Published in final edited form as:
Psychiatr Clin North Am. 2012 September ; 35(3): 613–631. doi:10.1016/j.psc.2012.06.004.

Is early intervention for psychosis feasible and effective?

Vinod H. Srihari, MD[a], **Jai Shah, MD**[b], and **Matcheri S. Keshavan, MD**[c]

[a]Associate Professor, Department of Psychiatry, Yale University; and Director, Clinic for Specialized Treatment Early in Psychosis (STEP), Connecticut Mental Health Center, New Haven, Connecticut

[b]Resident in Psychiatry and Dupont-Warren Research Fellow, Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

[c]Stanley Cobb Professor and Vice-Chair for Public Psychiatry, Department of Psychiatry, Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, Harvard Medical School, Boston, Massachusetts

Synopsis

Services that provide comprehensive, early intervention (EI) have shown promise in improving long-term outcomes in schizophrenia. This paper reviews the rationale and salient concepts relevant to understanding the growing EI literature. A selective review of studies evaluating the effectiveness of integrated EI is followed by a discussion of feasibility, especially in the U.S. context. Finally, the authors present a framework that seeks to integrate activities traditionally categorized and separated as discovery and implementation. This framework is offered as one way to advance both goals.

Keywords

first episode psychosis; critical period; schizophrenia; early intervention; knowledge translation

Intervening early for psychosis: Why bother?

Psychotic disorders are common, disabling and costly under usual care. The prototypic psychotic illness, schizophrenia, affects between 0.55 and 1 percent [1, 2] of people during their lives, typically manifests in adolescence or early adulthood – an especially formative period for social and vocational trajectories - and is amongst the top ten causes worldwide of years lived with disability. [3] With routine care, less than one-fifth of patients achieve full recovery after a first episode of psychosis [4] and less than one-third achieve minimal age appropriate employment or education. [5] Schizophrenia leads annual U.S. mental illness

[a]Corresponding author for proof and reprints: Vinod H. Srihari, MD, 34 Park Street, Connecticut Mental Health Center; Room 273A, [CMHC, 2nd floor mailroom], New Haven, CT 06519, (203) 974-7816, (203) 974-7322 (fax), vinod.srihari@yale.edu.
[b,c]Co-author addresses: Jai Shah, MD, Harvard Longwood Psychiatry Residency Training Program, c/o Silvia Graziano, 330 Brookline Avenue, Rabb-2, Boston, MA 02215, 617-667-2300 x13332, 617-754-1250 (fax), jai_shah@bidmc.harvard.edu
Matcheri S. Keshavan, MD, Address: room 610, MMHC 75 Fenwood Road, Boston MA 02115, (617) 754-1256, (617) 754-1250 (fax), mkeshava@bidmc.harvard.edu

Disclosures: Dr. Keshavan has received grant support from GSK and Sunovion.

expenditure, with $22.7 billion in direct healthcare costs (2002) attributed mostly to acute hospitalizations. This, however, represents only about a third of the larger estimated total costs that include the burden of unemployment, reduced workplace productivity, premature mortality from suicide, and family caregiving [6]

Early intervention services can improve the poor outcomes of usual care. There are intuitively compelling arguments for intervening early in the course of schizophrenia spectrum disorders. We review these arguments within Birchwood's framework of the critical period hypothesis, present evidence from experimental tests of this hypothesis and review the effectiveness and feasibility of early intervention services. We conclude with a discussion of how further efforts in this active area of investigation can better address the public health challenge of caring for those with chronic psychotic disorders.

The course of psychotic illnesses and the 'critical period'

Beginning with Bleuler's classic follow-up study of schizophrenic illnesses that proposed stable rather than progressive functional decline as the norm in psychotic illnesses, [7] the pessimistic prognostications embedded in early Kraepelinian classifications – exemplified by the term 'dementia praecox' – have been strongly challenged. The weight of evidence accumulating against a uniformly deteriorating, degenerative course was summarized in a seminal paper in 1988, which also introduced the concept of a 'critical period' for psychotic illnesses. [8] This includes three propositions elaborated below, with updated evidence:

Mental and social deterioration in schizophrenia-spectrum illnesses is non-linear—Prospective studies have shown that most of the clinical and psychosocial deterioration occurs within the first 2 to 5 years after psychosis onset. [9] This period is notable for high risk for relapse, re-hospitalization and suicide. A 15-year follow-up, study of first episode non-affective psychosis (in which 63% were eventually diagnosed with DSM III-R schizophrenia) reported relapse rates of: [10]

- 43% (1 year)
- 55% (2 years)
- 70% (5 years)

As many as two-thirds of completed suicides in schizophrenia occur within six years of diagnosis [11] with risk particularly elevated 1 year after a first psychiatric hospitalization. [12]

This early, turbulent period is not usually followed by progressive decline but rather a 'plateau' in symptoms and impairment, even under usual systems of care. Long-term follow-up studies in predominantly chronic populations have confirmed this medium-term stability followed by gradual improvement for as many as a third of patients. [13, 14] A landmark study of 90 early psychosis patients followed over 10 years confirmed a steep decline to a stable 20 to 25% prevalence of residual positive or negative symptoms within 2 years of onset. [15] A recent meta-analysis of longitudinal studies of first-episode psychosis confirmed that the proportion of patients with poor outcomes does *not* increase over time. [5]

Desynchrony between clinical and functional variables is evident early in the course of schizophrenia—While studies in chronic illness samples have demonstrated that symptom remission is not necessary for functional recovery, [16, 17] early psychosis populations also express this desynchrony, albeit in the opposite direction: here early symptomatic remission is often the norm and out of proportion to the levels of functional

recovery, at least under usual care. As many as 75% or more of individuals with first-episode psychosis show symptom remission within the first year, [18, 19] but less than one-third achieve minimal age-appropriate employment or educational functioning in the first few years after frank psychosis has emerged.[5]

The first few years around the onset of psychosis witness the emergence of several important predictors of outcome—Several factors have been associated with poor long-term outcomes in schizophrenia. Some of these present opportunities for delivering or developing interventions, including prolonged untreated psychosis, social isolation, drug use, insidious onset, living in industrialized countries, and immigration (16). More recent additions to the list of potentially modifiable factors are affective symptoms, non-adherence to medications, the presence of early negative symptoms, and cognitive dysfunction [20]. While this list likely represents a mixed bag of factors that are either causally implicated in outcomes, secondary effects of the illness or confounding variables, many are sources of distress at clinical presentation and have provoked efforts to better understand and modify the disease course.

One factor known for some time to be a correlate of relapse risk in psychosis is the level of Expressed Emotion (EE, conceptualized as including emotional over-involvement, hostility and critical comments) by caregivers of affected individuals. [21] Hospitalized patients returning to high-EE home settings have a relapse risk more than double those returning to low-EE homes [22]. The association between EE and psychosis relapse appears to be valid in early psychosis [23] with evidence that critical engagement by relatives can increase as the illness becomes more chronic,[24] pointing to the potential utility of early intervention.

A more recent addition to this list is the emergence of cardiovascular risk factors in early psychosis samples. The markedly premature mortality of patients with chronic psychotic disorders is primarily of cardiovascular origin, results in an estimated shortening of lifespan of up to 20 years [25] with emerging evidence of a worsening of this mortality gap. [26] This cardiometabolic risk emerges quite early in treatment. [27] Along with antipsychotic choice, the emergence of established risk factors such as smoking and obesity amongst younger patients [28] offers an important opportunity for primary prevention of cardiovascular morbidity and mortality.

