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Transforming the Treatment of Schizophrenia in the United States: The RAISE Initiative

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Abstract

The schizophrenia spectrum disorders are neurodevelopmental illnesses with a lifetime prevalence near 1%, producing extensive functional impairment and low expectations for recovery. Until recently, treatment in the United States has largely attempted to stabilize individuals with chronic schizophrenia. The identification and promotion of evidence-based practices for schizophrenia via the Patient Outcomes Research Team, combined with international studies supporting the value of early intervention, provided the foundation for the Recovery After an Initial Schizophrenia Episode (RAISE) project. The RAISE studies further supported the value of reducing the duration of untreated psychosis and providing a multi-element treatment called coordinated specialty care (CSC) to improve outcomes for patients in usual treatment settings. Although CSC programs have proliferated rapidly in the United States, many challenges remain in the treatment and recovery of individuals with schizophrenia in the aftermath of RAISE.

Contents

1. INTRODUCTION

The schizophrenia spectrum disorders (henceforth referred to as schizophrenia) are neurodevelopmental illnesses with a lifetime prevalence near 1%; they can cause extensive functional impairment and have for too long carried low expectations for recovery (Lieberman et al. 2013). Only 10–15% of people with schizophrenia are employed, and many remain on disability (Harvey et al. 2012). In 2013, excess total costs of schizophrenia in the United States were estimated at $155.7 billion, including significant direct health care costs but mostly indirect costs related to losses to the labor market (Cloutier et al. 2013). In 2009 the National Institute of Mental Health (NIMH) funded a set of research studies called Recovery After an Initial Schizophrenia Episode (RAISE) in order to build on national and international studies to change this gloomy state of affairs (Heinssen et al. 2017). The RAISE studies contributed to the creation of a new way to organize treatment, called coordinated specialty care (CSC), which has the promise of improving the course of schizophrenia (Dixon et al. 2015, Kane et al. 2016). The creation and dissemination of CSC programs across the United States and the contribution of the RAISE projects can be understood as the intersection of trends in both science and policy that converged to create the foundation for changes in care and care delivery (Dixon 2017a,b). This article discusses the key dimensions of these dramatic changes anchored in the RAISE projects.

This review is divided into four sections. Section 2 considers the pre-RAISE era, with a focus on the scientific and policy context of the project in the United States: What led to RAISE? Section 3 focuses on the findings of the RAISE studies, including both scientific and policy/service delivery dimensions. We emphasize the RAISE early treatment program (RAISE-ETP) project, which is the large randomized trial of a CSC model (Kane et al. 2016). Section 4 discusses key unanswered questions and challenges in the aftermath of the RAISE studies. Section 5 concludes.

2. UNDERSTANDING THE SCIENTIFIC AND POLICY CONTEXT FOR RAISE AND OTHER FIRST-EPISODE PSYCHOSIS SERVICES IN THE UNITED STATES

2.1. Policy and Service System Issues

Early intervention services for psychotic disorders have been implemented in Australia and Northern Europe for over two decades, survived experimental tests for efficacy in Denmark and the United Kingdom, and have since 2000 been part of a national implementation plan in England (Dep. Health 2000, Srihari et al. 2012). The prospect of rapidly providing care after the onset of psychosis is consistent with approaches to other medical disorders, and it presented itself as a "best bet" for many national health care systems that invested in this opportunity even as research and testing of specific models were still underway (McGorry 2012). Why was the United States so late in developing a national strategy for early psychosis?

The rise of the community mental health movement in the middle of the twentieth century reflected the belief that early intervention would reduce chronic disability for many mental illnesses (Grob & Goldman 2006). This had been a central promise of the moral treatment era in the mid-nineteenth century, embodied in the rise of asylums, and also a central promise of the mental hygiene movement of the early-twentieth-century progressive era, embodied in the development of psychopathic hospitals and youth guidance centers. Unfortunately, the interventions at each turn of these reform cycles failed to deliver on their promises. By the mid-1970s the community mental health centers were criticized for their failure to sufficiently prevent the severe disability associated with chronic mental illnesses (Gen. Account. Off. 1977, Tessler & Goldman 1982).

Thus, the disappointment following the initial optimism led to a series of policies that turned away from early intervention and neglected the potential for such treatments and services. It did not help that the clinical and neuroscience evidence at the time did not support moving further. A weak technology does not advance service delivery.

The mid-1970s critique of the NIMH community mental health center program for its failure to focus on chronic mental illness led the NIMH to support the development of community support programs and system reforms, redirecting public sector attention to improving services for individuals already disabled by mental illness. These individuals, such as people with mostly chronic schizophrenia, became the target population for public mental health systems now in the throes of a community support reform cycle. Individuals with less disabling or early-stage mental illnesses were not targeted, or even eligible, for services (Grob 1994, Grob & Goldman 2006, Tessler & Goldman 1982).

The lack of public sector priority for individuals in the early stages of psychosis was exacerbated by the fact that the system increasingly relied on Medicaid for funding (Frank et al. 2003). Access to Medicaid for young adults at the peak age of onset for psychosis was dependent on eligibility for the Supplemental Security Income (SSI) disability program. To be eligible one had to be disabled already. Single individuals in the early stages of psychosis typically did not qualify for SSI, and thus they were also ineligible for Medicaid unless they had dependent children and were impoverished. In some states, access to public sector services was difficult for individuals who were not on Medicaid (Goldman et al. 2013).

Individuals in the private sector were also disadvantaged by insurance rules. They were removed from parental health insurance unless they paid very high COBRA premiums or were full-time students. They lost insurance if they left the workplace due to their illness. The classification of their mental illness as a preexisting condition allowed commercial payers to place them into a new high-risk insurance pool and thereby inflate their premiums or exclude them from coverage

altogether. In any case, they fell out of the private sector and, as we learned above, also had trouble qualifying for public sector services (Goldman et al. 2013).

