Do the Benefits of Early Intervention Services for Psychosis Generalize and Persist in the Real World?

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The question of whether integrated psychosocial and pharmacological intervention services provided early in the course of psychotic disorders have appreciable benefits has been of considerable interest to researchers, clinicians, and policy makers over the past 30 years. Randomized controlled trials provide crucial tests of the potential advantages of such early intervention services compared with treatment as usual. In one such study, the Danish OPUS trial, patients receiving a package of services including family involvement and social and occupational skills training showed better outcomes compared with patients receiving treatment as usual in terms of positive and negative symptom severity, everyday functioning, and substance abuse (1). A systematic meta-analytic review of all such studies found that bundled early intervention services are associated with reduced symptom severity, improved functioning, and decreased rates of hospitalization, indicating robust evidence of better outcomes when compared with treatment as usual at least through the period of active treatment (typically 2 years) (2). Nevertheless, before the public health significance of these findings can be fully appreciated, it is important to assess whether the benefits of early intervention services as observed in these controlled study contexts will generalize when implemented as part of routine clinical care and to determine how long the advantages persist beyond the active intervention period.

In this issue of the *Journal*, Posselt et al. (3) apply the logic of a phase 4 comparison of the effectiveness of an intervention in a randomized controlled trial to that in a real-world implementation (4) in relation to early intervention services for psychosis in Denmark. Their analysis is based on comparing patient outcomes for those enrolled in the original Danish OPUS trial, conducted from 1998 to 2001 with early-psychosis patients randomized to receive a package of psychosocial services (OPUS-RCT; N=275) or treatment as usual (control-RCT; N=273), to those of early-psychosis patients undergoing treatment in Denmark from 2003 to 2014 (OPUS-real-world; N=3,328), after the OPUS treatment approach had been implemented as a standard of care throughout the country (5). The outcomes available for comparison across patients in the original trial and those in the real-world implementation cohort were limited to those obtained from Danish national registries concerning hospitalizations, drug prescriptions, marital and occupational status, and deaths. Remarkably, compared with OPUS-RCT participants, patients who received OPUS treatment after country-wide implementation had fewer and shorter psychiatric admissions and higher rates of employment and of being in a couple relationship, with trends for lower mortality and fewer filled prescriptions of antipsychotic medications.

The finding that on many metrics, outcomes of patients in the OPUS-real-world cohort were superior to those in the OPUS-RCT treatment group is surprising because, in general, the expectation is that an intervention will be of maximal efficacy in more controlled study contexts, in which significant attention is given to provider training, program fidelity, and recruitment of patients meeting relatively restrictive inclusion criteria. That is, one is generally hoping that the effectiveness of the intervention as demonstrated in a randomized controlled trial will not be so watered down as to fail to register in the real world.

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What, then, would account for the OPUS real-world implementation being associated with *better* patient outcomes than the OPUS implementation in the context of a randomized controlled trial? The primary possibilities relate to temporal changes between study cohorts. One possibility is that, independently of changes in treatment practices, average severity of illness in patients with first-episode psychosis in Denmark may have declined over the years, such that average severity may have been higher in the OPUS-RCT cohort than in the OPUS-real-world cohort. Although this possibility cannot be completely ruled out, the authors took care to adjust analyses for pre-OPUS-treatment levels of hospitalization and other parameters and to note trends across other Danish cohorts that do not support an interpretation based on cohort differences in symptom severity (6). Another

possibility is that provider attitudes and practices have changed, such that OPUS-real-world was implemented against the backdrop of a health care system more attuned to the potential benefits of early intervention in psychosis and thus potentially more potent in delivering these services. This interpretation seems more likely, particularly given that the country-wide implementation of early intervention services in Denmark was based in large part on the success of the original Danish OPUS trial (5). As noted by the authors, a more robust basis of comparison for assessing such temporal trends would be the use of a contemporaneous national cohort of non-OPUS-treated patients, but this was not possible after the country-wide implementation.

That the OPUS early intervention package may have found a particularly permissive foothold in the Danish health care system raises the possibility that the degree of benefits may differ for implementations in other cultures and/or health care environments. Certainly, it is likely to be easier to implement a broad set of services such as those in OPUS within a socialized medical system in which there is no ambiguity about coverage of the costs of such services. Nevertheless, even if the benefits of early intervention services as implemented in other cultures or health care settings are simply the same as (or even somewhat less than) those observed in randomized controlled trials, public health interests would still be served by pursuing these programs. It is encouraging in this regard to note the positive findings associated with early intervention services observed in the Recovery After an Initial Schizophrenia Episode (RAISE) study in the United States, given that this study used a randomization procedure by clinic, which is closer to a real-world implementation (wherein all patients in a particular community health center have access to the same treatment regimen) than randomization by individual patient, as in the typical randomized controlled trial (7). Nevertheless, generalization of effects to real-world implementation within a private insurance system is still an open question.

Although OPUS and other early intervention services are associated with robust improvements in symptoms and functioning compared with treatment as usual during the active treatment period of randomized controlled trials, these differences seem to dissipate over time, after the assertive intervention services are completed (8–11). Upon close inspection of the results of the Posselt et al. study, a similar interpretation would appear to apply to real-world implementation of these services. In regard to inpatient and outpatient treatment utilizations, differences between OPUS-real-world, OPUS-RCT, and control-RCT, while strong during and immediately after the 2-year treatment period, are entirely absent 5 years after the initiation of treatment (see the supplementary figures that accompany the Posselt et al. article). When adjusting for pre-OPUS-treatment levels of service utilization (for which OPUS-real-world patients are higher than the other groups), some advantages in favor of OPUS-real-world emerge, but these trends are not evident in the raw data. The OPUS-real-world treatment shows continuity of benefits relative to the OPUS-RCT treatment through 3 years posttreatment in regard to living in a couple relationship. However, this pattern may primarily reflect a lower-than-expected rate of living in a couple relationship among OPUS-RCT patients, given that control-RCT patients also had higher rates of living in a couple relationship than OPUS-RCT patients. OPUS-real-world was associated with significantly *lower* rates of working/studying status than OPUS-RCT for the 2 years of treatment and the year immediately following treatment, but a higher rate 5 years after initiation of treatment (in adjusted data only), a pattern that could represent a chance fluctuation given that no control for multiple testing was conducted within families of statistical tests (e.g., year by year over 5 years for each outcome variable) or overall (across 11×5 years$=55$ different outcome variables). In short, evidence of potential persistence of outcome advantages in the real-world implementation of OPUS compared with OPUS-RCT is mixed at best. Further, no direct comparisons of OPUS-real-world and control-RCT are reported, making it difficult to determine whether early advantages of OPUS relative to treatment as usual are likely to persist posttreatment in the real-world implementation, something that seems unlikely given that on the whole, outcome differences in favor of OPUS-RCT relative to control-RCT do not persist posttreatment (8). Note that these concerns in no way diminish the validity and importance of the benefits of OPUS and other early intervention services during and immediately following treatment, but they do suggest caution in modeling persistence of these advantages in health economic analyses.

Posselt et al. have presented what appears to be the first phase 4 analysis of the generalizability of integrated early intervention service treatment effects as determined in randomized controlled trials to real-world implementation in the context of early psychosis. Their work is laudable for its breadth and rigor; it is also visionary for the field of psychiatric research in pointing to the necessity of extending our interrogation of treatment effectiveness beyond randomized controlled trials by examining potential benefits of interventions when implemented as a standard of care in our communities.

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