Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Excluded Studies and Reasons

Case report (n=2)


Lack of adequate control (n=15)


Meta-analysis (n=2)


Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 11/26/2019
Not human clinical trial (n=5)


Not human clinical trial in the part of anxiety study (n=1)


Not related to omega 3 supplement effect on anxiety (n=38)


29. Sanchez-Villegas A, Henriquez P, Figueiras A, Ortuno F, Lahortiga F, Martinez-


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61. Nieminen LR, Makino KK, Mehta N, Virkkunen M, Kim HY, Hibbeln JR.


Not simply treat with omega-3 related product (n=3)


Protocol but no result of studies (n=2)


Review article (n=7)


The same sample source from Buydens-Branchey, L. (2008) (n=1)


The same sample source from Nishi, D. (2013) (n=1)


The same sample source from Matsuoka, Y. (2015) (n=1)


Database study but not clinical trials (n=1)

79. Adams J, Sibbritt D, Lui CW, Broom A, Wardle J. {Omega}-3 fatty acid

No detailed information about changes of anxiety symptoms despite of our request of detailed data (n=6)


### eTable. Study Design and Jadad Scores of Recruited Studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Diagnosis</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe, N. (2018)</td>
<td>Double-blind randomized placebo controlled</td>
<td>Junior nurses work in hospital</td>
<td>1 2 1 4</td>
</tr>
<tr>
<td>Bellino, S. (2014)</td>
<td>Randomized controlled</td>
<td>Borderline personality disorders</td>
<td>1 0 1 2</td>
</tr>
<tr>
<td>Pomponi, M. (2014)</td>
<td>Double-blind randomized placebo controlled</td>
<td>Parkinson's Disease</td>
<td>2 1 1 4</td>
</tr>
<tr>
<td>Widenhorn-Muller, K. (2014)</td>
<td>Double-blind randomized placebo controlled</td>
<td>Children with ADHD</td>
<td>2 1 1 4</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Population</td>
<td>Outcome Measure</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Sauder, K.A. (2013)</td>
<td>Double-blind randomized placebo control cross-over</td>
<td>Healthy, nonsmoking men and postmenopausal women with moderate hypertriglyceridemia</td>
<td>1 1 1 3</td>
</tr>
<tr>
<td>Sohrabi, N. (2013)</td>
<td>Double-blind randomized placebo controlled</td>
<td>Healthy women with premenstrual syndrome</td>
<td>1 2 1 4</td>
</tr>
<tr>
<td>Gabbay, V. (2012)</td>
<td>Double-blind randomized placebo controlled</td>
<td>Tourette syndrome</td>
<td>1 2 1 4</td>
</tr>
<tr>
<td>Kiecolt-Glaser, J.K. (2011)</td>
<td>Double-blind randomized placebo controlled</td>
<td>Generally healthy subjects</td>
<td>2 1 1 4</td>
</tr>
<tr>
<td>Rogers, P.J. (2008)</td>
<td>Double-blind randomized placebo controlled</td>
<td>Mild to severe depression</td>
<td>1 2 1 4</td>
</tr>
<tr>
<td>van de Rest, O. (2008)</td>
<td>Double-blind randomized placebo controlled</td>
<td>Elderly volunteers</td>
<td>2 2 1 5</td>
</tr>
<tr>
<td>Yehuda, S. (2005)</td>
<td>Case-placebo control trial</td>
<td>Undergraduate college students with test anxiety</td>
<td>0 1 1 2</td>
</tr>
</tbody>
</table>
**eFigure 1. Whole Flowchart of Current Meta-Analysis**