It was not until the Affordable Care Act (ACA) was passed in 2009 that some of those exclusionary rules were weakened, allowing more individuals with a first episode of psychosis to retain insurance coverage (Goldman 2010). Patients gained access to parental and other private sector insurance through new underwriting rules for health insurance exchanges, and they could qualify for Medicaid in states that accepted federal support to extend this entitlement to low-income individuals. There were other reforms in the ACA that provided better services for individuals experiencing the early stages of a psychotic illness. Furthermore, supplements to the federal block grant specifically earmarked for early intervention made more services available (Goldman & Karakus 2014).

2.2. The Development and Identification of Evidence-Based Practices for Schizophrenia in the United States: The PORT Initiative

An important antecedent to the RAISE studies and the dissemination of CSC programs was the identification of evidence-based practices in general. The components of CSC tested in RAISE were based almost entirely on evidence-based interventions for established schizophrenia, applied to the early stages of psychosis. The Agency for Health Care Policy and Research (now called the Agency for Healthcare Research and Quality) began to fund so-called Patient Outcomes Research Teams (PORTs) in the late 1980s and early 1990s in recognition of the fact that many (if not most) treatment decisions in medicine were made without any systematic input from scientific data about efficacy, effectiveness, and cost. The earliest PORTs focused on management of back pain, acute myocardial infarction, and cataracts (Goldberg & Cummings 1994). The first PORT that addressed a mental illness was awarded to investigators at the University of Maryland and Johns Hopkins, and it focused on schizophrenia. The PORT studies attempted to systematically review evidence from relevant clinical studies to make treatment recommendations to clinicians for specific patient populations.

Subsequently, three sets of PORT recommendations for schizophrenia were published, all of which largely identified recommended treatments based on empirical support rather than expert opinion (Buchanan et al. 2010, Dixon et al. 2010, Kreyenbuhl et al. 2010, Lehman & Steinwachs 1998a, Lehman et al. 2003). In the first set of PORT recommendations (Lehman & Steinwachs 1998a), 18 of the 30 recommendations focused on the use of antipsychotic medications for acute and maintenance treatment. The recommendations identified appropriate dosage ranges and also highlighted the utility of clozapine. Relevant to early psychosis treatment, one of the original recommendations specified that patients experiencing a first acute episode should be treated with dosages in the lower end of the overall recommended range for people with more long-standing conditions.

Regarding psychologic and psychosocial treatments, the team recommended vocational rehabilitation (for individuals having characteristics associated with good employment outcomes), family support, individual and group therapies consisting of education and cognitive and behavioral skills training, and assertive community treatment (ACT). The first Schizophrenia PORT was also funded to assess the extent to which routine care conformed to evidence-based treatment recommendations; Lehman & Steinwachs (1998b) found that overall conformance to the recommendations was modest (generally below 50%) and higher for pharmacological than for psychosocial treatments. The findings of the initial Schizophrenia PORT underscored the gap between science and practice.

By the time the second PORT recommendations for schizophrenia (Lehman et al. 2003) were issued, the scientific literature had been able to address the impact of second-generation

antipsychotic agents, and the specificity and availability of psychosocial interventions had improved. This updated report continued to recommend implementation of ACT and family interventions lasting at least nine months and including illness education, crisis intervention, emotional support, and training in how to cope with illness symptoms and related problems. The update also elaborated on group and individual therapy to include cognitive behavioral therapy (CBT) as the therapy of choice for residual psychotic symptoms. Social skills training was newly recommended. The team also identified supported employment as the service of choice in place of the broader concept of vocational rehabilitation for anyone interested in obtaining employment. It is notable that the second PORT continued to clarify the empirical foundation for future CSC programs.

The last set of PORT recommendations, published in 2010, continued to highlight the need to use lower doses of antipsychotic medications and to avoid the use of clozapine and olanzapine as a first-line treatment in early psychosis (Buchanan et al. 2010, Kreyenbuhl et al. 2010). The emerging evidence for psychosocial treatments provided more precise information on relevant populations and expected outcomes (Dixon et al. 2010). In addition, these recommendations supported alcohol and substance use services and weight management, given the high co-occurrence of these comorbidities with schizophrenia and the availability of effective treatments. The key elements of treatment for alcohol or drug use disorders for persons with schizophrenia include motivational enhancement and behavioral strategies that focus on engagement in treatment, coping skills training, relapse prevention training, and its delivery in a service model that is integrated with mental health care. Regarding weight loss, a psychosocial intervention that is at least 3 months long that includes psychoeducation focused on nutritional counseling, caloric expenditure, and portion control; behavioral self-management including motivational enhancement; goal setting; regular weigh-ins; self-monitoring of daily food and activity levels; and dietary and physical activity modifications was recommended. This 2010 review did not find sufficient evidence for an overall recommendation of a specific single or multicomponent treatment for early psychosis. However, as discussed below, several preliminary studies found results favoring family interventions, CBT, and supported employment, all in antipsychotic-treated populations. Furthermore, the review reported on evidence from international randomized controlled trials (RCTs) supporting multielement interventions for early psychosis that provide comprehensive packages of psychosocial and medication supports.

The most recent Schizophrenia PORT identified five published papers on CBT for early psychosis, of which three included actual CBT trials. Three of the five papers came from a UK longitudinal study named the Study of Cognitive Reality Alignment Therapy in Early Schizophrenia (SoCRATES) (Lewis et al. 2002, Tarrier & Wykes 2004, Tarrier et al. 2006). In the study, the SoCRATES intervention group received a stage-based, manualized CBT intervention, whereas the control groups received supportive counseling or treatment as usual. The SoCRATES intervention group showed greater improvements on delusions and auditory hallucinations indexes compared to treatment as usual (TAU) and supportive counseling groups, but SoCRATES was only better than TAU on the Positive and Negative Syndrome Scale (PANSS) positive symptom subscale. Moreover, whereas individuals in the CBT and supportive counseling groups appeared to get better faster than those in TAU, medical records indicated that the three groups did not differ significantly on rehospitalization or relapse rates. The fourth CBT paper reported on a quasi-experimental study conducted in Australia and found no differences between the CBT intervention group and standard care (Jackson et al. 2005). However, the lack of an adequate control sample, a weak CBT intervention, and enriched standard care (offered in the pioneer EPPIC program) limited inferences. The final CBT study compared active cognitive therapy for early psychosis to befriending as part of an early intervention program in the United States. Again, this study found no significant differences between the CBT and comparison groups (Jackson et al. 2008).

