Psychosocial Intervention Without Antipsychotic Medication for Brief Psychotic Episodes?

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We read with interest the randomized noninferiority clinical trial by Dr Francey et al.¹ in this journal. The authors evaluated, in the context of a specialized early intervention (EI) service, whether antipsychotic medication offers a substantial improvement for people with first episode psychosis (FEP); or rather, whether a cognitive-behavioural case management without low-dose antipsychotics is non-inferior to this intervention plus low-dose antipsychotics. This study has had significant impact on social media, including twitter, with some responses from some mental health professionals regarding lack of need for antipsychotic medication in FEP². In our opinion, this is a sub-optimal interpretation of a rigorous, well-conducted trial, and we have the following comments:

1. Selection criteria
Firstly, among 1279 FEP individuals attending specialist EI services who were assessed for eligibility into the trial, only 90 individuals (i.e. about 7%) were eventually randomized. As the authors acknowledge, the findings of this study are therefore likely not fully representative of the general FEP population. On scrutinizing inclusion and exclusion criteria, it is understandable why such a small percentage (7%) of FEP people fulfilled entry criteria. For instance, low suicidality, low aggressiveness, a stable accommodation and a duration of untreated psychosis (DUP) <6 months were required. Shorter DUP is, per se, expected to be associated with better symptom outcomes and functioning³. This is partially consistent with the results from the clinical trial for both groups, as they both improve in the outcomes evaluated, although modestly.

2. Minimum effective antipsychotic dosage
An additional consideration relates to the actual dosage of the antipsychotics employed, which was generally low. The impact of a higher dose of antipsychotic medication would have had is unknown, though we acknowledge that a significant number of participants (62.6%) received risperidone at a dose of at least 2mg, which shows efficacy in FEP studies⁴.

3. The effect of first episode services
In this clinical trial, both groups received prompt, intensive psychosocial intervention. It is essential to highlight that receiving an EI service itself (comparator in this trial) is associated with more favourable outcomes than treatment as usual⁵. Thus, both groups are in a favourable position compared to the vast majority of real-world FEP individuals around the world.
4. Translating into clinical practice

Based on this, a central issue would be how to implement the trial findings into clinical practice, i.e. which FEP patients would not require antipsychotics? Given the heterogeneity of people within EI services, and the plausible effects on antipsychotic response, the question arises as to which individuals should be targeted for such research? This would require precision medicine approaches and the development and external validation of individualised predictive models. Research in these areas is still in its infancy. Interestingly, the most frequent diagnosis of those enrolled in the trial was psychosis not otherwise specified. This residual diagnosis, coupled with a short DUP, may have led to the inclusion of people presenting with brief psychotic episodes. Accumulating research has demonstrated a more favourable clinical course of brief psychotic episodes compared to first-episode schizophrenia, even compared to those FEP in remission. These finding make individuals with brief psychotic episodes lasting less than 3 months an ideal subgroup to implement the findings of this trial. Very closely monitoring the evolution of individuals with brief psychotic episodes, to whom antipsychotic medication may not typically be administered because of the short-living symptoms, is possible. In the current classifications, brief psychotic episodes include Acute and Transient Psychotic Disorder (ATPD) as per ICD-11, whose duration should not exceed 3 months; Brief Psychotic Disorder (BPD) as per DSM-5, which lasts up to 1 month; and Brief Intermittent Psychotic Symptom (BIPS, which can last up to 3 months) and Brief Limited Intermittent Psychotic Symptoms (BLIPS, which can last up to 7 days), operationalized within clinical high risk for psychosis (CHR-P). Interestingly, for BIPS/BLIPS individuals, NICE guidelines are already recommending treatments other than antipsychotics. Viceversa, for those FEP individuals presenting with persistent psychotic symptoms exceeding that of brief psychotic episodes (i.e. >3 months), antipsychotic may remain the mainstream treatment. It would have been interesting to see the author’s results on the 3 levels of DUP stratification they describe (0-1month, 1-3months and >3 months), to fully test our suggestion.

5. Conclusions

The results of this clinical trial, although promising, should be interpreted with caution. Further research is needed, in the appropriate setting and targeting individuals in whom this approach is more likely to be fruitful. Comprehensive EI services, in which the evolution of psychosis can be closely monitored and individuals with brief psychotic episodes are well-placed for such research projects.
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