Increasing evidence in recent years also points to progressive brain changes during the early phases of psychosis. Structural alterations in medial temporal, prefrontal, anterior cingulate and insular cortex might occur during the acute process of transition to psychosis.[29, 30] On the other hand, other brain structural changes (i.e. superior temporal gyrus volume reductions) found in early psychosis may progress during the early phase of the illness[31] but show no further reductions during the chronic phase. [32] Progressive gray matter reductions have been reported during the first several years after the onset of frank psychosis. [33]

Recent data suggest that brain structure and function (‘cerebral reserve’) prior to or at the onset of illness may predict better response to treatment, perhaps because of availability of larger neural resources in the service of such adaptive neuroplasticity. [34–36] Earlier stages of psychotic illness, when significant gray and white matter alterations have not yet set in, may therefore respond better to therapeutic interventions. For example, Eack et al. [37] have recently shown a lack of progressive gray matter reductions and increases in gray matter in some brain regions in early course schizophrenia patients treated for 2 years with cognitive remediation by contrast to supportive interventions. Taken together, these observations support a neurobiological basis for the critical period concept.

The critical period hypothesis and Early Intervention

This hypothesis suggests that intensive efforts to intervene during the critical period (i.e., within 2–5 years) after the onset of psychosis can disproportionately alter the trajectory of schizophrenia spectrum illnesses in comparison to usual models of care. Usual care is often organized around the dual tasks of acute management of relapses coupled with rehabilitative interventions that typically begin in earnest long after a 'plateau' of functional loss has been reached. This hypothesis makes explicit what has long served as the intuitive basis for improving upon such models of care.

The trajectories under usual care are depicted in Figure 1. The 3 course types (A, B and C) are a simplification imposed over the considerable heterogeneity reported in outcomes studies. This likely reflects heterogeneity within any diagnostic class but also the variable impact of environmental factors on genetic risk. Nevertheless, the replicated finding of a subset of patients who recover after a single episode (A) and those who are refractory to present treatments (C) is illustrated in this figure to make the point that current EI services are best positioned to target the various courses collapsed into B which includes patients who, under ordinary care, suffer multiple relapses with variable an potentially malleable levels of return to premorbid functional trajectories.

Early Intervention (EI) for 'first-episode' psychosis can be conceptualized as including one or more of an interlocking set of strategies composed of 2 main elements: reducing delay to treatment or reducing the duration of untreated psychosis (DUP); and the provision of more intensive intervention during the 2 to 5 years following identification of a psychotic disorder.[38] The second task includes the provision of 'phase-specific' interventions that are adapted for younger, early course patients and their families. EI, for the rest of this discussion, is used to refer to service approaches that focus on these 2 tasks, primarily the second.

Outside of the scope of this discussion, but addressed by *Clarke et al* in this issue of the *Clinics*, are the important efforts to predict and prevent conversion to psychosis in high-risk samples. Such efforts to intervene before what is, after all, an arbitrarily defined threshold of positive psychotic symptoms is consistent with a neurodevelopmental conception of schizophrenia spectrum illnesses [39–41]. However, current limitations on both accurate prediction and the lack of established preventive treatments make systematic implementation or assessment of feasibility outside research settings, premature.

Reducing the Duration of Untreated Psychosis (DUP)—The largest experimental study of the impact of reducing DUP has been the impressive TIPS project. [42] A comprehensive education and detection system was delivered by randomized allocation to a healthcare sector in Norway while two control sectors in Norway and Denmark delivered comparable care but without the benefit of efforts to reduce DUP. While prior systematic reviews of observational studies had documented a strong correlation of DUP with outcome, [43, 44] the TIPS project succeeded in experimentally manipulating DUP to address the question of whether this measure is a mere confound associated with poor prognosis cases or a causal mediator of outcomes. TIPS demonstrated that reducing DUP (from a median of 1.5 to 0.5 years) led to markedly improved clinical presentations and improved medium and longer term (5-year) outcomes. [45, 46] Notably, when the intervention was interrupted, this resulted in measurable increases in DUP followed by attendant worsening in outcomes, further validating the causal inference. [47] While one other study in Singapore used a broad, multi-focal campaign that reduced DUP and improved pathways to care [48] other less intensive attempts failed to reduce DUP, exemplifying the significant logistical challenge to replicating this finding. [49]

Providing enriched (multi-component) care during the critical period—While TIPS demonstrated that intervening *earlier* improves outcomes, most studies have chosen to focus on the arguably more tractable goal of enriching care after presentation for treatment. Centers in Australia, Northern Europe, England and Canada have pioneered the development and implementation of service models adapted for early psychosis samples. [50] Within this burgeoning area of research are multiple ongoing studies testing one or more of a number of pharmacologic and psychosocial approaches to improve outcomes in first-episode psychosis. [51] As is common in an area of intensive research, there are multiple definitions of 'first-episode'[52] and multiple measures of outcome[51]. This diversity in samples, interventions and definitions of outcome preclude any simple inferences about the overall success of the early intervention paradigm. [53]

We focus, in the rest of this paper, on integrated early intervention services i.e. those that incorporate several component interventions designed to comprehensively serve the needs of individuals presenting early in the course of a chronic psychotic disorder. In contrast to trials testing the delivery of single treatments (pharmacologic or psychotherapeutic) or interventions focused on demonstrating changes in particular domains (e.g. suicidality, co-morbid substance use) we will draw specifically on studies that evaluate overall, comprehensive services. These models of care are designed to address the wide range of needs presented by early psychosis patients and their caregivers. Such work seeks to integrate care over the overlapping categories of medical/psychiatric treatment and referral, access to social service, case management, liaison with community supports, social and vocational rehabilitation and education and support of caregivers. As such, these service models envision the multiple and variable needs of the heterogeneous samples identified as early or 'first-episode,' and are thus the most relevant to a current evaluation of whether EI is effective and feasible.

Does Early Intervention (EI) work?

We divide this question in four broad domains (Box 1: *Evaluating Healthcare Interventions*) that require distinct responses. These are worth explicating in the context of EI before reviewing the salient evidence.

Box 1

Evaluating healthcare interventions

1. Efficacy: Can it work?
2. Effectiveness: Does it work?
3. Costs: Is it worth it?
4. Translation: Can it be disseminated?

The first question raises the issue of *efficacy* or of whether and how much a treatment improves outcomes under relatively ideal conditions (*Can it work?*). In the context of a clinical trial, this would imply recruiting a homogenous population, delivering well-defined treatments in as uniform a manner possible and measuring outcomes that relate most closely to the putative mechanism of action of the treatment. Such *explanatory* trials, in essence, attempt to estimate the core therapeutic effects of a treatment. [54] This is in contrast to trials that seek to answer the second question about *effectiveness* or the impact of a treatment under conditions that are intended to more closely approximate 'real world' clinical settings (*Does it work?*). With the example of a pharmacological intervention in mind, it is easy to appreciate the argument that the 'core' therapeutic effect needs to first be

demonstrated in an efficacy trial, as a negative result might help avoid futile and expensive effectiveness trials in larger samples. Effects seen in more ideal efficacy conditions might become diluted in effectiveness studies that recruit patients who are more heterogeneous with respect to their response or collect outcomes that may be less closely related to the direct biological effect of the drug. This linear progression from the establishment of efficacy to the study of effectiveness in more generalizable clinical samples is, however, often not appropriate for complex interventions such as EI services.