The Schizophrenia PORT identified four published papers on family interventions, of which two were controlled studies. Of the controlled studies, one study that took place in China found greater symptom improvement and lower rates of hospitalization among those who received the family intervention (Zhang et al. 1994). The second controlled study, which took place in the Netherlands, found no differences between individuals receiving the family intervention and individuals not receiving it (Linszen et al. 1996). In the follow-up study, five years later, individuals who had received the family intervention had spent less time living in institutional settings (Lenior et al. 2001, 2002).

With regard to supported employment, only one study had been identified at the time of the 2010 Schizophrenia PORT. This study evaluated an occupational intervention for early psychosis (Killackey et al. 2008). Specifically, the EPPIC program in Australia randomly assigned patients either to receive individual placement of support (IPS) along with EPPIC's services for early psychosis or to receive EPPIC services alone. Both groups were followed for six months, and the results indicate that those individuals who received IPS had better employment outcomes.

In addition to the monotherapies mentioned above, PORT took into account three RCTs across eight publications of comprehensive, multielement, psychosocial treatment programs in Europe. Each of these programs used ACT or an equivalent approach as the treatment structure and enhanced it by including various evidence-based treatments, including CBT, skills training, and psychoeducation. Five of the studies came from the OPUS project in Denmark (Bertelsen et al. 2008; Jeppesen et al. 2005; Kassow et al. 2002; Petersen et al. 2005a,b), two came from the Lambeth Early Onset (LEO) project in the United Kingdom (Craig et al. 2004, Garety et al. 2006), and one came from a small RCT in Norway (Grawe et al. 2006). Notably, these studies were pragmatic in design: They tested ecologically relevant interventions in real-world samples and measured a range of salient outcomes across clinical (relapse, remission, rehospitalization), functional (social, education, and employment) and economic (cost) domains. Notably, these second-generation studies (Srihari et al. 2012) went beyond establishing efficacy for single-component interventions (e.g., CBT) to test comprehensive models of care that responded to the diverse needs of patients and families presenting for care. Positive outcomes compared to usual care were reported over follow-up periods of up to two years across these domains. Notably, as discussed below, these improvements were not sustained when individuals were assessed three years after being discharged from these specialized services to usual care (Bertelsen et al. 2008, Gafoor et al. 2010).

In summary, research conducted in other countries had made great strides in demonstrating the effectiveness of comprehensive early intervention services (Srihari et al. 2012). These countries did not have in place policies, such as those in the United States, which impeded the development and widespread dissemination of these services. Notable public sector pioneers in the United States included Oregon's EASA program (established in 2001; **http://www.easacommunity.org/**), Massachusetts's PREP (2003; Caplan et al. 2013), North Carolina's OASIS (2005; Uzenoff et al. 2012), San Francisco's PREP (2006; **http://felton.org/social-services/early-psychosisschizophrenia-prep/**), and Connecticut's Specialized Treatment Early in Psychosis (STEP) program, which launched the first US pragmatic RCT of team-based care for early psychosis (2006; Srihari et al. 2009). All these programs were serving early psychosis patients, beginning to move beyond delivering standard psychopharmacology trials and toward delivering different types of comprehensive treatment models. Thus, by the first decade of the millennium, there was an emerging foundation for an evidence-based approach for first-episode psychosis. The United States had clearly lagged behind many other countries in developing the clinical and policy context necessary to launch such programs. The time was ripe for the RAISE studies to tackle this situation and build on the evidence base that international colleagues had developed.

3. THE CREATION AND RESULTS OF RAISE PROJECTS

The NIMH RAISE initiative aimed to develop and test an intervention that would engage individuals with early psychosis, improve recovery trajectories, and prevent or limit long-term disability, while reducing the costs associated with psychotic disorders. RAISE supported the development, testing, refinement, and implementation of CSC in real-world, community-based behavioral health centers in the United States. The focus was on the feasibility, effectiveness, and acceptability of the program in real-world settings. Clinicians who were already members of the behavioral health workforce, rather than specially trained research staff, delivered the program after modest amounts of training, within already existing treatment centers, and using preexisting billing/reimbursement structures to pay for the services whenever possible. The RAISE initiative also intended to foster the rapid expansion of CSC services in the community once the studies ended (Azrin et al. 2015). The initiative funded two studies: the RAISE Early Treatment Program (RAISE-ETP) and the RAISE Implementation and Evaluation Study (RAISE-IES). The initial contracts were funded with economic stimulus dollars made available as a response to the Great Recession of 2008.

3.1. Key Findings from RAISE-ETP

The RAISE-ETP was built around the CSC intervention labeled NAVIGATE (Mueser et al. 2015). The four manual-based key interventions were psychopharmacology, for which a computerized prescriber decision support system called COMPASS was developed (Robinson et al. 2018); individual resilience therapy; family therapy/psychoeducation; and supportive employment/education (see **http://raiseetp.org** for manuals). A cluster-randomized design was employed and involved 34 nonacademic, community mental health centers in 21 states across the United States. Seventeen clinics were randomized to deliver NAVIGATE and 17 clinics were randomized to provide usual care. The staff at the NAVIGATE-assigned clinics were then trained in all four modalities utilizing a variety of tools and techniques. Research diagnostic interviews and major outcome assessments were conducted by blinded, remote, centralized raters using live two-way video. The primary outcome measure was the Heinrichs-Carpenter Quality of Life Scale. A total of 404 first-episode psychosis patients with a mean age of 23 were enrolled (Kane et al. 2015).