**Identification**
- PubMed: (omega 3 OR eicosapentaenoic acid OR EPA OR DHA OR docosahexaenoic acid) AND (anxiety OR anxiety disorder OR generalized anxiety disorder OR agoraphobia OR panic disorder OR post-traumatic stress disorder)
  - Limits: N/A
  - Date: 2018/03/04
- Embase: (omega 3 OR eicosapentaenoic acid OR EPA OR DHA OR docosahexaenoic acid) AND (anxiety OR anxiety disorder OR generalized anxiety disorder OR agoraphobia OR panic disorder OR post-traumatic stress disorder)
  - Limits: N/A
  - Date: 2018/03/04
- ProQuest: (omega 3 OR eicosapentaenoic acid OR EPA OR DHA OR docosahexaenoic acid) AND (anxiety OR anxiety disorder OR generalized anxiety disorder OR agoraphobia OR panic disorder OR post-traumatic stress disorder)
  - Limits: N/A
  - Date: 2018/03/04
- ScienceDirect: (omega 3 OR eicosapentaenoic acid OR EPA OR DHA OR docosahexaenoic acid) AND (anxiety OR anxiety disorder OR generalized anxiety disorder OR agoraphobia OR panic disorder OR post-traumatic stress disorder)
  - Limits: N/A
  - Date: 2018/03/04
- Cochrane Library: (omega 3 OR eicosapentaenoic acid OR EPA OR DHA OR docosahexaenoic acid) AND (anxiety OR anxiety disorder OR generalized anxiety disorder OR agoraphobia OR panic disorder OR post-traumatic stress disorder)
  - Limits: N/A
  - Date: 2018/03/04
- ClinicalKey: (omega 3 OR eicosapentaenoic acid OR EPA OR DHA OR docosahexaenoic acid) AND (anxiety OR anxiety disorder OR generalized anxiety disorder OR agoraphobia OR panic disorder OR post-traumatic stress disorder)
  - Limits: N/A
  - Date: 2018/03/04
- Web of Science: (omega 3 OR eicosapentaenoic acid OR EPA OR DHA OR docosahexaenoic acid) AND (anxiety OR anxiety disorder OR generalized anxiety disorder OR agoraphobia OR panic disorder OR post-traumatic stress disorder)
  - Limits: N/A
  - Date: 2018/03/04
- ClinicalTrials.gov: (omega 3 OR eicosapentaenoic acid OR EPA OR DHA OR docosahexaenoic acid) AND (anxiety OR anxiety disorder OR generalized anxiety disorder OR agoraphobia OR panic disorder OR post-traumatic stress disorder)
  - Limits: N/A
  - Date: 2018/03/04

**Screening**
- Removal duplication (n=2141)

**Eligibility**
- Screen for eligibility (n=104)
  - Excluded articles which not discussed this topic, case reports/series, not humane clinical trials (n=2037)
  - Not meet the inclusion criteria (n=85)

**Included**
- Recruited studies (n=19)
**eFigure 2.** Funnel Plot of Changes in Anxiety Symptoms in Patients With and Without n-3 PUFA Treatment
**eFigure 3. Subgroup MA of Anxiolytic Effect Based Upon Placebo Controlled or Non–Placebo Controlled Design**