While initial efficacy or 'proof of concept' trials by pioneer EI programs have sought to demonstrate the value of one or more interventions or models of care in selected early psychosis populations, [50] these have varied in terms of their definition of the sample, intervention and outcome measures and their success at minimizing common sources of systematic bias and generating adequate power to precisely measure effects. A recent systematic review concluded that this presented the risk that the implementation of early intervention services will far outpace the strength of the supporting evidence. [51] One argument, based on the logic of knowledge development described above, would seek to thus limit further implementation of services until we better can better understand and codify the 'active ingredients' or 'essence' of these new approaches to care. An alternative appraisal is that legitimate differences in goals and attendant methodological decisions in efficacy vs. effectiveness trials should encourage appropriate deviations from this hierarchical convention. [55] Given the inevitable heterogeneity introduced by our current best diagnostic practice in early psychosis populations and the variety of their treatment needs, the more pragmatic position of determining whether a realistically defined service works for a recognizable target population is more relevant to evaluating the value of EI. This would allow empirically based improvements in service delivery to continue even as the effort to better define pathophysiologically meaningful subtypes continues.[56]

The pragmatic randomized trial [57] operationalizes an approach that combines elements of traditional explanatory trials with considerations of real-world effectiveness that is well suited to the current state of knowledge in schizophrenia. Subjects are randomly allocated to alternative service options, thus deviating from 'real-world' clinical practice, but allowing minimization of selection bias. On the other hand, these studies:

- **a.** embrace more biologically heterogenous samples that seek to mirror those that actually present to systems of care;
- **b.** employ interventions that attempt to reflect what could be realistically delivered in such systems and
- **c.** assess outcomes – often long term – that are most salient to stakeholders in such systems, including patients, families and policy-makers.

There are four such second-generation trials in the early intervention literature that are focused on determining the effects of integrated EI service models. Consistent with the pragmatic focus, these trials from four different countries reflect local system resources and constraints in their design and fall on different positions along the efficacy – effectiveness continuum in the domains of sample, intervention and outcome measurement. (Table 1)

The UK-based Lambeth Early Onset (LEO) study randomized individuals with early psychosis to an intensive and case-managed treatment regimen of assertive community-based interventions comprising cognitive behavioral therapy, family counseling, vocational services and low-dose antipsychotic medication. Subjects receiving specialized services had lower rates of relapse and dropout, improved measures of social and vocational functioning, satisfaction, quality of life and medication adherence at 18-month follow-up. [58, 59] The Danish OPUS study offered a similar set of specialized interventions, using a model of

home-based assertive case management integrated with pharmacotherapy that favored lower dose antipsychotics, and included family and individual psycho-education with social skills training and vocational assistance as needed. This enriched intervention was applied over 2 years and, compared to involvement with a standard community mental health team, [60] delivered benefits in positive and negative symptom control, secondary substance abuse, treatment adherence and higher satisfaction with care. [61] A Norwegian study of a similar home-based integrated approach compared to standard office based care, reported 2-year improvements in the number and duration of hospitalizations and the frequency of 'excellent' outcomes (a composite that included relapse in symptoms and adherence to treatment) in the group receiving the enriched intervention. Finally, the ongoing STEP trial, directed by one of the authors, delivers an office-based integrated package that includes structured family psycho-education, cognitive behavioral individual and group therapy, antipsychotic medications and vocational and educational supports as needed. The treatment is delivered in a U.S. community mental health center and compared to usual care will soon report similar trends in reduction of hospital utilization and improvement in vocational and social outcomes. [62]

All four studies utilized a rigorous, albeit pragmatic, randomized design and demonstrated measurable and non-trivial improvements in outcomes across four distinct healthcare systems. While the first three trials utilized a particularly resource intensive model of home-based outreach with enriched clinician: patient ratios (~1:01) that could be sustained only over a limited period of 2 years, the last trial has employed a more pragmatic intervention that is office based, with a clinician: patient ratio that mirrors the usual care arm (~1:30). This has allowed the integrated intervention to be sustained without a time limit but instead with gradual transfer to usual services in a stepped, individualized manner.

In both OPUS and LEO, much of the demonstrated benefit was not durable at 5- year follow-up i.e. approximately 3 years after specialized care was discontinued. [63, 64] This has raised questions of how long intensive care should be sustained and how to mitigate the presumed adverse effects of transferring care from specialized servicea. Some have raised ethical concerns about offering such enriched interventions for less than 5 years, given that this can be a particularly vulnerable period in development. [65] The STEP approach of offering a less resource intensive approach that can be sustained longer with an individualized and gradual transition out of specialized care was designed to test an alternative approach. Similar approaches of using stepped reductions in intensity to prolong care through 5 years after entry have demonstrated durable effects in a Canadian public-sector program. [66]

Are EI services worth the cost?

The emergence of psychotic disorders in adolescence and young adulthood, their chronicity, and their widespread effects on cognitive functioning make them immensely disabling over the lifespan, placing them in the top 10 causes of disability in developed countries worldwide. [3] The direct health care ($22.7 billion) and total ($62.7 billion) costs in the U.S. [6] are comparable to estimates for far more common depressive disorders. [67] Similar cost estimates undertaken in the U.K. have shown a comparable economic burden.[68] While there is a clear need to improve outcomes to reduce these costs, the fact of limited healthcare resources implies that investments in one area of public health need will need to be diverted from another. Economic analyses are emerging as the dominant way to quantify such 'opportunity costs' and to inform the relative value placed on healthcare services such as EI.

Several methodological choices determine whether an economic analysis can provide valid justification for resource allocation.[69]

Measure costs—First, is the measurement of costs. Focusing solely on *direct* expenditures or the costs of providing treatment (including inpatient, outpatient and community health and social services) may seriously underestimate the overall costs of a serious mental illness. In a study of schizophrenia in England, such expenses accounted for less than a fifth of the total cost estimate.[70] The latter ideally includes comprehensive measures of *indirect costs* such as lost opportunities for work and leisure and the cost of informal care provided by caregivers.

Measure benefits—Second, choices made in the measurement of benefits can prejudice the scope of cost analyses. For instance, the surrogate outcomes of symptom control in psychosis may or may not adequately predict vocational functioning or overall quality of life, although these are far more challenging to measure.

Define comparator—Third, it is important to define an adequate comparator to early intervention services against which economic gains or losses can be measured. The best available local alternative would provide the most stringent test of an EI service, while a poor quality comparator might inflate estimates of the effectiveness of an integrated approach.