At the two-year follow-up, the NAVIGATE-treated patients did significantly better on the Quality of Life Scale, the Positive and Negative Syndrome Scale, the Calgary Depression Scale for Schizophrenia, the length of time staying in treatment, and the degree of improvement in work/school engagement. There was no significant difference in the rate of hospitalization between the two groups, though rates overall were relatively low (Kane et al. 2016). The median duration of untreated psychosis (DUP) in this sample was 74 weeks (Addington et al. 2015). When the influence of DUP on quality of life outcomes was examined, it proved to have a highly significant moderating effect, with individuals having a DUP shorter than 74 weeks deriving significantly more benefit from the CSC than those with longer DUP (Addington et al. 2015, Kane et al. 2016). These findings further underscore the potential value of reducing DUP.

RAISE-ETP utilized a computerized prescriber decision support system, which also helped to facilitate evidence-based care (Robinson et al. 2018). Over the two years, the 223 NAVIGATE participants compared to the 181 clinician-choice participants had more medication visits, were more likely to be prescribed an antipsychotic (and also an antipsychotic conforming to NAVIGATE prescribing principles), and were less likely to be prescribed an antidepressant. (As noted previously, at the same time they also had significantly lower scores on the Calgary Depression Scale for Schizophrenia.) NAVIGATE participants experienced fewer side effects and also gained less weight; other vital signs and cardiometabolic laboratory findings did not differ between treatments.

Adherence estimator scores (McHorney 2009) decreased (fewer beliefs associated with nonadherence) with NAVIGATE but not clinician-choice care.

The recruitment of 404 individuals receiving treatment at community mental health centers across the United States after the onset of a first episode of psychosis also provided a window into the medication histories and medical status of these individuals at the time of referral (Robinson et al. 2015b). A total of 159 patients (39.4% of the sample) were identified as potentially benefiting from changes in their psychotropic prescriptions. Of these, 8.8% received prescriptions for recommended antipsychotics at higher-than-recommended dosages; 32.1% for olanzapine (often at high dosages); 23.3% for more than one antipsychotic; 36.5% for an antipsychotic and also an antidepressant without a clear indication; 10.1% for psychotropic medications without an antipsychotic; and 1.2% for stimulants.

With regard to medical status (Correll et al. 2014), in 394 of 404 patients with cardiometabolic data [mean (SD) age = 23.6 (5.0) years; mean (SD) lifetime antipsychotic treatment = 47.3 (46.1) days], 48.3% were obese or overweight, 50.8% smoked, 56.5% had dyslipidemia, 39.9% had prehypertension, 10.0% had hypertension, and 13.2% had metabolic syndrome. Prediabetes (glucose based = 4.0%; hemoglobin A_{1c} based = 15.4%) and diabetes (glucose based = 3.0%; hemoglobin A_{1c} based = 2.9%) were less frequent. Total psychiatric illness duration correlated significantly with higher body mass index, fat mass, fat percentage, and waist circumference (all $P < 0.01$) but not elevated metabolic parameters [except triglycerides to HDL-C ratio ($P = 0.04$)]. Conversely, antipsychotic treatment duration correlated significantly with higher non-HDL-C, triglycerides, and triglycerides to HDL-C ratio and with lower HDL-C and systolic blood pressure (all $P < 0.01$). Olanzapine was significantly associated with higher triglycerides, insulin, and insulin resistance, whereas quetiapine fumarate was associated with significantly higher triglycerides to HDL-C ratio (all $P < 0.02$).

In patients with first-episode schizophrenia syndrome, cardiometabolic risk factors and abnormalities are present early in the illness and are likely related to the underlying illness, unhealthy lifestyle, and antipsychotic medications, which interact with each other. Given that these risk factors become even more pronounced in chronic psychosis populations, CSC providers are presented with an opportunity to engage in prevention of cardiovascular morbidity and mortality (Srihari et al. 2013). Specific approaches include smoking prevention and cessation, counseling and lifestyle modification to prevent or limit weight gain, preferred use of lower-risk antipsychotics (Tek et al. 2015), routine monitoring, and referral to and coordination of access to appropriate medical care.

In terms of cost effectiveness, the Net Health Benefits Approach was used to evaluate the probability that the value of NAVIGATE benefits would exceed the program's costs relative to community care from the perspective of the health care system (Rosenheck et al. 2016). The NAVIGATE group improved significantly more on the Quality of Life Scale (QLS) and had higher outpatient mental health and antipsychotic medication costs. Effectiveness was measured as a one standard deviation change on the Quality of Life Scale (QLS-SD). The incremental cost-effectiveness ratio was $12,081/QLS-SD, with a 0.94 probability that NAVIGATE was more cost effective than community care at $40,000/QLS-SD. When converted to monetized quality-adjusted life years (QALY), NAVIGATE benefits exceeded costs, especially at future generic drug prices. Notably, low-DUP and high-DUP patients had a somewhat different pattern of cost effectiveness. Among low-DUP patients, the total costs of NAVIGATE averaged $1,368 per patient per six months less than community care (14.8%; $P = 0.72$); among high-DUP patients, NAVIGATE showed increased costs of $3,839 (64%; $P = 0.05$) per patient per six months. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in average annualized total costs divided by the difference in effectiveness (improvement in the QLS from baseline).

Bootstrap analyses produced an ICER of $1,035/QLS-SD among low-DUP patients, compared to an ICER of $41,307/QLS-SD among high-DUP patients, with wide 95% confidence intervals (CIs).

RAISE-ETP investigators performed a number of secondary analyses that shed light on some of the core processes and relationships among symptoms in early psychosis. NAVIGATE-treated patients experienced increased perceived autonomy support, which was related to improved quality of life (Browne et al. 2017). NAVIGATE treatment was also associated with a greater increase in participation at work or in school; this difference appeared to be mediated by the use of supported employment and education services. No group differences were observed in earnings or public support payments (Rosenheck et al. 2017a). Interestingly, obtaining benefits was predicted by more severe psychotic symptoms and greater dysfunction and was followed by increased total income, but it was also associated with fewer days of employment and reduced motivation (e.g., sense of purpose, greater anhedonia) (Rosenheck et al. 2017b). At the same time, during the first year of NAVIGATE treatment, tests of the bidirectional associations between motivation and social and occupational functioning suggest that motivation contributes to better occupational functioning but not better social functioning. Higher social functioning, on the other hand, predicted increased motivation. This suggests that improving occupational functioning in this population may benefit from targeting patient motivation directly (e.g., through motivational interviewing) or indirectly (e.g., by improving relationships and support networks) (Fulford et al. 2017).

