>
<td>-0.491</td>
<td>0.607</td>
<td>.836</td>
<td>[ ]</td>
<td>19.87</td>
</tr>
<tr>
<td>Frangou et al, 2007&lt;sup&gt;31&lt;/sup&gt;</td>
<td>0.451</td>
<td>-0.610</td>
<td>1.512</td>
<td>.405</td>
<td>[ ]</td>
<td>7.13</td>
</tr>
<tr>
<td>Frangou et al, 2006&lt;sup&gt;23&lt;/sup&gt; (1 g)</td>
<td>0.612</td>
<td>-0.077</td>
<td>1.302</td>
<td>.082</td>
<td>[ ]</td>
<td>14.44</td>
</tr>
<tr>
<td>Frangou et al, 2006&lt;sup&gt;23&lt;/sup&gt; (2 g)</td>
<td>0.452</td>
<td>-0.226</td>
<td>1.130</td>
<td>.191</td>
<td>[ ]</td>
<td>14.80</td>
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<tr>
<td>Keck et al, 2006&lt;sup&gt;32&lt;/sup&gt;</td>
<td>0.042</td>
<td>-0.323</td>
<td>0.406</td>
<td>.823</td>
<td>[ ]</td>
<td>31.38</td>
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<tr>
<td>Stoll et al, 1999&lt;sup&gt;33&lt;/sup&gt;</td>
<td>1.016</td>
<td>0.254</td>
<td>1.778</td>
<td>.009</td>
<td>[ ]</td>
<td>12.38</td>
</tr>
<tr>
<td>Pooled data</td>
<td><strong>0.338</strong></td>
<td><strong>0.035</strong></td>
<td><strong>0.641</strong></td>
<td><strong>.029</strong></td>
<td>[ ]</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 3. Meta-Analysis: Omega-3 Versus Control in Bipolar Mania

<table>
<thead>
<tr>
<th>Study</th>
<th>Standard Difference in Means</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>P Value</th>
<th>Standard Difference in Means and 95% CI</th>
<th>Relative Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gracious et al, 2010&lt;sup&gt;19&lt;/sup&gt;</td>
<td>0.123</td>
<td>-0.427</td>
<td>0.672</td>
<td>.661</td>
<td>[ ]</td>
<td>18.36</td>
</tr>
<tr>
<td>Frangou et al, 2006&lt;sup&gt;23&lt;/sup&gt; (1 g)</td>
<td>0.425</td>
<td>-0.257</td>
<td>1.107</td>
<td>.222</td>
<td>[ ]</td>
<td>11.93</td>
</tr>
<tr>
<td>Frangou et al, 2006&lt;sup&gt;23&lt;/sup&gt; (2 g)</td>
<td>0.103</td>
<td>-0.567</td>
<td>0.774</td>
<td>.763</td>
<td>[ ]</td>
<td>12.33</td>
</tr>
<tr>
<td>Keck et al, 2006&lt;sup&gt;32&lt;/sup&gt;</td>
<td>0.184</td>
<td>-0.181</td>
<td>0.549</td>
<td>.323</td>
<td>[ ]</td>
<td>41.67</td>
</tr>
<tr>
<td>Chiu et al, 2005&lt;sup&gt;20&lt;/sup&gt;</td>
<td>0.117</td>
<td>-0.931</td>
<td>1.166</td>
<td>.827</td>
<td>[ ]</td>
<td>5.04</td>
</tr>
<tr>
<td>Stoll et al, 1999&lt;sup&gt;33&lt;/sup&gt;</td>
<td>0.277</td>
<td>-0.444</td>
<td>0.997</td>
<td>.452</td>
<td>[ ]</td>
<td>10.68</td>
</tr>
<tr>
<td>Pooled data</td>
<td><strong>0.198</strong></td>
<td><strong>-0.037</strong></td>
<td><strong>0.433</strong></td>
<td><strong>.099</strong></td>
<td>[ ]</td>
<td></td>
</tr>
</tbody>
</table>
Figure 4. Meta-Regression for Sample Size Bias

Circles represent individual studies. Regression slope: $z = -1.92; P = .05$. 
Clinical Recommendations

Take Home Messages

• Current evidence supports omega-3 in adjunctive treatment of bipolar depression.

• Current evidence, however, does not support omega-3 in the adjunctive treatment of bipolar mania.

• Clinicians are advised to recommend increased dietary omega-3 or daily supplementation of approximately 1 g to 1.5 g of mixed EPA and DHA (higher ratio of EPA).

• Effect size appears to be decreasing as more studies are done of better methodological rigour

• May have an especially beneficial role in comorbid cardiovascular conditions or if diet is deficient

Food Sources

- Unsaturated fats
  - Polyunsaturated fats
    - Omega 3 fatty acids: Eicosapentanoic acid (fish, shellfish), Docosahexanoic acid (fish, shellfish, α-linolenic acid: flaxseed, soybean, walnut, rapeseed oils)
    - Omega 6 fatty acids: Corn oil, Safflower oil, Sunflower oil
    - Omega 9 fatty acids: Olive oil, Avocados, Peanuts, Almonds
  - Monounsaturated fats

- Saturated fats
  - Animal fats, butter, lard

Fats and fatty acids

BMJ
S-Adenosyl Methionine (SAMe)

- SAMe serves as a necessary methyl donor of methyl groups involved with the metabolism and synthesis of neurotransmitters
- Folate deficiency is implicated in causing increased homocysteine levels, linked to poor response to antidepressants
- Metabolism of homocysteine to SAMe or back to methionine requires folate, B6 & B12
- SAMe and folate are involved with the methylation pathways in the ‘one-carbon’ cycle, responsible for the metabolism and synthesis or various monoamines

(Williams et al. 2005)
S-Adenosyl Methionine/ Folate Cycle

(Mischoulon & Fava cited in Papakostas 2009)
S-Adenosyl Methionine (SAMe)

• Several human clinical trials using SAMe in MDD have been conducted

• All have revealed beneficial antidepressant effects, and comparable effects to synthetic antidepressants

• Increases alacrity of response of SSRIs

• Parental or oral administration effective

• Good safety profile

(Papakostas 2009)
A 6-week RCT using adjunctive oral SAMe (target dose: 800 mg twice daily: n=73) in MDD patients unresponsive to stable SSRIs.
S-Adenosyl Methionine (SAMe) versus Escitalopram and Placebo in Major Depression

Sarris J, Papakostas GI, Vitolo O, Fava M, Mischoulon D (2012 in submission)

AIMS

- SAMe versus antidepressant (escitalopram) and placebo in treating MDD
- Aims to assess outcome depression outcome &
- Analyze the relationship between histamine and carnitine levels and response &
- To determine if histamine or carnitine levels changed during the course of antidepressant treatment

METHODOLOGY

- We examined a subsample (n=144) from one site of a two-site study of adults with diagnosed MDD
- After washout, eligible subjects were randomized to SAMe (1600mg-3200mg/daily), escitalopram (10mg-20mg/day), or placebo
- 12 weeks of double-blind treatment (titration at week 6 in non-response)
SAMe vs. Escitalopram- 12wk RCT

CURRENTLY IN SUBMISSION
S-adenosyl methionine (SAMe)

Clinical Considerations

- SAMe should be used with caution in patients with a history of (hypo)mania due to concerns over switching from unipolar depression to mania.
- SAMe is expensive and the cost may be prohibitive for some.
- Not suited for “over-methylators”, or in folate or B12 deficiency.
- 200mg bid titrated to 400-800mg bid (be aware of stimulation).
CONCLUDING COMMENT

References Available Upon Request