Integrate life expectancy gains with quality of life gains—Fourth, economic analyses attempt to integrate life expectancy gains with quality of life gains experienced during a particular time window. In the most common type of evaluation, or cost utility analyses, [71] interventions are assigned a weighted score representing quality of life over a time period, measured in terms of “quality adjusted life years” (QALYs). Comparing interventions in a ratio of currency (e.g. Dollars) per QALY allows for assessment of the relative benefits conferred by treatments *across* diseases. Over the last decade QALYs have been frequently utilized in the evaluation of health benefits. [72] The UK-based National Institute for Health and Clinical Excellence, which provides service planners in England with QALY-based guidance, has endorsed EI services and recommends that they include “a full range of relevant pharmacological, psychological, social, occupational and educational interventions for people with psychosis.” [73] The use of QALYs has however met with criticism, especially in their lack of responsivity to real improvements in mental distress and disability. [74]

Take a broad societal perspective—Finally, it is generally recommended that economic evaluations take a broad societal perspective. This is in contrast to measuring costs solely from the perspective of an insurer, provider, caregiver or consumer of mental healthcare who each bear only a fraction of the costs exacted by psychotic illnesses. With respect to early intervention, even small reductions in unemployment and family burden with long term implications (indirect costs) might offset more immediate but larger per-patient costs of intensive, integrated care (direct costs). Aside from quantifying these costs, a societal rather than a provider perspective would be required to favor resource allocation to such an early intervention service whose greatest gains might manifest many years after initiation of the intervention [69]

With the above considerations in mind, available evidence on the potential for EI to deliver cost-effective care is not definitive. [75] An initial analysis from PEPP-Montreal investigated differences in expenditures before and after initiation of early intervention services, showing cost reductions but with uncertainty over whether this could be attributed

to the EI service. [76] A similar pre-post study design for new EI services in Hong Kong and Italy found intervention to be good value for money as measured by limited outcomes and costs over the short-term (24 months, Hong Kong) [77] and medium-term (5 years, Italy). [78] In both Sweden and Australia, specialized EI services were found to have lower costs (mostly due to decreased inpatient hospitalizations) and improved symptomatic and functional outcomes, although the durability of these differences remained in question. [79, 80] Extending their analysis to 8 years in a smaller sample, the Australian group subsequently found lower levels of positive symptomatology, improved remission rates and illness course, trends towards increased employment, and significantly lower direct service costs amongst the EI group. [81] This study is important in that it suggests that EI confers long-term advantages if more comprehensive indirect costs are taken into account.

Additional data from the Lambeth study evaluated a range of costs in detail. [82] Baseline and 18 month mental health service contacts and service utilization costs were overall higher for individuals receiving EI, with a small but insignificant total cost savings (primarily due to reduced hospitalization). EI subjects trended towards greater vocational recovery and significantly elevated quality of life, effects that if sustained in longer-term follow-up, will deliver significant indirect costs reductions.

The notion of whether a broad societal perspective is possible for a system to adopt and to thereby promote the goals of public health over the generally shorter term and narrower incentives faced by specific agents in the healthcare arena, highlights the importance of appreciating the cultural and policy context in which inferences about cost-effectiveness are made. [81] Health systems ensuring universal coverage (through either social insurance or single-payer schemes) might be more enabled to adopt such a perspective compared with systems in which healthcare coverage is less consistent. In latter systems, such as in the U.S., strong incentives exist to shift costs between different payers with measurably adverse outcomes for patients and their families early in the course of psychotic illnesses.[83]. Also, service utilization patterns and the costs associated with them can vary between sites and across countries. [84] This severely limits extrapolation of economic analyses across systems of care.

Is Early Intervention feasible?

It is worth noting that the development of multiple early intervention services across the globe have occurred in response to a pervasive dissatisfaction with standard services that were well known to be inadequately addressing the needs of these patients and their families.[85] After weighing the emerging evidence for these new approaches, the U.K.'s NHS announced in 2000, the implementation of 50 early intervention teams across the country. [86]. This signaled a commitment toward resourcing EI, which while meeting stakeholder demand has made possible further study and refinement of models of care.

The large number and range of innovative early intervention services in several countries has in effect, demonstrated the acceptability of this approach to a wide range of stakeholders. [87] A more stringent requirement for feasibility however, might also reference the last question (Box 1) i.e. whether EI services can be disseminated across usual systems of care. Services that are demonstrated to work but cannot be implemented on a wide scale will have marginal public health impact. This 'implementation gap' has been documented in the U.S. for several mental illnesses [88, 89] and for schizophrenia in particular. [90, 91] This experience has suggested the impact of a complex set of barriers and the tasks of dissemination and implementation of effective interventions has itself become an active focus of study. [92].

Healthcare systems in the U.K., Northern Europe and Australia have already made substantial commitments to specialized early intervention (EI) services, while in the U.S. a comparable national strategy for improving systems of care is conspicuously absent. While a detailed consideration of the barriers specific to the different regions in the US is beyond the scope of this discussion, certain factors known to many clinicians are illustrative.

1. First is the public-private sector divide. Privately insured patients struggling with the emergence of a serious mental illness can rapidly lose health insurance [83] and typically arrive at the public state mental health system long after the critical period for early intervention has elapsed.
2. Second, several states care for adolescents and young adults via separate agencies, thus fragmenting care during the peak ages of risk for psychosis onset. Working across organizational cultures with their different emphases on protection of vulnerable children versus the treatment of serious mental illness proves challenging.
3. Third, the division of public mental health care by geographic catchments in the public sector can limit the collection of a critical mass of early psychosis patients around which to organize care.

Reassuring cost data from other countries, reviewed above, have had limited impact so far on EI service development in the U.S. An important factor, as explicated in the earlier section, is that there are powerful non-societal perspectives on economic burden at play in U.S. healthcare delivery. Added to this is a paucity of U.S. data on reduction of direct costs that would respond to the perspectives of private and public insurance providers in this country. The feasibility of EI, as for any complex intervention, will thus depend as much on the particular perspective adopted within a particular system of care as the data on locally relevant costs. Such data, from the most salient pragmatic trials reviewed earlier, suggests consistently positive effects on a variety of domains of outcome but only one such trial will deliver U.S. based data. Given this, there is reason to remain uncertain about the feasibility of disseminating EI in the U.S., beyond research-funded settings.

What next? Doing what we know while also knowing better what to do

There are important gaps in our knowledge of psychotic disorders that span the range from basic knowledge of etiology, pathogenesis and clinical classification to the more complex domains of dissemination and implementation. A few examples of basic uncertainties in the first domain are instructive.

1. First is the knowledge that early exposures to biological and/or psychosocial stressors in utero, during the perinatal period, or around childhood could be causal and may be difficult to address or modify by the time of a ‘first-episode’ of psychosis in early adolescence or adulthood. Truly *early* intervention for these neurodevelopmental processes may thus have to await knowledge that will allow us to act in the perinatal period or long before the currently discernible critical period.
2. Second, cognitive impairments can be broad and established by the time of a first-episode [93] so the opportunity to prevent or ameliorate these deficits awaits more reliable identification of patients prior to their first break.[94]
3. Third, ongoing structural brain alterations have been reported up to 20 or more years after the onset of symptoms and are associated with poor outcomes.[95, 96] This suggests that whatever the claims made for early course corrections, active attention will need to be paid over the longer term to ensure optimal outcomes.