Overall, the RAISE-ETP project demonstrated that CSC could be delivered at a range of community mental health centers, and that such care was associated with significantly better outcomes in a number of different domains. Health economic analysis also indicated that overall the intervention was cost effective (Rosenheck et al. 2016). These results provided further encouragement to national efforts to make CSC more broadly accessible to patients (and their families) experiencing a first episode of schizophrenia.

3.2. Key Findings and Products of RAISE-IES

The RAISE-IES study was initiated as an RCT comparing the RAISE connection model—what we would now call a CSC—to case management plus usual care. However, NIMH redirected the project in 2010 to other tasks, as described below. First, the program was implemented in two sites, recruiting a total of 65 individuals and following them for up to two years. Participants had reduced symptoms and improved social and occupational functioning over time (Dixon et al. 2015). Processing speed was identified as a significant moderator of improvement in occupational global assessment of functioning; treatment fidelity, engagement, and family involvement were found to be mediators of improvement in occupational and social functioning; and processing speed was identified as a significant moderator of improvement in occupational functioning (Marino et al. 2015). A closer examination of work and school participation revealed that individuals who engaged in vocational activity typically did so within months: 28 participants (43%) engaged in work or school at baseline, rising to 44 participants (68%) reporting vocational activity at some time in the first 6 months and 51 (78%) reporting activity in the first 12 months; only two additional participants began vocational activity after their first year of participation. Almost all participants ($N = 59$) met with the supported employment and education specialist at least three times (Humensky et al. 2017).

RAISE-IES also conducted two qualitative sub-studies focusing on engagement of clients and family members (Lucksted et al. 2015, 2017). Four factors were associated with engagement of clients, including tailored care, engagement of family members, attributes of the program, and personal factors. A main factor contributing to engagement was the program's ability to focus

on the patients' goals and to demonstrate that the team cared about helping individuals achieve these goals. Participants found nonclinical services such as those focused on employment and education to be a key facilitator of engagement. Other important components included shared decision making, individualized care, flexibility, and warm and respectful communication from staff (Lucksted et al. 2015). The authors concluded by recommending that teams provide recovery-oriented, flexible services that show compassion and warmth while focusing on patients' life goals (Lucksted et al. 2015).

The study of engagement among family members underscored that critical family member experiences of engagement included outreach, communication and support from teams, flexibility within the program model, and individualized treatment. Family members also shared their own challenges to engagement, which included personal responsibilities, lack of time and resources, and balancing the autonomy of their loved one with providing care and support (Lucksted et al. 2017). The authors concluded by recommending that teams provide families with individualized support while also helping them manage the stress related to their members' experiences (Lucksted et al. 2017).

The RAISE-IES project developed resources and tools to help administrators and individuals start their own CSC programs, including treatment manuals and program guides (see **https://www.nimh.nih.gov/health/topics/schizophrenia/raise/coordinated-specialty-care-for-first-episode-psychosis-manual-i-outreach-and-recruitment.shtml** and **https://www.nimh.nih.gov/health/topics/schizophrenia/raise/csc-for-fep-manual-ii-implementation-manual_147093.pdf**). RAISE-IES devised practical strategies to monitor treatment fidelity (Essock et al. 2015b), created an online interactive tool to estimate costs and resources for early psychosis care across a population (Humensky et al. 2013), and outlined approaches to financing the CSC program (Frank et al. 2015). RAISE-IES also showed it was possible to sustain a long-term program by collaborating with state mental health authorities to fund CSC services (Essock et al. 2015a). As a result, the New York Office of Mental Health (OMH) implemented the OnTrackNY initiative, a statewide first-episode psychosis treatment program which builds on the successful RAISE initiatives in New York State (Bello et al. 2017). This study demonstrated the feasibility of starting and maintaining a CSC program within the US health care system.

As the RAISE studies were being completed and reports published, the US Congress recognized the value of CSC programs by adding 5% to the community mental health block grant program. This amounted to an additional $25 million for states and federal territories to share. Notably, the legislation required that the monies be used to develop and support evidence-based programs for individuals experiencing early psychosis. The 5% set-aside for CSC programs continued in 2015, and the allocation was doubled in 2016, providing an additional $50 million for states to share to develop CSC programs (Dixon 2017a). In 2008, only a few states had such programs. By 2016, 36 states had begun implementing one or more CSC programs. By 2018, that number will grow to 48 states (R. Heinssen, personal communication).

4. THE US LANDSCAPE POST-RAISE: WHAT NEXT?

The RAISE studies are best contextualized within a two-decade-long international literature that began with observational studies of increasingly mature service interventions and resulted in a growing consensus on the principles that should inform the care of early schizophrenia (Edwards & McGorry 2002). This set the stage for a progression of experimental studies, which were necessary for translating knowledge from research into public health benefit. This project was advanced by a series of pragmatic randomized trials that retained the experimental benefit of minimizing selection bias (via randomization) while also allowing for more realistic samples, interventions,

and patient-oriented outcome measures (Hotopf et al. 1999). The pioneering OPUS and LEO trials both tested ACT-style services with the ability to provide community outreach as well as high-intensity and well-resourced care (clinician:patient ratios of 1:10 to 1:12), and established the efficacy of comprehensive specialty care services for early psychosis (Srihari et al. 2012). The STEP RCT extended these results with a model of care designed for the constraints of a US public mental health center, with office-based care, limited outreach and clinician:patient ratios of 1:50. This trial demonstrated the effectiveness of CSC in a real-world US setting (Srihari et al. 2015), a finding that was further elaborated by the RAISE-ETP (Kane et al. 2016). Subsequent reports from RAISE have supported cost effectiveness in the United States (Rosenheck et al. 2016), again adding to the similar conclusions of the international literature on societal economic benefit (Alison et al. 2012) and strengthening consensus on the need for policy commitments to support further implementation and refinement of models of care (Fleischhacker et al. 2014, Lieberman et al. 2013). EASA in Oregon and OnTrackNY in New York State provide two examples of the increasing number of states that are attempting to disseminate CSC statewide.

