Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
The objective was to assess the cost-effectiveness of ethyl-eicosapentaenoic acid (ethyl-EPA) compared with placebo, for the treatment of bipolar disorder. The authors concluded that ethyl-EPA was highly likely to be a cost-effective addition to treatment. There were limitations in the reporting and methods: full results were not reported, the time horizon was short, the effectiveness data were based on strong assumptions, and not all relevant costs were included. The results should be used with caution.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to assess the cost-effectiveness of ethyl-eicosapentaenoic acid (ethyl-EPA) compared with placebo, for the treatment of bipolar disorder.

Interventions
The intervention was ethyl-EPA at a dose of either 1g or 2g per day. This was given with other medications including lithium, sodium valproate, carbamazepine, antipsychotics, antidepressants, and benzodiazepines. The comparator was placebo.

Location/setting
UK/secondary care.

Methods
Analytical approach:
A Markov model was developed to assess the cost-effectiveness of ethyl-EPA for a hypothetical cohort of 1,000 patients. The main time horizon was one year; a five-year time horizon was also considered. Patients started the model in a stable (euthymic) state, and could move between stable, manic or depressive health states between every three-month cycle. The perspective was stated to be that of the UK NHS.

Effectiveness data:
The key effectiveness input was the relative risk of transition with ethyl-EPA. This was estimated from a 12-week clinical trial in which all patients received lithium and valproate (see Other Publications of Related Interest). Patients experiencing manic or depressive episodes were assumed to return to the stable state at the end of each cycle, and remain there for the next cycle, before developing any subsequent acute episode. In the five-year analysis, the transition probabilities and health state utilities were assumed to remain constant.

Monetary benefit and utility valuations:
Utility values were assigned to the depressive, manic and stable health states. These were from a published study that used a standard algorithm and the SF-36 health survey, combined with published information. The estimate for the manic health state utility was adjusted using data from the published literature.

Measure of benefit:
The health benefit was measured using quality-adjusted life-years (QALYs). In the five-year analysis, the costs and benefits were discounted at an annual rate of 3.5%.
Cost data:
Due to a high number of missing values and the small sample, it was not possible to use the costs from the clinical trial. The unit costs were also not available, so these were from a published study. The resource use was estimated for the control group by health state, and it was assumed to be equivalent for ethyl-EPA by health state, with the addition of £24 for the cost of ethyl-EPA. The costs were assumed to be constant in the five-year analysis. All costs were adjusted to 2008 to 2009 prices in UK £, using the Hospital and Community Health Services (HCHS) index.

Analysis of uncertainty:
Sensitivity analyses were conducted to assess the impact of parameter uncertainty on the results. In one- and two-way deterministic analyses, the input parameters were varied by ±25%. In probabilistic sensitivity analysis, probability distributions were applied to all parameters to assess the impact of joint parameter uncertainty. The results were presented in a graph of cost-effectiveness likelihood for a range of willingness-to-pay values.

Results
Over one year, ethyl-EPA was estimated to dominate placebo, as ethyl-EPA produced more QALYs at a lower cost. The results for the five-year analysis were stated to be very similar to those of the one-year analysis.

One-way sensitivity analyses, over one year, indicated that varying the utility of the stable health state had the greatest impact on the results, followed by the cost of each state and the relative risk of transition. For most analyses, ethyl-EPA remained dominant.

The results were robust in the two-way analyses. The cost-effectiveness acceptability curve indicated that ethyl-EPA had a 94.67% likelihood of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY gained.

Authors' conclusions
The authors concluded that ethyl-EPA was highly likely to be a cost-effective addition to treatment, but further research was needed in routine clinical practice.

CRD commentary
Interventions:
The intervention and comparator were clearly reported; no details of the placebo were given. The authors indicated that there were other treatments for bipolar disorder, such as olanzapine, valproate, lamotrigine and lithium. The results are therefore unlikely to represent the cost-effectiveness of ethyl-EPA in clinical practice, where these other treatments could be used in place of ethyl-EPA, rather than placebo.

Effectiveness/benefits:
The transition probabilities and utilities were clearly reported. The authors did not justify their selection of the sources for these estimates, so it is unclear if the best available evidence was used. No QALY results were reported, reducing the transparency of the reporting. The authors highlighted several limitations to their analysis: the assumption of one cycle gap could have been inappropriate for certain cases; the utilities were likely to depend on the severity of the episodes; and adherence to treatment was assumed constant, but expected to be low after an acute episode. They mentioned the possibility of different adverse effects between groups, but nothing further was stated. There was a significant difference in the number of patients taking antipsychotic medication between the groups, which could bias the results. It was assumed that the transition probabilities from the 12-week trial remained constant over the year, which might not be the case. These limitations increase the uncertainty in the QALY results; given that we don't know the magnitude of the difference in QALYs between the two groups, the impact of this uncertainty is unclear.

Costs:
No resource use information was reported, which reduces the transparency and reproducibility of the analysis. A clear breakdown of unit costs was given. No justification was given for the sources used for the resource use and cost data, so it is unclear if the most appropriate evidence was used. No actual cost results were reported, so the magnitude of the difference in costs is unclear. The cost estimates did not include any differences in health state costs between treatment and placebo, other than the additional drug costs for ethyl-EPA. As the authors acknowledged, health state costs were likely to differ between groups due to different resource use and adverse effects of treatment. The cost results are therefore unlikely to accurately reflect the differences between the two groups. The costs and QALYs were discounted.
only for the five-year analysis, which was reasonable.

Analysis and results:
As the authors reported, a one-year time horizon was short for a chronic disease, as alternative treatments might have an impact on the long-term costs and outcomes. Research over a longer period was required to accurately assess the lifetime costs and benefits of treatment. The authors suggested caution when interpreting their five-year results, as the cost and utility data were extrapolated from the 12-week trial, so the results are likely to be highly uncertain. Appropriate sensitivity analyses were conducted, but there remained high uncertainty due to the limitations in the cost and QALY estimates. The authors recommended research to assess the intervention in ordinary care, which could not be assessed in this study due to a lack of observational data.

Concluding remarks:
There were limitations in the reporting and methods. In particular, the full results were not reported, the time horizon was short, the effectiveness data were based on strong assumptions, and not all the relevant costs were included. The results should be used with caution.

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Other publications of related interest

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