In the second domain is the recognition, across disorders, that the success of disseminating a model of care – what we refer to as feasibility in this article - depends on a host of factors that range from the more generic challenges of changing clinician behavior to the more specific, parochial concerns of individual healthcare systems. Furthermore, there are distinct methodological challenges in evaluating complex interventions – such as EI services – which deploy multiple interventions that are variably utilized by different participants. This makes it difficult and sometimes impossible for even large trials to confirm the active ingredients of the integrated service. [97]

It is important to recognize that gaps in the areas of both knowledge ('knowing what to do') and implementation ('doing what we know') impair our ability to most effectively intervene in the early phases of illness. Distinct attention to both these areas is necessary. However, this distinction between knowledge and its translation, can itself present a barrier to progress. We will argue that especially in the field of early interventions for schizophrenia spectrum disorders, reified divisions between *discovery* vs. *translation* or implementation oriented activities present another potential barrier.

Current consensual standards of evidence among U.S. experts that result, for instance, in recommendations for broader implementation of models such as Assertive Community Treatment (ACT) or Supported Employment [90] do not endorse EI. Commentators have reasonably questioned what the essential ingredients of EI might be and whether existing models of EI are merely providing what should be normal best practice. Such knowledge, that would permit more personalized and illness phase-specific treatment, will require access to populations who are early in the course of psychotic illness. Such populations are well known to be extremely difficult to recruit and retain in studies, a project that would be greatly aided by the kinds of EI services that have demonstrably improved pathways into and through care.

The current dichotomy between implementation and research can thus lead to an impasse. There are several lines of work that suggest a way forward. First, managers of healthcare resources, especially in the U.S., should pay attention to how nationalized health systems elsewhere have responded to the suggestive, even if not definitive, evidence on secondary prevention in psychosis. Programs in the U.K and Australia, have demonstrated that vital information – across the domains of disease physiology to cost-effectiveness of models of care – can emerge from implementations of EI services. The ongoing STEP trial (Table 1) and the large ongoing RAISE initiative [98] will deliver more U.S. relevant economic data. In an important respect, at least limited implementation may be necessary to generate locally actionable evidence on the range of questions in Figure 1.

The Knowledge Translation framework [99] used by the Canadian Institutes of Health Research suggests a more reciprocal organization of knowledge creation and implementation in an 'action cycle.' In the context of meeting the dual challenge of delivering better early care and improving our ability to study the early course of schizophrenia, we propose a further weakening of this division with 3 elements that could help advance the field. Given the context specificity of feasibility discussed earlier, this proposal is specific to the U.S., but likely of relevance to other countries that are less able to rely on a societal perspective for resource allocation:

- The implementation of EI services within public-academic collaborations. Ideally the intensity and range of clinical services would be supported but also limited by the available resources of the public community center. Such an ecologically 'real-world' model would also be protected from changes in grant funding and could revive and draw upon a traditional hub of community psychiatry in the U.S. [100];

- The use of a pragmatic RCT design to select locally relevant samples, deliver manageable interventions and measure locally salient outcomes with a minimum of extra resourcing. [101]
- A commitment to measure outcomes, including costs, and to use this information to alter local processes of care. Ineffective or overly expensive services, from the perspective of the local healthcare agency, could then be discontinued or refined as necessary.

An important aspect of this proposal is the attempt to decentralize the development and implementation of EI services and to embrace the reality of the differing perspectives of actors in the current healthcare system. The perspective of the public-academic collaboration is suggested as the most likely to advance public health goals. This is suggested in contrast to the traditional approach of developing, testing, refining and then manualizing services in mostly research settings before devising strategies to have these adopted more widely. This *develop then disseminate* approach is slow, cumbersome, inflexible to emerging knowledge and does not adequately address the different incentives that agencies may have toward particular problems or populations. Also, as evidenced in successive national reports for schizophrenia, this approach has not been successful in increasing the uptake of empirically based interventions. [90, 91]

The enthusiasm generated by work in early interventions for psychotic disorders is evidenced by the wide implementation of services and the wealth of data accumulating from studies across the translational continuum. Beyond having an impact on schizophrenia spectrum disorders, this work can suggest frameworks for other serious mental illnesses. Most are after all chronic diseases of adolescence [102] and as such, offer similar opportunities for societal investment in health. [103]

Acknowledgments

This work was supported by NIH grant MH088971 and a grant from the Donaghue Foundation (Srihari, PI), NIMH grants MH 64023 & MH 78113 (Keshavan, PI) and aDupont-Warren Research Fellowship, Harvard Medical School (Shah).

References

1. Goldner EM, Hsu L, Waraich P, et al. Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature. Can J Psychiatry. 2002; 47(9):833–43. [PubMed: 12500753]
2. Perala J, Suvisaari J, Saarni SI, et al. Lifetime Prevalence of Psychotic and Bipolar I Disorders in a General Population. Arch Gen Psychiatry. 2007; 64(1):19–28. [PubMed: 17199051]
3. Lopez, AD. A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Murray, CJL.; Lopez, AD., editors. Boston, MA: Harvard University Press; 1996.
4. Geddes J. Prevention of relapse in schizophrenia. N Engl J Med. 2002; 346(1):56–8. [PubMed: 11778005]
5. Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis [Review]. Psychol Med. 2006; 36(10):1349–62. [PubMed: 16756689]
6. Wu EQ, Birnbaum HG, Shi L, et al. The economic burden of schizophrenia in the United States in 2002. J Clin Psychiatry. 2005; 66(9):1122–9. [PubMed: 16187769]
7. Bleuler, M. The Schizophrenic Disorders: Long Term Patient and Family Studies. Clements, S., translator. New Haven, CT: Yale University Press; 1978.
8. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. Br J Psychiatry Suppl. 1998; 172(33):53–9. [PubMed: 9764127]

9. Lieberman JA, Perkins D, Belger A, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry. 2001; 50(11):884–97. [PubMed: 11743943]
10. HARRISON G, HOPPER K, CRAIG T, et al. Recovery from psychotic illness: a 15- and 25-year international follow-up study. Br J Psychiatry. 2001; 178(6):506–17. [PubMed: 11388966]
11. Westermeyer JF, Harrow M, Marengo JT. Risk for suicide in schizophrenia and other psychotic and nonpsychotic disorders. J Nerv Ment Dis. 1991; 179(5):259–66. [PubMed: 2022953]
12. Mortensen PB, Juel K. Mortality and causes of death in first admitted schizophrenic patients. Br J Psychiatry. 1993; 163:183–9. [PubMed: 8075909]
13. Carpenter WT Jr, Strauss JS. The prediction of outcome in schizophrenia. IV: Eleven-year follow-up of the Washington IPSS cohort. J Nerv Ment Dis. 1991; 179(9):517–25. [PubMed: 1919553]
14. McGlashan TH. A selective review of recent North American long-term followup studies of schizophrenia. Schizophr Bull. 1988; 14(4):515–42. [PubMed: 3064280]
15. Eaton WW, Thara R, Federman B, et al. Structure and course of positive and negative symptoms in schizophrenia. Arch Gen Psychiatry. 1995; 52(2):127–34. [PubMed: 7848048]
16. Strauss JS, Carpenter WT Jr. Prediction of outcome in schizophrenia. III. Five-year outcome and its predictors. Arch Gen Psychiatry. 1977; 34(2):159–63. [PubMed: 843175]
17. Shepherd M, Watt D, Falloon I, et al. The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. Psychol Med Monogr Suppl. 1989; 15:1–46. [PubMed: 2798648]
18. Tohen M, Strakowski SM, Zarate C, et al. The McLean–Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. Biological Psychiatry. 2000; 48(6):467–76. [PubMed: 11018220]
19. Lieberman J, Jody D, Geisler S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry. 1993; 50(5):369–76. [PubMed: 8098203]
20. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res. 2004; 72(1):41–51. [PubMed: 15531406]
21. Brown GW, Birley JL, Wing JK. Influence of family life on the course of schizophrenic disorders: a replication. Br J Psychiatry. 1972; 121(562):241–58. [PubMed: 5073778]
22. Hooley JM. Expressed emotion and relapse of psychopathology. Annu Rev Clin Psychol. 2007; 3:329–52. [PubMed: 17716059]
23. Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. Arch Gen Psychiatry. 1998; 55(6):547–52. [PubMed: 9633674]
24. Hooley, JMRJ. Expressed Emotion: A Developmental Perspective. In: Cichetti, DTS., editor. Rochester, NY: University of Rochester Press; 1995. p. 133
25. Brown S, Kim M, Mitchell C, et al. Twenty-five year mortality of a community cohort with schizophrenia. Br J Psychiatry. 2010; 196(2):116–21. [PubMed: 20118455]
26. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007; 64(10):1123–31. [PubMed: 17909124]
27. Foley DL, Morley KI. Systematic Review of Early Cardiometabolic Outcomes of the First Treated Episode of Psychosis. Arch Gen Psychiatry. 2011
28. Phutane VH, Tek C, Chwastiak L, et al. Cardiovascular risk in a first-episode psychosis sample: a ‘critical period’ for prevention? Schizophr Res. 2011; 127(1–3):257–61. [PubMed: 21242060]
29. Pantelis C, Velakoulis D, McGorry PD, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet. 2003; 361(9354): 281–8. [PubMed: 12559861]
30. Smieskova R, Fusar-Poli P, Allen P, et al. Neuroimaging predictors of transition to psychosis--a systematic review and meta-analysis. Neurosci Biobehav Rev. 2010; 34(8):1207–22. [PubMed: 20144653]