In this context, the status quo of current care systems in the United States is indefensible. Individuals with new-onset psychosis and their families face unnecessary suffering: delays to care are inordinately long (Addington et al. 2015, Compton et al. 2011), and best-practice services are not routinely available (Dixon 2017a). The stakes are high, with mounting morbidity, premature mortality (Pompili et al. 2011, Schoenbaum et al. 2017), and economic costs (Alison et al. 2012) that only partially measure the true human costs of delayed and inadequate care. This is an important and optimistic moment in US healthcare policy for vulnerable early schizophrenia patients. The community mental health block grant set-asides of 2014 and 2016 seeded the growth of CSC programs. The inclusion of this funding in the recently passed 21st Century Cures Act (**http://docs.house.gov/billsthisweek/20161128/CPRT-114-HPRT-RU00-SAHR34.pdf**) has established this modest but important financial incentive within US health care policy, and it offers a backbone upon which the US implementation gap can be closed. Several influential national agencies, including the NIMH, the Robert Wood Johnson Foundation, the National Association of State Mental Health Program Directors (NASMHPD), the Centers for Medicare and Medicaid (CMS), the National Alliance on Mental Illness (NAMI), and Mental Health America (MHA), have supported wider dissemination of specialized models of care for early psychosis. The United States thus appears poised to catch up with implementations of early intervention services in other developed economies.

Several challenges and questions delimit the potential impact of CSCs on the disease course and overall health of individuals diagnosed with schizophrenia; they will be the focus of this final section. These include both failures to implement what we know and significant knowledge gaps that require research. One way to structure these challenges is to consider the gaps and what patients need before, during, and after CSC is delivered.

4.1. Before Coordinated Specialty Care

The time from onset of diagnosable illness to effective treatment is measured in months to years across mental illnesses in the United States (Kessler et al. 2005); psychotic disorders are no exception, with an average DUP of over a year (Addington et al. 2015). DUP has been robustly associated with poor outcomes across health care systems (Marshall et al. 2005, Perkins et al. 2005). These unacceptable delays to care occur during periods of highest risk for self-harm and aggression (Nielssen & Large 2010, Pompili et al. 2011), but they more commonly cause avoidable suffering for the affected youth and their families as they traverse chaotic and disorganized pathways to care. Therefore, maximizing the benefits of CSC requires optimized efforts to identify, refer, and

promote engagement with CSC treatment as soon as possible after onset. [Notably, ongoing and interleaved research efforts have focused on identifying those at risk and testing approaches to prevent the onset of psychosis (Fusar-Poli et al. 2012, 2014), but consideration of that important task is beyond the scope of this review.] Early psychosis populations in any area can be divided into two groups for outreach purposes: those who are yet to seek help and those who have already come into contact with the health care system but are yet to receive CSC or best-practice care. Each group requires separate attention.

Multiple attempts across the world to reduce DUP provide a wealth of lessons and some notable successful examples (Lloyd-Evans et al. 2011). The seminal TIPS program demonstrated that multipronged efforts that address lack of awareness (via a public information campaign) and at the same time provide clear direction on how to access responsive services can halve DUP in a large geographic sector (Friis et al. 2005). Several ongoing early detection efforts in the United States funded by a recent NIMH Request For Applications, including a quasi-experimental replication of TIPS (Srihari et al. 2014), will deliver more rigorous information on how to effect early detection and referral. Another project will address identification delays by using standard targeted provider education plus novel technology-enhanced screening and at the same time address engagement delays by using a mobile community-based, telepsychiatry-enhanced engagement team (Carter 2016). Other research studies will test methods to increase community literacy in the Latino population (Lopez 2017) and develop Internet-based strategies to reach young people through social media (Kane 2015). New York City has taken a public health approach and now requires all individuals hospitalized with first-episode psychosis to be identified and reported (**https://www1.nyc.gov/site/doh/providers/reporting-and-services/notifiable-diseases-and-conditions-reporting-central.page**); the city also offers a critical time intervention model staffed by a peer and a professional, called NYCStart, aimed at enhancing optimal follow-up care (**https://www1.nyc.gov/site/doh/health/health-topics/crisis-emergency-services-nyc-start.page**). Simon et al. (2017) have developed an algorithm to identify individuals experiencing the first presentation of psychosis using chart reviews and claims. Other strategies will need to reach into jails and prisons as well as schools and other community structures to identify and engage youth who are experiencing the onset of psychosis (Ford 2015).

4.2. During Coordinated Specialty Care

This category subsumes all of the questions we have about how to implement what we know and how to expand our knowledge of what works and for whom. Although CSC has been defined as including specific care components—including medication and primary care coordination, family support and education, case management, psychotherapy, and supported employment and education—there is to date no standard CSC program and no well-validated measure of fidelity, though Addington et al. (2016) have begun this process. Although the RAISE-ETP study and the block grant's facilitation of the national rollout of CSC have created a vast array of experiences across the chaotic US health care system, systematic knowledge regarding how to deliver CSC in different settings to different populations is lacking. Training of the workforce to deliver CSC and the development of strategies to sustainably finance it are two foundational challenges yet to be met (Dixon 2017a).

Several approaches are available to help organize the task of spreading evidence-based care models (Aarons et al. 2011). One approach from the Institute of Medicine offers a compelling way to address the challenges of delivering care in the US system, with its myriad regulatory demands, inefficient medical record systems, and limited reimbursement for psychosocial services. Learning health networks have been proposed as a means to engender a collaborative model

wherein "science, informatics, incentives, and culture are aligned for continuous improvement and innovation . . . and new knowledge is captured as an integral by-product of the care experience" (Inst. Med. 2013, p. ix). These, or related approaches, help support CSC implementations, allow knowledge sharing, and maintain quality. This approach to creating a learning community may be employed in the government evaluation of the use of the SAMHSA block grant supplement to support implementation of CSC. Participating sites are convening to evaluate technical assistance, with the added benefit of creating contacts among the various CSC sites across the United States.

