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INVITED COMMENTARY

More Treatment for Those Most in Need? A Foregone Conclusion?

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In the study of McFarlane et al[1] a community outreach program was set up to reduce the transition to psychosis in subjects at increased risk. A broad range of subjects (aged 15–25) was included, from low risk to frank psychosis. The design was not randomized on the basis of ethical considerations. Treatment consisted of family-aided assertive community treatment (FACT) and medication in the form of aripiprazole or, if not tolerated, other antipsychotics were allowed. The control condition (applied to only 25% of the study population) was monthly monitoring. Interestingly, conversion to psychosis was lower (2.3%) in the control group than the already quite low rate (6.3%) in the active condition group. Treatment was superior to the control condition in reducing symptoms.

Most importantly, this study shows that compromising methodology for so-called ethical considerations is a problematic setting of priorities. In fact, this study mainly demonstrates that those patients who had more room for improvement and who were exposed to more intensive treatment had better outcome after 2 years of follow-up. The reason is that, for the above-mentioned ethical considerations, the investigators steered the more severe patients into the active treatment condition. Is this really an ethical choice? The problem now is that we have a study involving enormous effort on the part of investigators, care-givers, and research subjects (not to mention the money involved), that fails to provide an answer to an important scientific question, ie, is early intervention really effective?

Indeed, several issues make it difficult to interpret the results. The percentage of patients treated with antipsychotics, even in the low-risk group (27% at baseline and 30% after treatment assignment), may obscure some of the treatment arm comparisons. The use of antipsychotics in this population seems to be larger than what would be expected in Europe. The mixture of premorbid subjects (some of whom could well be very early first-episode cases) and patients with an established first episode of psychosis also does not help to interpret the results.

The field of medicine is moving toward prevention and health promotion. Cardiovascular and endocrine disorders, where high blood pressure or abnormal glucose levels have been the subject of preventive measures, are good examples of the success of prevention in recent years. Psychiatry should follow suit. As 70% of mental disorders start during childhood and adolescence,[2] by definition, any primary prevention initiative has to take place earlier than that. More so, if we are dealing with a neurodevelopmental disorder in which the first psychotic episode is an expression of abnormal brain maturation, expressed as (relative) cognitive decline taking place many years before that episode.[3] In fact, effective preventive intervention should take place before late adolescence, when the brain is most plastic.[4] The problem is to identify who should receive those interventions, as resources are limited, and there is always a price to pay at many different levels for some of these interventions.

If we move toward the fine line between primary and secondary prevention, then we can take the early phases of psychosis as a good example. These early phases have been hypothesized to constitute a critical period, a therapeutic window where effectiveness of intervention is gradually lost as times goes by. How early is the key question. With transition rates in those identified at high risk for psychosis varying largely between studies (transition at 12 months ranged from 7.1% to 27% in a recent meta-analysis,[5] 6.3% in the high-risk group in the study by McFarlane et al), and most likely, as studies focus on cohorts at an earlier stages of psychopathology, being reduced with time,[6] the question is what we want to prevent. Is it just psychosis, or should we intend to improve global functional outcome? This seems to be a much more relevant outcome and one that has been relatively

little studied so far. In fact, the few studies assessing what happens with those that do not transit to psychosis are not very optimistic, as the functional outcome of "non-transiters" is not much better.[6,7]

There has been increasing interest in the topic of early intervention in prodromal and first-episode patients in Europe. Studies such as OPUS, EUFEST, OPTIMISE, and AESOP are good examples of this. European studies have also added another relevant piece of information about some of these interventions, eg, in first-episode clinics in the United Kingdom and their efficiency (rather than only effectiveness).[8]

In 2010, a challenging editorial in a prestigious journal entitled "A decade for psychiatric disorders" posited that the future of psychiatry lies in early intervention and that progress in the recognition of risk factors, mainly biomarkers, will increase the chances of preventing or mitigating mental disorders through the introduction of biomedical and psychosocial or cognitive interventions.[9] We should make haste, as almost half of the decade has already passed by.

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