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Evidence for preventive treatments in young patients at high risk of psychosis: The need for context

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Lancet Psychiatry - Comment

Evidence for preventive treatments in young patients at high risk of psychosis: The need for context

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While Cochrane reviews, as rigorous evaluations of evidence in health care, have substantial impact on clinical and policy decision-making, it is important to contextualize their findings as well as methods. These reviews are conducted by groups of academics who may or may not have adequate expertise or clinical experience in the field they examine and the methods are prescribed and conservative.

The recent Cochrane review of intervention trials for patients at high risk of psychosis[1] concludes that despite the considerable research effort in this area, the evidence base is weak and no firm conclusions can yet be drawn. They note that the 'strongest weak evidence' is for omega-3 fatty acids in preventing onset of psychosis in this population, but that the quality of evidence overall is low to very low.

We have several methodological concerns about the review. Firstly, a significant contributor to the low to very low-quality rating of studies is their risk of bias (e.g., randomisation and allocation concealment methods not being described, unblinding risk, and high attrition). However, most studies included are psychosocial/psychotherapy trials, where it is impossible to blind therapists and notoriously difficult to maintain patient blinding and high rates of attrition are common in all trials of youth with mental disorders. Moreover, many studies employed rigorous methods of randomisation and allocation concealment without detailing these in print.

Secondly, the 50% reduction in symptoms used to judge clinical improvement, derived from studies of medications for *acutely unwell* patients with psychosis[2], may be inappropriate as a criterion for this clinical group, setting the bar too high for a patient group who by definition have symptoms of moderate intensity. Indeed, even in clinical trials of pharmacological/psychological interventions for acutely ill FEP and schizophrenia patients, response is usually set between 20-50% symptom reduction.[e.g. 3]

Thirdly, the review takes the approach of comparing different categories of interventions across RCTs with control conditions. While this is arguably a better approach than network

meta-analyses, it means that the critical issue of whether specific targeted interventions *when all pooled together* are superior to standard treatment is left unaddressed. When this issue has been addressed, as has been done several times now[4-6] (although not including all intervention trials due to time of publication), it is clear that the onset of psychosis can at least be delayed in this clinical population through specific targeted treatments, with a 50% risk reduction over 12 months.

Other general concerns:

Despite the review demonstrating the benefits of CBT over supportive therapy with a number needed to treat (NNT) of 13 over one-year and a relative risk of 0.45 (~8% vs 16% transition rate), the conclusions and summary sections downplay this important finding. A NNT of 13 is certainly clinically meaningful and compares favourably with psychosis relapse prevention using antipsychotic medication[7] and treatments in other areas of medicine.[8] The diminution over time for the effect of CBT is not unique, with treatments needing to be sustained in many health conditions (antipsychotic medication for psychosis relapse prevention, insulin for diabetes, etc.).

The review ignores biological analysis from the RCTs that supports the protective function of omega-3 fatty acids. These studies[e.g. 9] indicate that omega-3 levels at baseline and their increase in trial participants predicts clinical improvement, highlighting the potential value of omega-3 fatty acids as a treatment option.

The authors correctly point out that treatment studies have consistently been underpowered. Although prioritising multisite studies to increase sample size is certainly one solution, the review ignores the importance of enriching samples in order to adequately evaluate preventive treatments. Stratification of risk within high risk cohorts is a highly active area of research.

Standard treatment is not a fixed entity. It is likely that background service-level contextual factors have improved over time and that standard treatment has been refined. This means that the control/comparison conditions have likely become more effective in recent trials,

which, coupled with the observed rise in placebo response, means that trial interventions need to improve on already effective treatments.

Finally, the authors suggest future treatment studies take a two-stage approach that firstly compares low-dose, antipsychotic medication versus psychosocial treatment-as-usual before progressing to a second step that compares different components of the psychosocial treatment-as-usual. The choice to first trial antipsychotic medications is incongruent with the evidence base, with an unfavourable risk-benefit ratio.

While it is of course necessary to regularly review the evidence base, details of the methodological approach taken and the broader context of treatment trials are essential. Although we agree that further high quality research (trials) is needed to enhance outcomes and determine the most effective type and sequence of interventions, the evidence base shows that help-seeking individuals at high risk for psychosis benefit from the available treatments, including 'standard treatment', without iatrogenic harm associated with antipsychotic medications.[10] This potential for improvement is a key message that patients, families and practitioners should be made aware of rather than negatively frame the evidence base and fail to convey any treatment benefits, which we are concerned is the inaccurate message of this recent Cochrane review. If heeded, the review's message would result in many help-seeking young people being denied much needed psychosocial care and exposed to risks of worsening symptoms and functioning.

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