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Treatments for depression: Side-effects, adverse events and health risks

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Debates over the benefits of n-3 long-chain polyunsaturated fatty acids (n-3PUFAs) or omega-3 oils for depression continue. Meta-analyses report small but statistically significant benefits compared to placebo (Appleton et al., 2015; Bai et al., 2018; Grosso et al., 2014; Lin et al., 2012), but the clinical significance of any reported benefit has not been adequately considered.

Clinical significance requires effect sizes that are large enough to produce important clinical improvements. In the UK, the National Institute for Health and Care Excellence (NICE, 2009) uses a standardized mean difference (SMD) between drug and placebo of 0.50 or a difference of 3 points on the Hamilton Rating Scale for Depression (HRSD) as cutoffs for clinical significance in the treatment of depression. However, in a patient-level meta-analysis by Leucht et al. (2013), a 3-point difference on the HRSD corresponded to a Clinical Global Impression of Improvement (CGI-I) rating of "no change". Minimal improvement on the CGI-I corresponded to an HRSD change of 7 points or an SMD of 0.88 (Moncreiff & Kirsch, 2005).

Effect sizes reported in reviews of n-3PUFAs as a treatment for depression are small to moderate (Appleton et al., 2015; Bai et al., 2018; Grosso et al., 2014; Lin et al., 2012), with 95% confidence intervals that are typically wide, suggesting low reliability (e.g., Appleton et al., 2015: SMD=0.30 (95%CIs 0.10, 0.50), Bai et al., 2018 (>1.5g/d n-3PUFA): SMD=0.43 (95%CIs 0.04, 0.82); Grosso et al., 2014: SMD=0.56 (95%CIs 0.20, 0.92); Lin et al., 2012: SMD=0.29 (95%CIs 0.10, 0.48)). Without even considering a likely overestimation of benefits (Appleton et al., 2015), only one of these effect sizes

meets the NICE criteria for clinical significance or comes close to the SMD corresponding to a minimal difference in CGI-I ratings. These small and unreliable effect sizes for n-3PUFAs indicate that they may not be a good choice for the treatment of depression (Appleton et al., 2015).

To investigate these effect sizes further, we have calculated the improvement for n-3PUFAs and placebo in studies using the HRSD that were included in the Appleton et al. (2015) meta-analysis. These analyses reveal a weighted mean improvement (WMI) of 9.75 for n-3PUFAs versus 8.00 for placebo, a clinically unimportant difference of 1.75 points on the HRSD. However, additional analyses demonstrate clinically meaningful improvements in both n-3PUFA and placebo groups from study start to study end - effect sizes of 1.72 and 1.31, respectively. A caution should be added to these findings, due to likely bias as above, but these findings suggest that n-3PUFAs can produce clinically significant improvements, but that these improvements may largely be due to a placebo response.

Small effect sizes in studies using n-3PUFAs versus placebo are comparable to those reported in meta-analyses of antidepressants (e.g. Kirsch et al., 2008: SMD=0.32 (95%CIs 0.25, 0.40), Cipriani et al., 2018: SMD=0.30 (95%CIs 0.26, 0.34)), although the effects for antidepressants are more likely to be robust, as confidence intervals are narrower. The differences in WMI on the HRSD found for antidepressants versus placebo are also comparable those of n-3PUFAs (e.g., Kirsch et al., 2008: WMI=1.80, Fournier et al., 2010: WMI=1.94, Stone et al., 2018: WMI=1.80), as are the within-group effect sizes. Kirsch et al. (2008) reported within-group improvements (from study start to study end) of 1.24 for antidepressants and 0.92 for placebo, and these benefits are not obtained in wait-list or supportive care control groups (Khan et al., 2012; Kirsch et al., 1998; Leuchter et al., 2014). Khan et al. (2012) compared the response to various treatments for depression and found all treatments to be equally effective and only slightly better than placebo or standard care. The percent improvement was 46% for antidepressants and 38% for placebo. Similarly, the data reported by Appleton et al. (2015) show 44% improvement for n-3PUFAs and 35% for placebo.

How then are we to decide between treatments? When the evidence does not warrant recommending a particular treatment on the basis of differences in efficacy, consideration of differences in side effects, adverse events and health risks is recommended (Gartlehner et al., 2011). We make no recommendations for treatment based on our analyses, but direct comparisons of the benefits and risks of n-3PUFAs, placebo and antidepressants would be of value.

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