31. Kasai K, Shenton ME, Salisbury DF, et al. Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. Arch Gen Psychiatry. 2003; 60(11):1069–77. [PubMed: 14609882]
32. Yoshida T, McCarley RW, Nakamura M, et al. A prospective longitudinal volumetric MRI study of superior temporal gyrus gray matter and amygdala–hippocampal complex in chronic schizophrenia. Schizophr Res. 2009; 113(1):84–94. [PubMed: 19524408]
33. Thompson PM, Vidal C, Giedd JN, et al. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proc Natl Acad Sci U S A. 2001; 98(20):11650–5. [PubMed: 11573002]
34. Koenen KC, Moffitt TE, Roberts AL, et al. Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. Am J Psychiatry. 2009; 166(1):50–7. [PubMed: 19047325]
35. Barnett JH, Salmond CH, Jones PB, et al. Cognitive reserve in neuropsychiatry. Psychol Med. 2006; 36(8):1053–64. [PubMed: 16854246]
36. Keshavan MS, Eack SM, Wojtalik JA, et al. A broad cortical reserve accelerates response to cognitive enhancement therapy in early course schizophrenia. Schizophr Res. 2011; 130(1–3): 123–9. [PubMed: 21645997]
37. Eack SM, Hogarty GE, Cho RY, et al. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. Arch Gen Psychiatry. 2010; 67(7):674–82. [PubMed: 20439824]
38. Joseph R, Birchwood M. The national policy reforms for mental health services and the story of early intervention services in the United Kingdom. J Psychiatry Neurosci. 2005; 30(5):362–5. [PubMed: 16151542]
39. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987; 44(7):660–9. [PubMed: 3606332]
40. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed). 1987; 295(6600):681–2.
41. Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J Psychiatr Res. 1994; 28(3):239–65. [PubMed: 7932285]
42. Johannessen JO, McGlashan TH, Larsen TK, et al. Early detection strategies for untreated first-episode psychosis. Schizophr Res. 2001; 51(1):39–46. [PubMed: 11479064]
43. Marshall M, Lewis S, Lockwood A, et al. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry. 2005; 62(9):975–83. [PubMed: 16143729]
44. Perkins DO, Gu H, Boteva K, et al. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry. 2005; 162(10):1785–804. [PubMed: 16199825]
45. Melle I, Larsen TK, Haahr U, et al. Prevention of Negative Symptom Psychopathologies in First-Episode Schizophrenia: Two-Year Effects of Reducing the Duration of Untreated Psychosis. Arch Gen Psychiatry. 2008; 65(6):634–40. [PubMed: 18519821]
46. Larsen TK, Melle I, Auestad B, et al. Early detection of psychosis: positive effects on 5-year outcome. Psychol Med. 2011; 41(07):1461. [PubMed: 20942996]
47. Joa I, Johannessen JO, Auestad B, et al. The key to reducing duration of untreated first psychosis: Information campaigns. Schizophr Bull. 2008; 34(3):466–72. [PubMed: 17905788]
48. Chong S, Mythily S, Verma S. Reducing the duration of untreated psychosis and changing help-seeking behaviour in Singapore. Social Psychiatry and Psychiatric Epidemiology. 2005; 40(8): 619–21. [PubMed: 16091855]
49. Lloyd-Evans B, Crosby M, Stockton S, et al. Initiatives to shorten duration of untreated psychosis: Systematic review. British Journal of Psychiatry. 2011; 198(4):256–63. [PubMed: 21972275]
50. Edwards, J.; McGorry, PD. Multi-Component Early Intervention - Models of Good Practice. Edwards, J.; McGorry, PD., editors. London: Martin Dunitz; 2002. p. 63
51. Marshall M, Rathbone J. Early intervention for psychosis. Cochrane Database Syst Rev. 2011; (6):CD004718. [PubMed: 21678345]

