It is always nice to have evidence about what is already nonempirical, well-established knowledge based on clinical practice. Five decades of research on first-episode psychosis have confirmed most of what was taken for granted in the clinical arena. For example, we now have evidence of certain things we knew in the past: that premorbid adjustment is one of the best predictors of prognosis, that the more subtle and insidious the onset the worse the prognosis, that schizophrenia is a syndrome with very heterogeneous course and outcome after a first psychotic episode, and that lack of adherence to antipsychotic medication is the best predictor of relapse after a first psychotic episode. However, we now know, and did not know then, that duration of untreated psychosis is very important for predicting long-term outcome, that IQ is one of the best resilience factors, that most of the (limited) progressive brain changes revealed by imaging studies take place within 2–5 years after the first psychotic episode (with potential implications for this therapeutic window), and that the observed progressive changes may be different at the level of brain developmental trajectories that result in a very similar final brain structure. We also know that investing in early intervention programs using assertive and integrated treatments is not only beneficial for patients, but also cost-effective. It has been calculated that for each dollar invested in early intervention in psychosis, the economic pay-off is almost 18 dollars. It is always nice to have evidence about what is already nonempirical, well-established knowledge based on clinical practice. Five decades of research on first-episode psychosis have confirmed most of what was taken for granted in the clinical arena. For example, we now have evidence of certain things we knew in the past: that premorbid adjustment is one of the best predictors of prognosis, that the more subtle and insidious the onset the worse the prognosis, that schizophrenia is a syndrome with very heterogeneous course and outcome after a first psychotic episode, and that lack of adherence to antipsychotic medication is the best predictor of relapse after a first psychotic episode. However, we now know, and did not know then, that duration of untreated psychosis is very important for predicting long-term outcome, that IQ is one of the best resilience factors, that most of the (limited) progressive brain changes revealed by imaging studies take place within 2–5 years after the first psychotic episode (with potential implications for this therapeutic window), and that the observed progressive changes may be different at the level of brain developmental trajectories that result in a very similar final brain structure. We also know that investing in early intervention programs using assertive and integrated treatments is not only beneficial for patients, but also cost-effective. It has been calculated that for each dollar invested in early intervention in psychosis, the economic pay-off is almost 18 dollars. 1 What a great way to increase quality in mental health services and save money at the same time! More importantly, we also know that intervening at the time of the first episode may already be too late. In fact we knew, for example, early in the 16th century, as Don Juan de Palafox y Mendoza stated, that “Kingdoms that are governed with remedies rather than prevention are headed for disaster,” or as we would say, an ounce of prevention is worth a pound of cure. We now know that this evidence is also applicable to mental health.

Ironically, knowledge and evidence are not always followed by action. Otherwise where are all the clinical resources needed to improve the outcome of a first psychotic episode? Where is the budget for mental health prevention commensurate with other areas of medicine (eg, cardiology, oncology)? A few notable exceptions (the change in how mental health services are now provided in Australia, and to a lesser extent, in some northern European countries and the United Kingdom) are stark proof of the rule. In fact, some countries such as the United States are very good at providing evidence that is not implemented in their health care system.

Along the same lines, after many years of first-episode research but little therapeutic advance, we recently published an editorial in this journal stating that the application and implementation of these treatments in first-episode schizophrenia is far from optimal. In this issue of Schizophrenia Bulletin, Robinson et al report on a 12-week clinical trial in 15- to 40-year-old first-episode patients with minimal previous exposure to antipsychotics, comparing aripiprazole (5–30 mg/d) or risperidone (1–6 mg/d), with follow-up. Results were as expected, ie, minor differences between the 2 antipsychotics, no difference in efficacy or time to response, and more akathisia with aripiprazole and more metabolic and prolactin side effects with risperidone. Although there was a medication-by-time interaction for avolition-apathy favoring aripiprazole, it is difficult to interpret the observation that one drug is associated with reduction for those symptoms while the other one worsens them with time, as a specific efficacy difference. We previously saw the same thing with the first studies comparing risperidone vs very high doses of haloperidol. The FDA approved risperidone with the indication for negative symptoms of schizophrenia, when the difference between the 2 drugs was driven by the worsening of patients treated with the comparator. Furthermore, we have also learned from acute-episode (including first-episode) studies that improvement in (secondary) negative symptoms is driven by improvement in other psychopathological domains (eg, positive symptoms). One of the major lessons we have learned from first-episode-study patients is that doses should be lower than those used in previous decades. The present study used around 15 mg for aripiprazole and 3 mg for risperidone as a mean. I was glad to see that the majority...
of first-episode patients received short-term treatment with benzodiazepines. These drugs are so helpful for the anguish caused by psychosis and are unfortunately underutilized in some countries. This represents a different category: the category of already known but forgotten.

Five decades of research have also not been able to come up with biomarkers for prognosis and, in fact, the best predictors are still clinical and premorbid markers of development. In a new effort to provide biomarkers for treatment response, using the same clinical trial mentioned above, Trampush et al.\(^4\) assess a cognitive battery as a predictor of response to the 2 antipsychotics used in the clinical trial. The MCCB reasoning domain (as measured by the NAB Mazes subtest, a test of planning and reasoning) was a predictor of response to antipsychotic treatment. Despite this, there was no overall improvement in cognition after correcting for improvement in positive and negative symptoms, nor was there any difference between antipsychotics (aripiprazole vs risperidone) in cognitive functioning, as was shown in a previous study comparing 2 other antipsychotics (olanzapine vs quetiapine).\(^5\) It is clear that blocking the D2 receptor may be harmful, to varying degrees, for cognition (and negative symptoms), but it is never beneficial. A second paper by the same group\(^6\) shows that a variant at or in close proximity to the DRD2 locus may be associated with treatment response, encouraging results that need replication.

The first episode is a crucial time to invest in integrated clinical services. We knew and know that we can accelerate improvement after a first psychotic episode with antipsychotics and we can also reduce the risk of relapse in a majority of patients, without much difference among available antipsychotic drugs other than in side effects. Can we move ahead looking backwards? By definition, with neurodevelopmental disorders (probably at least two-thirds of the syndrome that we still call schizophrenia clearly consists of neurodevelopmental disorders), secondary preventative measures need to take place before the brain manifests its failure through psychotic symptoms. Psychiatry has traditionally been based on tertiary prevention, and we are good at “palliative psychiatry,” but scientific evidence gathered in recent decades indicates that our field should advance to the more ambitious approach of primary (eg, prevention of neurodevelopmental disorders) and secondary prevention (prevention of a first psychotic episode in a person with an abnormal neurodevelopment with functional consequences) along with promotion of mental health. We must do more than gather evidence. Much evidence has been gathered relevant to risk, but the field is slow in implementing secondary prevention and very hesitant in approaching primary prevention.

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