Preventive treatments in patients at high risk of psychosis

We appreciate the comments and feedback of Barnaby Nelson and colleagues[1] regarding our Cochrane review about intervention trials for patients at high risk of psychosis.[2] We used widely accepted, rigorous methods in our Cochrane review, which were published in 2016, before the first data were extracted.[3] The work was supported by an experienced Cochrane editorial base, internal and external peer review, and additional Cochrane Network scrutiny because of the expected sensitivity of the topic.

We are aware of the considerable, and often pioneering, expertise of Nelson and colleagues, and we are conscious of the advantages that this expertise confers.

Nelson and colleagues[1] summarised some important methodological problems of studies included in the Cochrane review,[2] indicating that studies frequently fail to report information about methods for randomisation and allocation concealment. Such failure has inevitable consequences for the assessment of risk of bias. Nelson and colleagues highlighted an example of a trial in which the methods of allocation were undertaken correctly but "without detailing this in print".[1] We agree that the methods used in a trial might be adequate and that these methods should be reported in a manuscript. The PRISMA statement calls for high quality reporting of methods in reports of trial results.[4]

Nelson and colleagues were worried that studies would be downgraded on the basis of their risk of bias and underlined that the nature of studies from the field of psychosis and the prodromal stage of psychosis means that they cannot always be blinded. We agree that studies cannot always be blinded and see how this leaves these trials irrevocably exposed to some risks of bias. These biases can be offset by use of methodological techniques within the trial design but are highly unlikely to be fully compensated for, even by the most rigorous trial methods. Nelson and colleagues were also aware that high attrition is common in these studies. Again, we agree that attrition is a problem. Nevertheless, these trial characteristics still contribute to the risk of bias in such trials. Even though these problems might be common or unavoidable, this does not mean that they are not there.

The quality assessment used by Cochrane also downgrades evidence on the basis of imprecision of findings. The Cochrane review[2] included 20 trials (2151 participants) but these studies investigated 13 different interventions, and many interventions were tested solely in one, small trial. As Nelson and colleagues noted, the treatment studies were consistently underpowered (as clearly indicated in our review[2]), therefore imprecision was common. This observation is not a criticism of the remarkable researchers who have done exceedingly difficult and important studies. It is an observation that systematic reviewers are obligated to make, with justified consequences in the grading of the evidence.

Nelson and colleagues expressed concern regarding the threshold of 50% reduction of symptoms of psychosis for clinical improvement—albeit we stated that, should threshold data not be available, we would use "the primary cut-off presented by the original study authors"[3]. We understand that opinions on the threshold percentage might differ, however, this threshold was published long before the full review, and comment and criticism given at the protocol stage are less likely to be influenced by the results than those given after publication of the full review. However, in the full review, we actually used the primary cut-off reported by the researchers.

As for the intervention grouping, it is true that we did not pool different interventions into a single category to be compared to standard treatment. The interventions were highly heterogeneous, and grouping them into single categories of intervention or comparator would most likely have led to justified suggestions that the possibilities of synthesis had taken precedence over clinical common sense. This issue was given much consideration and we realise that opinions will differ.

Nelson and colleagues[1] have also criticised our absence of attention to biological analyses from the trials that supported the protective function of omega-3 fatty acids. Biological analyses and predictors of clinical response were not outcomes of our systematic review, and anticipated categories of outcomes were clearly reported in the protocol.[3] Nelson and colleagues consider that we might have ignored the importance of enriching samples. This issue could be true, but enrichment strategies, if they were used, should be clearly reported in trials and their consequences evaluated.

Nelson and colleagues[1] stated that the evidence base shows that individuals at clinical high risk, who seek help, benefit from the available treatments, including standard treatment, without the iatrogenic harm associated with antipsychotic medications. Most syntheses in our review[2] suggested no clear differences between intervention and comparator. As Nelson and colleagues acknowledge, "standard treatment is not a fixed entity", and also depends on background factors at the service level. Standard treatment might or might not include medication (various antipsychotics, but also other medication such as antidepressants, mood stabilisers, etc) and a variety of psychosocial approaches. We generally agree that if the standard treatment comprises psychotherapeutic or psychosocial methods, or both, it

might be without iatrogenic harm but delay in giving necessary medication can also result in harm.

While doing our Cochrane review, we noted that the potential iatrogenic harm of any interventions other than antipsychotic medication was either poorly reported or not reported at all. However, absence of evidence does not mean evidence of absence. We have tried to honestly and objectively reproduce data as reported in relevant clinical trials and, because Cochrane reviews are maintained, are able to improve the repository of evidence. The reader can then continue to consider these transparent data from their perspective.

Notably, there is a need for better characterisation of the types and duration of psychological and psychosocial approaches used in the treatment of prodromes, as many different approaches are used,[5] but only a few of these are tested in clinical trials. The predominance of studies on cognitive behavioural therapy in the literature might not necessarily suggest that other approaches do not work or are not given for first-episode psychosis. Because of this complexity, the two-stage approach in analysing studies was suggested as an attempt to break down the intervention to its main components.

We are sensitive to the concern of Nelson and colleagues[1] that the review's message could result in many young people who seek help being denied much needed psychosocial care and being at risk of worsening symptoms and functioning. This issue is certainly the most important, and we take this opportunity to stress again that the key message of the review was, by no means, that the current approaches for early detection and treatment of prodromes of psychosis do not work. Instead, we highlight that in this difficult field, the relatively little evidence we have, which is often from pioneering trials, contains considerable uncertainties.

With respect to the field, and the enormous progress made in the research and clinical treatment of the prodromes of psychosis in the past 20 years, we are aware that there are still many differences in the treatment of prodromes across early intervention services, even within one country. We are also acknowledging the common critique to the whole field that the methods of studies in the scientific psychiatric literature do not allow easy translation of scientific data to clinical practice.

We are glad to agree with Nelson and colleagues[1] that more, high quality, but independent, research is needed to evaluate approaches for young patients at high clinical risk of psychosis—as we concluded in our Cochrane review.[2]

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Mental health services in Italy during the COVID-19 outbreak

As of March 24, 2020, 63 927 confirmed cases and 6077 deaths due to coronavirus disease 2019 (COVID-19) make Italy one of the most severely affected countries of what has been defined a global pandemic by WHO.[1] In Lombardy, the epicentre of the outbreak in Italy, large metropolitan hospitals in cities like Milan and Bergamo are struggling to contain an exponential growth of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) case presentations requiring hospitalisation.

Italian mental health services are grounded on a community-based model of care, which is organised according to districts serving a defined geographical area.[2] Multidisciplinary teams of psychiatrists, psychologists, nurses, social workers, occupational therapists, rehabilitation counsellors, and auxiliary staff are distributed across inpatient and outpatient services. These services are coordinated by the department of mental health, which provides a full range of psychiatric care, from acute emergency treatment to long-term rehabilitation.

Within the ASST Santi Paolo e Carlo department of mental health, our unit serves a population of approximately 350 000 citizens in south Milan. Two inpatient units with a maximum capacity of 29 beds are used for voluntary and compulsory admissions with an estimated length of stay of 12·9 days.[3] These two locked psychiatric wards are in the context of a large university hospital, which includes 18–20 wards of medical and surgical specialties. Over the past 3 weeks, most wards have been converted to COVID-19 intensive and subintensive care units with a joint effort of pneumologists, infectious disease specialists, internists, anaesthesiologists, and a growing number of other specialists.