The challenge of refining and improving CSC is no less daunting than the challenge of delivering the current best practices. The knowledge gaps are vast. To name a few, problems with cognition (Revell et al. 2015), substance use (Seddon et al. 2016), and suicidality (Coentre et al. 2017) require further attention. Cognitive remediation is not considered a required component of CSC at this point, but models are being tested and there is some evidence of effectiveness. A recent systematic review of RCTs investigating cognitive remediation after a first episode of psychosis found that one of seven neurocognitive domains showed a significant positive effect (verbal learning and memory), and five others showed borderline significant benefits. There was a significant effect on functioning (0.18; CI = 0.01, 0.36; $p < 0.05$) and symptoms (0.19; CI = 0.02, 0.36; $p < 0.05$). The effect of cognitive remediation on functioning and symptoms was larger in trials with adjunctive psychiatric rehabilitation and small group interventions (Revell et al. 2015).

Although some studies have demonstrated reductions in hospitalization with CSC, hospitalization and psychotic relapse persist, stimulating efforts to improve the utilization of clozapine and long-acting injectable medications. Clinical trials have demonstrated the effectiveness of comparatively low doses of antipsychotic medication in the early stages of schizophrenia, with the majority of patients achieving substantial improvement in psychotic signs and symptoms (Robinson et al. 2015a). At the same time, first-episode patients are potentially more vulnerable to side effects, even with lower doses. In many cases, they are highly ambivalent about taking medication in the first place, so that tolerability and early identification and management of adverse effects become a high priority. The fact that no specific antipsychotic medication has shown to be superior in reducing positive symptoms in first-episode patients underscores the importance of selecting treatments based on tolerability. However, clozapine has shown to be effective when patients have failed two or more adequate trials of other medications, even during the first episode of treatment (Agid et al. 2011).

The recommendations for longer-term maintenance pharmacologic treatment have come a long way since the earliest controlled trials (Kane et al. 1982) indicating that patients who had recently recovered from a first episode of schizophrenia would benefit from continued antipsychotic medication to reduce the risk of subsequent psychotic relapse. Additional studies confirmed the efficacy of antipsychotic medications in reducing the risk of relapse following a first episode of psychosis (Robinson et al. 2005). However, not all patients will experience an exacerbation of symptoms following medication discontinuation, though the majority will (Robinson et al. 2005). At the same time, we remain hard pressed to identify the subgroup who might not require such treatment, at least during the early phase of illness. Alvarez-Jimenez et al. (2016) recently reviewed studies of treatment discontinuation in first-episode psychosis, including affective psychosis. They suggest that individuals who do not have a diagnosis of schizophrenia, achieve clinical remission for at least three months, and attain early functional recovery with strong support may be possible candidates for discontinuation of antipsychotic medication accompanied by effective psychosocial interventions. Further, there is a clear need to learn more about the adverse cardiometabolic effects of antipsychotic medications, even as they remain essential tools to manage psychotic symptoms and associated aggression and they can reduce suicidality (in the case of clozapine). Studies of CSC have also demonstrated that there is still a group of nonresponders whose care demands further research.

Overall, it is important not to permit awareness of the benefits of CSC to prevent consideration of the well-known heterogeneity in early psychosis samples in terms of prognosis (without treatment) and of responsiveness to available treatments and to efforts at early detection. A one-size-fits-all approach based on average effects from even rigorously conducted clinical studies risks over- and undertreating different subgroups and delaying identification of those who are refractory to current best practice. Careful ascertainment of sociodemographic and clinical characteristics can be leveraged in predictive models to allow us to determine what works for whom. Also, emerging knowledge of distinct etiologies and pathophysiologies currently categorized within the schizophrenia spectrum may yield more personalized treatments. Moreover, we need better-validated measures of functional outcome or community adaptation to help define the value of CSC for affected youth and their families, but also society at large. Whereas composite measures such as QALY allow comparisons across medical conditions, these may not be adequately sensitive to meaningful changes in the state of individuals with psychotic illnesses (McCrone 2011). A panel of measures that assess distress, impairment, and disability will likely be necessary to evaluate the societal value of early intervention services and to calibrate the level of policy support for wider dissemination of such services.

An additional question that inevitably arises when considering the implementation of CSC is to whom it should be offered. As discussed above, the RAISE-ETP study showed much greater benefits for individuals with DUP of less than 74 weeks (Kane et al. 2016). Here, DUP was defined as the time between onset of psychosis and exposure to antipsychotics in a sample in which participants did not have more than six months of total exposure to antipsychotic medication (Addington et al. 2015). DUP varies widely across the many early psychosis studies, which differ in inclusion criteria as well as definitions and assessment strategies for DUP, making cross-study comparisons difficult (Golay et al. 2016). Some CSC programs offer services only to individuals within a specified time of illness onset (e.g., two years) regardless of previous treatment, which will by definition cap the DUP of the individuals served (Bello et al. 2017). There is no evidence to support a DUP after which the CSC model has minimal value over usual care. Three months is a commonly accepted DUP target (Cotter et al. 2017) but the fact that CSC was compiled from treatment known to be effective in chronic schizophrenia suggests such team based, specialty care models may benefit patients later in the illness course.

Another common question facing policy makers is whether to offer CSC to individuals with affective psychotic disorders such as major depression and bipolar disorder. Arguments against this decision are that the CSC research has largely focused on schizophrenia-type disorders, the benefits of CSC in other psychotic illnesses are less well tested, and the impact of DUP is less clearly delineated. At the same time, other scholars argue that it is very difficult to differentiate these illnesses in youth, and there is not likely any specificity to the benefits of this comprehensive team-based model for all young people with psychosis. A policy framework that focuses on providing evidence-based treatment to youth with behavioral health care disorders at their earliest phases rather than focusing on specific disorders may be the most coherent population-based approach.