52. Breitborde NJK, Srihari VH, Woods SW. A Review of the Operational Defintion for First-Episode Psychosis. Early Intervention in Psychiatry. 2009 (In Press).
53. Review: more research needed on early intervention for psychosis. Evidence Based Mental Health. 2012; 15(1):23. [PubMed: 22058057]
54. Everitt, B.; Wessely, S. Clinical Trials in Psychiatry. Chichester, West Sussex, England; Hoboken, NJ: John Wiley & Sons; 2008.
55. Wells KB. Treatment research at the crossroads: the scientific interface of clinical trials and effectiveness research. Am J Psychiatry. 1999; 156(1):5–10. [PubMed: 9892291]
56. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167(7):748–51. [PubMed: 20595427]
57. Hotopf M, Churchill R, Lewis G. Pragmatic randomised controlled trials in psychiatry. Br J Psychiatry. 1999; 175(3):217–23. [PubMed: 10645321]
58. Craig TK, Garety P, Power P, et al. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. BMJ. 2004; 329(7474):1067. [PubMed: 15485934]
59. GARETY PA, CRAIG TKJ, DUNN G, et al. Specialised care for early psychosis: symptoms, social functioning and patient satisfaction. The British Journal of Psychiatry. 2006; 188(1):37–45. [PubMed: 16388068]
60. Jorgensen P, Nordentoft M, Abel MB, et al. Early detection and assertive community treatment of young psychotics: the Opus Study Rationale and design of the trial. Soc Psychiatry Psychiatr Epidemiol. 2000; 35(7):283–7. [PubMed: 11016522]
61. Petersen L, Jeppesen P, Thorup A, et al. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. BMJ. 2005; 331(7517): 602. [PubMed: 16141449]
62. Srihari VH, Breitborde NJK, Pollard J, et al. Initiating a First-Episode Psychosis Clinic in the U.S. Public Sector: Feasibility and Outcomes of the First Two Years. Community Ment Health J. 2009 (Submitted).
63. Bertelsen M, Jeppesen P, Petersen L, et al. Five-Year Follow-up of a Randomized Multicenter Trial of Intensive Early Intervention vs Standard Treatment for Patients With a First Episode of Psychotic Illness: The OPUS Trial. Arch Gen Psychiatry. 2008; 65(7):762–71. [PubMed: 18606949]
64. Gafoor R, Nitsch D, McCrone P, et al. Effect of early intervention on 5-year outcome in non-affective psychosis. Br J Psychiatry. 2010; 196(5):372–6. [PubMed: 20435962]
65. Linszen D, Dingemans P, Lenior M. Early intervention and a five year follow up in young adults with a short duration of untreated psychosis: ethical implications. Schizophr Res. 2001; 51(1):55–61. [PubMed: 11479066]
66. Norman RM, Manchanda R, Malla AK, et al. Symptom and functional outcomes for a 5 year early intervention program for psychoses. Schizophr Res. 2011; 129(2–3):111–5. [PubMed: 21549566]
67. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry. 2003; 64(12):1465–75. [PubMed: 14728109]
68. Mangalore R, Knapp M. Cost of schizophrenia in England. J Ment Health Policy Econ. 2007; 10(1):23–41. [PubMed: 17417045]
69. Meltzer D. Perspective and the measurement of costs and benefits for cost-effectiveness analysis in schizophrenia. J Clin Psychiatry. 1999; 60(Suppl 3):32,5. discussion 36–7. [PubMed: 10073375]
70. Davies LM, Drummond MF. Economics and schizophrenia: the real cost. Br J Psychiatry Suppl. 1994; (25):18–21. [PubMed: 7865193]
71. Barrett B, Byford S. Economic evaluations in evidence based healthcare. Evidence Based Mental Health. 2009; 12(2):36–9. [PubMed: 19395598]
72. Kind P, Lafata JE, Matuszewski K, et al. The Use of QALYs in Clinical and Patient Decision-Making: Issues and Prospects. Value in Health. 2009; 12:S27–30. [PubMed: 19250128]
73. National Institute for Health and Clinical Excellence. 2009; 2012(1/7) http://www.nice.org.uk/nicemedia/pdf/CG82NICEGuideline.pdf.

74. Knapp M, Mangalore R. The trouble with QALYs…. Epidemiol Psichiatr Soc. 2007; 16(4):289–93. [PubMed: 18333423]
75. Malla A, Pelosi AJ. Is treating patients with first-episode psychosis cost-effective? Can J Psychiatry. 2010; 55(1):3,7. discussion 7–8. [PubMed: 20113538]
76. Goldberg K, Norman R, Hoch J, et al. Impact of a Specialized Early Intervention Service for Psychotic Disorders on Patient Characteristics, Service Use, and Hospital Costs in a Defined Catchment Area. Canadian Journal of Psychiatry. 2006; 51(14):895–903.
77. Wong KK, Chan SK, Lam MM, et al. Cost-effectiveness of an early assessment service for young people with early psychosis in Hong Kong. Aust N Z J Psychiatry. 2011; 45(8):673–80. [PubMed: 21870925]
78. Angelo C, Vittorio M, Anna M, et al. Cost-effectiveness of treating first-episode psychosis: five-year follow-up results from an Italian early intervention programme. Early Intervention in Psychiatry. 2011; 5(3):203–11. [PubMed: 21729243]
79. Cullberg J, Mattsson M, Levander S, et al. Treatment costs and clinical outcome for first episode schizophrenia patients: a 3-year follow-up of the Swedish ? Parachute Project? and Two Comparison Groups. Acta Psychiatr Scand. 2006; 114(4):274–81. [PubMed: 16968365]
80. Mihalopoulos C, McGorry PD, Carter RC. Is phase-specific, community-oriented treatment of early psychosis an economically viable method of improving outcome? Acta Psychiatr Scand. 1999; 100(1):47–55. [PubMed: 10442439]
81. Mihalopoulos C, Harris M, Henry L, et al. Is Early Intervention in Psychosis Cost-Effective Over the Long Term? Schizophrenia Bulletin. 2009; 35(5):909–18. [PubMed: 19509308]
82. McCrone P, Craig TKJ, Power P, et al. Cost-effectiveness of an early intervention service for people with psychosis. The British Journal of Psychiatry. 2010; 196(5):377–82. [PubMed: 20435964]
83. Dodds TJ, Phutane VH, Stevens BJ, et al. Who is paying the price? Loss of health insurance coverage early in psychosis. Psychiatr Serv. 2011; 62(8):878–81. [PubMed: 21807825]
84. Knapp M, Chisholm D, Leese M, et al. Comparing patterns and costs of schizophrenia care in five European countries: the EPSILON study. European Psychiatric Services: Inputs Linked to Outcome Domains and Needs. Acta Psychiatr Scand. 2002; 105(1):42–54. [PubMed: 12086225]
85. Norman RM, Malla AK, Verdi MB, et al. Understanding delay in treatment for first-episode psychosis. Psychol Med. 2004; 34(2):255–66. [PubMed: 14982131]
86. Department of Health. The NHS Plan: A Summary. London: 2000.
87. Edwards, J.; McGorry, PD. Implementing Early Intervention in Psychosis: A Guide to Establishing Early Psychosis Services. London; Florence, KY, USA: Martin Dunitz; Distributed in USA by Fulfilment Center, Taylor & Francis; 2002.
88. Drake RE, Goldman HH, Leff HS, et al. Implementing evidence-based practices in routine mental health service settings. Psychiatr Serv. 2001; 52(2):179–82. [PubMed: 11157115]
89. Torrey WC, Drake RE, Dixon L, et al. Implementing evidence-based practices for persons with severe mental illnesses. Psychiatr Serv. 2001; 52(1):45–50. [PubMed: 11141527]
90. Dixon LB, Dickerson F, Bellack AS, et al. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. Schizophr Bull. 2010; 36(1):48–70. [PubMed: 19955389]
91. Lehman AF, Kreyenbuhl J, Buchanan RW, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. Schizophr Bull. 2004; 30(2):193–217. [PubMed: 15279040]
92. Bero LA, Grilli R, Grimshaw JM, et al. Getting research findings into practice. Closing the gap between research and practice: An overview of systematic reviews of interventions to promote the implementation of research findings. Br Med J. 1998; 317(7156):465–8. [PubMed: 9703533]
93. Mesholam-Gately RI, Giuliano AJ, Goff KP, et al. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology. 2009; 23(3):315–36. [PubMed: 19413446]
94. Rund BR. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr Bull. 1998; 24(3):425–35. [PubMed: 9718634]

95. Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull. 2008; 34(2):354–66. [PubMed: 18283048]

96. Mitelman SA, Brickman AM, Shihabuddin L, et al. A comprehensive assessment of gray and white matter volumes and their relationship to outcome and severity in schizophrenia. Neuroimage. 2007; 37(2):449–62. [PubMed: 17587598]