<table>
<thead>
<tr>
<th>Compared to Placebo</th>
<th>Study name</th>
<th>Sample size</th>
<th>Hedges’ g</th>
<th>95% Low CI</th>
<th>95% Up CI</th>
<th>p-Value</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-placebo</td>
<td>Bellino, S. (2014)</td>
<td>18/16</td>
<td>0.172</td>
<td>-0.457</td>
<td>0.331</td>
<td>0.61</td>
<td>13.75</td>
</tr>
<tr>
<td></td>
<td>Nioli, D. (2013)</td>
<td>86/86</td>
<td>0.302</td>
<td>0.002</td>
<td>0.693</td>
<td>0.61</td>
<td>66.31</td>
</tr>
<tr>
<td></td>
<td>Haberka, M. (2013)</td>
<td>26/26</td>
<td>0.610</td>
<td>0.062</td>
<td>1.150</td>
<td>0.03</td>
<td>19.91</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.399</td>
<td>0.154</td>
<td>0.643</td>
<td>&lt; 0.01</td>
<td>160.00</td>
</tr>
<tr>
<td>Placebo</td>
<td>Sauder, K.A. (2013)</td>
<td>52/26</td>
<td>-0.296</td>
<td>-0.769</td>
<td>0.178</td>
<td>0.22</td>
<td>6.41</td>
</tr>
<tr>
<td></td>
<td>van de Rest, G. (2008)</td>
<td>186/106</td>
<td>-0.214</td>
<td>-0.450</td>
<td>0.023</td>
<td>0.68</td>
<td>7.05</td>
</tr>
<tr>
<td></td>
<td>Freund-Lovi, Y. (2008)</td>
<td>36/24</td>
<td>-0.149</td>
<td>-0.669</td>
<td>0.362</td>
<td>0.57</td>
<td>6.27</td>
</tr>
<tr>
<td></td>
<td>Cohen, L.S. (2014)</td>
<td>177/178</td>
<td>-0.138</td>
<td>-0.347</td>
<td>0.069</td>
<td>0.19</td>
<td>7.10</td>
</tr>
<tr>
<td></td>
<td>Matsumoto, Y. (2015)</td>
<td>53/57</td>
<td>-0.107</td>
<td>-0.479</td>
<td>0.264</td>
<td>0.57</td>
<td>6.71</td>
</tr>
<tr>
<td></td>
<td>Comto, C. (2017)</td>
<td>79/81</td>
<td>-0.077</td>
<td>-0.365</td>
<td>0.232</td>
<td>0.63</td>
<td>6.88</td>
</tr>
<tr>
<td></td>
<td>Widenhorn-Müller, K. (2014)</td>
<td>46/49</td>
<td>0.081</td>
<td>-0.318</td>
<td>0.481</td>
<td>0.69</td>
<td>6.63</td>
</tr>
<tr>
<td></td>
<td>Fux, M. (2004)</td>
<td>6/5</td>
<td>0.165</td>
<td>-0.022</td>
<td>1.252</td>
<td>0.77</td>
<td>4.18</td>
</tr>
<tr>
<td></td>
<td>Rogers, P.J. (2008)</td>
<td>109/109</td>
<td>0.200</td>
<td>-0.065</td>
<td>0.465</td>
<td>0.14</td>
<td>6.99</td>
</tr>
<tr>
<td></td>
<td>Watanabe, N. (2010)</td>
<td>40/40</td>
<td>0.217</td>
<td>-0.219</td>
<td>0.652</td>
<td>0.33</td>
<td>6.52</td>
</tr>
<tr>
<td></td>
<td>Gabbay, V. (2012)</td>
<td>17/16</td>
<td>0.306</td>
<td>-0.364</td>
<td>0.976</td>
<td>0.37</td>
<td>5.69</td>
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<tr>
<td></td>
<td>Ponzoni, M. (2014)</td>
<td>12/12</td>
<td>0.477</td>
<td>-0.308</td>
<td>1.261</td>
<td>0.23</td>
<td>5.26</td>
</tr>
<tr>
<td></td>
<td>King-Glasser, J.K. (2011)</td>
<td>34/34</td>
<td>0.607</td>
<td>0.126</td>
<td>1.088</td>
<td>0.61</td>
<td>6.37</td>
</tr>
<tr>
<td></td>
<td>Buydens-Branchey, L. (2003)</td>
<td>11/11</td>
<td>0.101</td>
<td>0.153</td>
<td>1.958</td>
<td>0.02</td>
<td>4.96</td>
</tr>
<tr>
<td></td>
<td>Yehuda, S. (2006)</td>
<td>80/38</td>
<td>1.550</td>
<td>1.220</td>
<td>2.979</td>
<td>&lt; 0.001</td>
<td>6.54</td>
</tr>
<tr>
<td></td>
<td>Soltan, N. (2013)</td>
<td>63/61</td>
<td>2.459</td>
<td>1.594</td>
<td>3.933</td>
<td>&lt; 0.001</td>
<td>6.42</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.372</td>
<td>0.032</td>
<td>0.712</td>
<td>&lt; 0.05</td>
<td>160.00</td>
</tr>
</tbody>
</table>

Subgroup meta-analysis of the anxiolytic effect by n-3 PUFAs based upon placebo-control or non-placebo-control. There was significantly better improvement in anxiety symptoms in patients treated with n-3 PUFAs compared with controls in subgroups of both placebo controls (k = 16, Hedges’ g = 0.372, 95% CI = 0.032 to 0.712, p = 0.032) and non-placebo-control (k = 3, Hedges’ g = 0.399, 95% CI = 0.154 to 0.643, p = 0.001)