

# What Is Necessary to Enhance Development and Utilization of Treatment?

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## Abstract

This chapter is framed by four perspectives. The first views schizophrenia as a heterogeneous disorder that may present itself very differently across individuals. Heterogeneity has important implications for treatment approaches: for treatments to be optimally effective, they need to be tailored to the individual. The second perspective integrates what are often considered separate and divergent approaches to treatment in schizophrenia, bringing together, in both complementary and synergistic combination, the biological and the psychosocial. Within this perspective, clinical treatment models capable of being personalized to heterogeneous, individual profiles are proposed. The third perspective is a practical one that examines how the two extreme ends of the treatment continuum, treatment development and service delivery, can be optimized to ensure enhanced outcomes for people with schizophrenia. Finally, treatment is viewed from the perspective of the whole person. This not only has implications for mental and physical well-being and quality of life in people with schizophrenia, but also takes into consideration the social context in which these individuals are placed. Overall, the approach offered, with its integration across multiple domains, emphasizes the potential for improved recovery rates and hope for prevention and cure in this devastating disorder.

## Schizophrenia: Cure and Recovery

### A Cure for Schizophrenia

This is a very exciting time for schizophrenia research. The journal *Nature* has declared the decade beginning in 2010 to be the “decade for psychiatric

disorders” in the hope that the neuroscience tools and paradigms developed in the “decade of the brain” can now be applied to identify new and better treatments for mental illness.

Nowhere is this more urgent than for schizophrenia. The number of mechanistically novel pharmacological treatments for schizophrenia has been disappointingly low. Government-sponsored large-scale naturalistic trials have suggested that there is little difference in efficacy between newer antipsychotic agents compared to older drugs. Most patients with schizophrenia still do not marry, have a severely compromised educational and job trajectory, and die on average 15 years earlier than the general population. The illness definition is currently based on a combination of psychopathological features observed by patients and their caregivers as well as duration criteria. To be useful for treatment, our understanding of the individual processes lumped together under the label “schizophrenia” will have to be refined for individualization to be possible.

The most useful entry points into this process are the clear biological risk factors for the illness: genetic and environmental factors. The pursuit of risk mechanisms is therefore a major strategy to individualize treatment and to find new treatments (Meyer-Lindenberg 2010a) because truly novel targets for molecular therapies can only emerge from the detailed understanding of the molecular mechanisms of the illness; genes with their products, if they have been found through hypothesis-free searches, are pointers to such novel mechanisms. Ever better designed, better characterized, and larger multinational studies are necessary and are being pursued to identify new genetic and environmental risk factors. Longitudinal studies which focus on the period around adolescence are underway in several countries and are expected to give us a better understanding of the way these risk factors interact with brain development. Another potentially paradigm-changing advance is that, through techniques such as induced pluripotent stem cells, we are now able to generate neurons from a person with a known disease history and genetic makeup and study the metabolism and activity in these cells across their development, giving us access to the “target tissue” of psychiatry in a way that seemed impossible even a few years ago (Brennand et al. 2011).

The pursuit of these new targets necessitates, in principle, the use of the entire armamentarium of modern neuroscience. For the first time in history, psychiatrists truly need and can use techniques from whole brain genome sequencing and epigenetics to expression mapping, proteomics, and lipidomics to pursue their goals. One critical and specific task for psychiatric neuroscience is to integrate this information with an understanding on the neural systems level (e.g., in the technique of “imaging genetics”) so as to bridge the gap between cellular–molecular mechanisms and disturbed behavior.

An understanding of the mechanisms underlying schizophrenia is also critical for the generation of better animal models for use in the identification of new drug molecular candidates. Schizophrenia affects human-specific faculties

such as language and higher cognition. Clearly, these features cannot be modeled in animals. Animal models currently used for schizophrenia have been directly derived from the profile of the currently used antipsychotic agents that are related to dopaminergic blockade. There is little evidence that these behavioral features are a good model for schizophrenia. A better understanding of mechanisms could be decisive in designing a new generation of animal models that are more predictive for efficacy through delineating neural systems that are implicated in schizophrenia.

Sometimes, however, “the best experimental animal is the human.” This is especially true in psychiatric drug development, where the success rate in predicting which new medications are effective is disappointing. A new generation of applying systems-level neuroscience in early drug trials in humans will constitute a revival and focusing of experimental medicine in psychiatry. This concept, which has been extraordinarily fruitful in bringing about advances in oncology and hematology, is ripe for application for schizophrenia.