97. Campbell NC, Murray E, Darbyshire J, et al. Designing and evaluating complex interventions to improve health care. BMJ. 2007; 334(7591):455–9. [PubMed: 17332585]

98. National Institute of Mental Health. Recovery After an Initial Schizophrenic Episode (RAISE. May 11.2009 :1.

99. Straus SE, Tetroe J, Graham I. Defining knowledge translation. Canadian Medical Association Journal. 2009; 181(3–4):165–8. [PubMed: 19620273]

100. Talbott JA. The evolution and current status of public-academic partnerships in psychiatry. Psychiatr Serv. 2008; 59(1):15–6. [PubMed: 18182532]

101. Hotopf M. The pragmatic randomised controlled trial. Adv Psychiatr Treat. 2002; 8(5):326–33.

102. Insel TR. Translating Scientific Opportunity Into Public Health Impact: A Strategic Plan for Research on Mental Illness. Arch Gen Psychiatry. 2009; 66(2):128–33. [PubMed: 19188534]

103. Fielding JE, Teutsch SM. An Opportunity Map for Societal Investment in Health. JAMA: The Journal of the American Medical Association. 2011; 305(20):2110–1. [PubMed: 21610244]

Key Points

Services that provide comprehensive, early intervention (EI) have shown promise in improving long-term outcomes in schizophrenia.

Beyond having an impact on schizophrenia spectrum disorders, early interventions can suggest frameworks for other serious mental illnesses.

Most clinical and psychosocial deterioration occurs within the first 2 to 5 years after psychosis onset, a periodnotable for high risk for relapse, re-hospitalization and suicide.

Structural alterations in medial temporal, prefrontal, anterior cingulate and insular cortex might occur during the acute process of transition to psychosis; earlier stages of psychotic illness, when significant gray and white matter alterations have not yet set in, may respond better to therapeutic interventions.

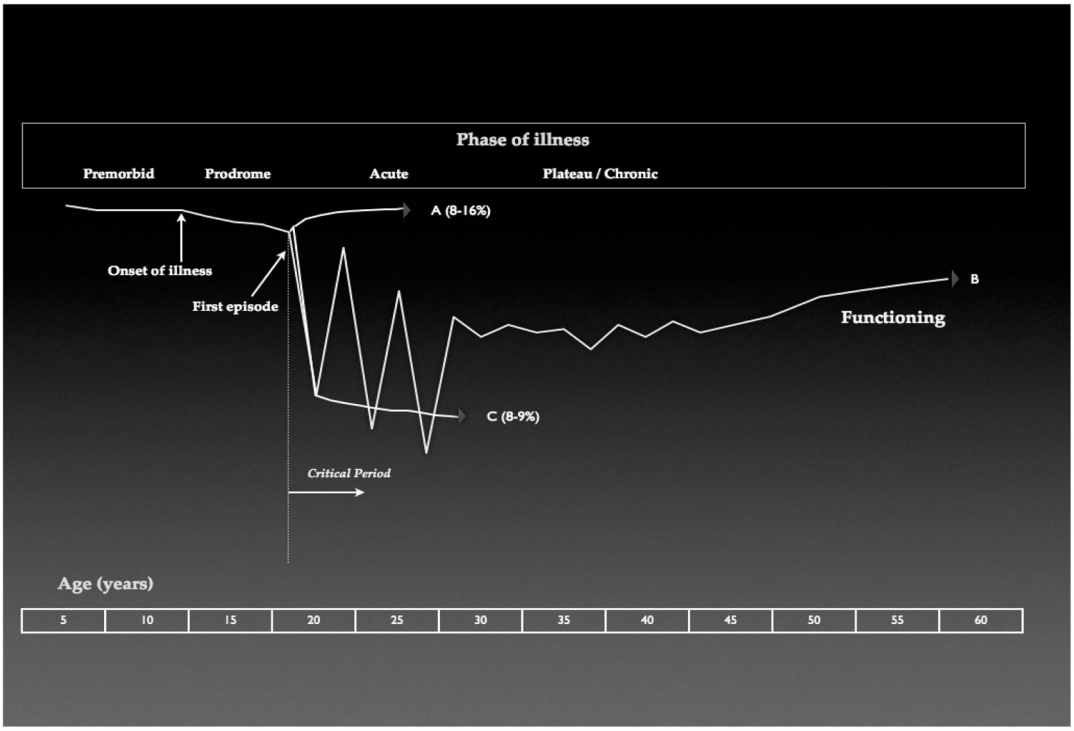

Figure 1.
The course of psychotic illnesses and the ‘critical period’

Table 1

Pragmatic Randomized Controlled Trials of integrated Early Intervention Services: Design characteristics

Study	Sample	Interventions	Outcomes measured
LEO: Lambeth (U.K.)	Setting: Mental Health Service in Lambeth, London, UK. Recruitment January 2000 to October 2001. Broad inclusion criteria: 16–40 year olds with first or second presentation for non-affective psychosis and no previous routine community mental health treatment.	**1** Specialized multi-disciplinary team: assertive outreach team with patient: clinician ratio of ~ 10:1/LD-SGAs/ Family counseling/CBT **2** Standard care from community mental health teams with LD-SGA	Broad, including clinical (e.g. relapse, readmission), functional (e.g. vocational functioning) and economic (e.g. service utilization)
OPUS: Copenhagen (Denmark)	Setting: Community based mental health services in Copenhagen and Aarhus Counties. Recruitment from January 1998 to December 2000. Inclusion criteria: 18–45 years, Schizophrenia spectrum diagnosis by ICD-10/F2 category, no more than 12 weeks of continuous antipsychotic drug treatment.	**1** Specialized multi-disciplinary team assertive outreach team with patient: clinician ratio of ~ 10:1/LD-SGA/MFG, SST group/vocational strategies. **2** Standard care in a community mental health center, patient: clinician ratio ~ 30:1	As above
Grawe – Sør-Trøndelag County (Norway)	Setting: Community based county mental health services. Recruitment initiated in 2001. Inclusion criteria: consecutive referrals ages 18–30 years, DSM IV schizophrenia spectrum disorders, within 2 years of psychosis onset.	**1** Integrated Treatment: home-based outreach with patient: clinician ratio of 10:1, multidisciplinary team; family psychoeducation, cognitive behavioral therapy based communication strategies for families and individual therapy for patients and LD-A. **2** Standard care: office-based, focused on pharmacotherapy and problem-based case management.	Clinical (relapse, re-admission), functional (GAF), ?economic
STEP-New Haven (USA)	Setting: Community Mental Health Center in New Haven county. Broad inclusion criteria: psychosis onset within past 5 years, no more than 12 weeks lifetime exposure to antipsychotic treatment.	**1** Integrated care: Specialized multidisciplinary team, office-based, patient: clinician ratio ~30:1; structured family psychoeducation; cognitive behavioral therapy based group and individual problem solving, vocational and educational assistance as needed and pharmacotherapy. **2** Standard care: office based, focused on pharmacotherapy and rehabilitative case management.	Broad, including clinical (e.g. relapse, readmission), functional (e.g. vocational functioning) and economic (e.g. service utilization)

LD-SGA = low dose second generation antipsychotics; LD-A = low dose antipsychotics; CBT = Cognitive-Behavioral Therapy; SST = Social Skills Training; GAF = Global Assessment of Functioning scale