4.3. After Coordinated Specialty Care

The issue of patients' needs after CSC includes a consideration of how long CSC should last and what young people experiencing psychosis and CSC care need in an ongoing way. Follow-up studies of several CSC RCTs to date, including OPUS and LEO, suggest that the benefits observed at the time of program completion are not sustained 5 and 10 years later (Bertelsen et al. 2008, Gafoor et al. 2010, Secher et al. 2015, Sigrúnarson et al. 2013). Interestingly, the TIPS study that focused on early detection did observe greater rates of recovery in the early-detection versus

usual-detection group after 10 years (Hegelstad et al. 2012). Would extending the duration of CSC programs mitigate the erosion of benefits? The Prevention and Early Intervention Program for Psychoses in Ontario provided extended continuity of lower-intensity care for three additional years after the two-year standard CSC program (Norman et al. 2011). Scholars examining the program found that the improvements observed at two-year follow-up were maintained at five years, with ongoing improvement in global functioning. Chang et al. (2015, 2017) performed an RCT in Hong Kong that compared individuals who had a one-year extension of the two-year CSC program called EASY to individuals who got stepped-down care. Individuals with extended EASY had improved outcomes in numerous domains immediately after the one-year extension (Chang et al. 2015), but there were no group differences one year later (Chang et al. 2017). Another RCT compared individuals who had received two years of OPUS followed by usual treatment with individuals who had received five years of OPUS. Group differences were limited to increased likelihood of remaining in contact with specialized mental health services, higher client satisfaction, and stronger working alliance (Albert et al. 2017). Overall, the treatment extension and follow-up studies do not reveal uniform findings. There are signs indicating that ongoing treatment produces persistent benefits, whereas evidence of the persistence of such benefits after CSC is lacking. There are many possible explanations for these findings, including sampling and attrition issues, variability in the quality of treatments compared, limited implementation of CSC treatment, and variability in DUP, to name a few. More research is clearly needed on the overall optimal length of CSC and what should come next.

The overall failure to produce sustained benefits in the aftermath of CSC treatment presents the field with an enormous challenge. Alvarez-Jimenez et al. (2013) have developed an online approach called HORYZONS that uses expert moderation and "super-users" (peer moderators) to provide follow-up care to young people as they are completing their course of CSC treatment at the Orygen program. This is being tested in a randomized trial. CSC programs are focusing on developing approaches to step down and follow up, including ongoing vocational and educational supports, family education, and alumni groups (personal communication, T. Sale, EASA). The heterogeneity of responses to CSC demands tailored solutions. Within the US health care system, the separation of CSC programs from the overall delivery system likely hinders the seamless integration of CSC into optimal longitudinal care. The transformation and integration of CSC programs into learning health networks may produce self-correction of CSC practices as systems learn what works and what does not, and it may perhaps contribute to an overall improvement of usual care.

5. CONCLUSION

In the end, evidence is mounting for the positive impact of CSC on a range of outcomes for individuals in the early stages of psychosis. The studies hint at the benefits of early intervention to reduce DUP and to improve outcomes. To some extent, implementing CSC within a system of mental health services increases its capacity to provide evidence-based care for individuals at any stage of a psychotic illness. Earlier treatment means earlier benefits in terms of immediate outcomes but may not improve longer-term outcomes and prevent disability. The ultimate promise of prevention of long-term disability, which has motivated so many of the cycles of mental health service reform in the past, remains elusive. CSC programs have established their value in improving early outcomes; they should be available as standard care for new-onset psychosis and can provide a humane and rigorous platform upon which to build further studies, develop new treatments, and refine the delivery of services. Doing what we know works can thus support ongoing research to answer lingering questions and to avoid paralysis in the face of important uncertainties.

SUMMARY POINTS

1. Mental health policy has shifted its priorities away from services for already disabled individuals and toward including early intervention services. This shift was encouraged by accumulating international evidence of the effectiveness of early interventions and by the RAISE studies in the United States, and it was resourced by provisions of the ACA and a supplemental set-aside in the federal mental health block grant.
2. The Schizophrenia PORT identified an array of evidence-based practices for individuals with schizophrenia and, along with several pioneer US early intervention clinics, set the stage for the RAISE studies, which adapted evidence-based practices for early illness.
3. The NIMH-funded RAISE-ETP study tested a team-based, multielement CSC program labeled NAVIGATE in a cluster randomized trial and found that NAVIGATE produced superior quality of life, reduced symptoms, and greater improvement in attendance at work or school compared to usual community care, especially for individuals with shorter DUP.
4. A separate NIMH-funded RCT of a public sector "FEP program," STEP, established improvements in hospitalization and vocational outcomes.
5. The success of the RAISE-ETP study combined with positive results from both US and international tests of CSC contributed to the creation of clinical, policy, and financing opportunities to expand CSC nationally.
6. Many questions remain regarding how to reduce DUP, optimize CSC programs, and sustain the benefits of CSC after patients complete the program.
7. It was feasible to implement CSC in usual community settings.
8. Analysis of baseline data revealed that first-episode patients have a median DUP of 74 weeks, have excess medical morbidity, and have suboptimal pharmacological treatment.
9. NAVIGATE, the RAISE-ETP CSC program, produced significantly improved treatment engagement, quality of life, and vocational functioning as well as reduced symptoms compared to usual community care.
10. DUP moderated the effect of NAVIGATE on outcome, such that those with shorter DUP experienced greater improvements in quality of life and greater reductions in symptoms than those with longer DUP.
11. Use of the net health benefits approach showed a high probability that the value of NAVIGATE benefits would exceed the program's costs relative to community care from the perspective of the health care system.

FUTURE ISSUES

1. What are effective strategies to reduce DUP in the United States? Will reducing DUP further improve outcomes?
2. What specific service components and processes are critical to the success of CSC?
3. Is CSC superior to usual care for other psychotic disorders, including affective psychosis?

4. What is the optimal length of CSC and what is needed for individuals to retain benefits and/or recover more fully after completing CSC?

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