Treatment Timing vs Treatment Type in First-Episode Psychosis: A Paradigm Shift in Strategy and Effectiveness

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The Cochrane Corner review of early intervention for psychosis in the Schizophrenia Bulletin by Marshall & Rathbone finds no difference between treatment types applied earlier in the course of psychotic disorders. Given that the title of the article is “Early Intervention for Psychosis,” their endorsement of the null hypothesis about treatment can all too easily be taken to mean that the timing of treatment, not the type of treatment, makes no difference. In fact, their review is not a compilation and comparison of studies focusing on similar treatments applied at different times in the course of an unfolding first psychosis. Instead, they reviewed studies of different types of treatment in schizophrenia at an “early” stage of disorder. A review of the effects of timing, in fact, has yet to be done.

It may be that Cochrane-type reviews cannot ever target treatment timing because the pivotal difference between comparison samples random assignment of the timing variable would be ethically challenging and cannot practically be blinded. Clearly, no one is about to advocate randomizing a sample of persons with first psychosis to immediate vs delayed treatment or to immediate-active treatment for comparison Group 1 vs immediate-placebo treatment followed by delayed active treatment for comparison Group 2.

The only test to date of the timing of treatment in first-episode psychosis (FEP) is the Norwegian Early Treatment and Intervention in Psychosis Study (TIPS) where early detection and treatment of such cases (ED-FEP) was engineered (and attained) in one healthcare district (or catchment area) in Western Norway. Usual or no ED and treatment of FEP cases (NoED-FEP) was pursued in two comparison healthcare districts, one in eastern Norway and one in neighboring Denmark. The earlier diagnosis (and treatment) of first-episode cases in the ED sector was engineered through public education campaigns about the signs and symptoms of FEP, easy access of the sector population to newly created first episode psychosis early detection and evaluation clinical teams, and immediate standard treatment upon meeting criteria for first psychosis.

The TIPS experiment was successful in finding and treating cases of FEP earlier in the initial active phase of disorder. Furthermore, compared with usually detected FEP patients in control sectors, these earlier detected and treated FEP patients displayed a disorder of milder severity at first admission and at 2-, 5-, and 10-year follow-ups.

The Cochrane report did not include studies of this type. It reviewed treatment types, not treatment timing.

For centuries, psychosis was regarded as a state of possession. Once it was released from demonology and came to be viewed as a physical disorder of the brain, persons affected (or infected) by psychosis were assumed to be ill and treated as such in long-term hospitals and asylums. This medicalization of madness and the sequestering of those afflicted may be regarded as the first paradigm shift in our understanding and treatment of psychosis. A second paradigm shift, led by social psychiatry’s emphasis on community-based treatment with feasibility enhanced by antipsychotic pharmacotherapy, began in the mid-20th century. This revolution eliminated most asylum beds and made community treatment of psychosis the norm, not the exception. It also made antipsychotic pharmacotherapy the sine qua non of psychosis treatment.

Limitations are reflected in homelessness, incarceration, and inadequate housing for the mentally ill.

Pharmacotherapy works mainly by quieting the positive symptoms of psychosis, but it fails to reverse the development of deficits in brain capacity that are most prominently expressed as negative symptoms and cognition impairments. Chronic institutional care is no longer routine, but patients remain disabled and dysfunctional from deficits in capacities for feeling, thinking, working, and caring.

Against this backdrop, the TIPS data suggest a new paradigm shift in our treatment of psychosis (ie, that earlier timing of detection and treatment may prevent...
to significant degrees the neurodevelopmentally based silent accumulation of deficit psychopathologies that constitute the crippling core of this disorder. Of particular relevance here is the comparison between the outcomes of two longitudinal studies of first-episode schizophrenia, the 5-year follow-up of the TIPS sample and the 5-year follow-up of the Danish intervention in early (first) psychosis (OPUS) sample. Both were studies of debut schizophrenia and both had baseline and 2-year and 5-year follow-up assessments of their respective cohorts. The experimental variable of the OPUS project was the intensity of treatment, and of the TIPS project, it was the timing of treatment. In the OPUS project first-episode patients at baseline were assigned to intensive vs standard treatment. At 2-year follow-up, those receiving more intensive treatment were rated as being significantly better than those receiving the less intensive treatment. Following the 2-year assessment, all OPUS patients started receiving treatment that was no longer different between groups. At the 5-year follow-up, the initial 2-year advantages shown by the more intensively treated patients were lost. Comparing the 2- and 5-year outcomes of the first-episode samples from TIPS vs OPUS, a striking divergence emerges. In TIPS, differences in disorder severity at 2 years between ED and NoED sites are maintained and carried out to the 5-year follow-up, with the earlier detected and treated sample continuing to be less ill and functionally compromised. In OPUS, however, the 2-year outcome differences between intensive vs non-intensive treatments are lost at 5 years once the gradient of intensity between treatment groups was lost.

The conclusion offered by this comparison is that in early psychosis treatment, timing makes a lasting difference, whereas treatment type and/or intensity does not. The TIPS project attests to the former, and the Cochrane review plus the OPUS project attest to the latter. Treatment timing may be the next paradigm shift in the therapeutics of schizophrenia. To asylum and antipsychotics add anticipation. Furthermore, such a change may be timely insofar as the Cochrane Corner review suggests that the last paradigm shift of the pharmacotherapy of psychosis may well have plateaued.

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**References**