It is entirely possible that, in the end, “the answer” about schizophrenia is sufficiently complex as to require the study of the multiple risk pathways that combine in a given person to push him or her over the threshold to develop the illness. For schizophrenia research, computational approaches and especially computational neuroscience will be tremendously important to be able to quantify the effects that perturbations on genetic and environmental levels have on systems-level function. A comprehensive characterization of the neural risk architecture of schizophrenia through these various approaches, and their integration, provides a crucial translational research strategy for advancing new treatments for the illness.

## Recovery in Schizophrenia

Over the past twenty years, the recovery movement has evolved to become a driving force in changing how major mental illnesses, including schizophrenia, are understood and treated (Silverstein and Bellack 2008). “Consumers” of mental health services (also called “service users”) have protested against the pessimistic messages they have been given about the long-term outcome of serious mental illness, pointing to longitudinal research that shows symptom remission and functional improvement in significant proportions of people with schizophrenia (Davidson et al. 2005; Deegan 1991). Consumers have also argued for the reduction of coercive interventions and a change from hierarchical decision making to more collaborative approaches that respect their individual preferences and their need to determine their own treatment priorities (Chamberlin 1997b; McLean 1995). Perhaps the most significant impact of this movement has been its challenge of traditional medical perspectives on recovery from mental illness that have emphasized remission of symptoms and associated impairments, in favor of more nuanced and personally meaningful definitions. For example, *remission* from schizophrenia has been defined in the

medical community in terms of meeting distinct thresholds of sustained improvement in symptomatic, cognitive, and functional domains of the disorder (Andreasen et al. 2005). Although there is less agreement about how *recovery* from schizophrenia should be defined, it has been broadly conceptualized as encompassing remission of symptoms and functional impairments, while also extending to improved quality of life (Leucht and Lasser 2006).

New conceptualizations of recovery focus on personal growth, and establishing meaning and sense of purpose in life, despite having a mental illness (Anthony 1993). The desire for a more personally meaningful definition of recovery than symptom remission frequently evokes different areas of psychosocial functioning. For example, the President's New Freedom Commission on Mental Health (2003:6) defines recovery as "...the process in which people are able to live, work, learn, and participate fully in their communities." Thus, according to the recovery movement, improvements in psychosocial functioning are a greater treatment priority than symptom management or remission.

### Is Prevention Feasible?

Prevention of illness is preferable to cure, but what is the disease target of the prevention? Is it psychosis generally or schizophrenia specifically? The two are not the same, and the focus of the intervention may differ, depending on the disease target. Most studies of risk intervention prior to illness onset focus on psychotic-like experiences. However, to date, there has been minimal success in identifying which young people will convert to psychosis within high-risk and prodromal samples (i.e., help-seeking groups whose at-risk status is determined in the clinic, generally on the basis of psychotic symptoms). Moreover, it remains unresolved whether these interventions prevent schizophrenia or ameliorate its course. Psychotic symptoms may be too far along the illness trajectory to be a viable target for the prevention of schizophrenia. It is likely that, by the time first episode cases are manifest, a critical point for primary prevention has been missed. In this regard, several studies have demonstrated that psychosis is preceded by cognitive and social dysfunction by almost a decade, suggesting that prevention may need to start years earlier, targeting cognition and social function, rather than the more common target of psychotic-like experiences. This does not reject the at-risk state and prodrome as targets for secondary prevention, which we examine in some detail later.

### Defining Prevention

We use the term *primary prevention* to refer to broad public health interventions that reduce incidence of illness or comparable problems in the general population, for example, nutritional programs, after-school activity programs,

general health education. We use this to refer to interventions in the *pre-prodromal* period in schizophrenia.

We use the term *secondary prevention* to refer to focused interventions that target subpopulations identified as being at risk for developing illnesses or comparable problems, for the purpose of preventing the actual onset. We use this to refer to interventions in the *at-risk* or *prodromal* period in schizophrenia.

We use the term *tertiary prevention* to refer to focused interventions that target subpopulations *after* the onset of illnesses or comparable problems, for the purpose of minimizing morbidity or chronicity. We use this to refer to interventions *after illness onset* in schizophrenia.

### **A Target for Primary Prevention in Schizophrenia: Relative Decline in Cognition in Early Adolescence**

As described by Kahn (this volume), a decline in cognition relative to peers (developmental lag) in late childhood/early adolescence may be the strongest indicator of early manifestations of the illness. We distinguish cognitive decline from enduring cognitive deficit. While both forms of cognitive deficit may increase the risk of schizophrenia, our focus here is on cognitive decline as it is likely to be more reflective of eventual psychosis, and may be most amenable to primary prevention. We note also that cognitive decline is distinguished from normal variability in IQ that has been observed in adolescence (Ramsden et al. 2011).

Our proposal, in its current state, is not a model of clinical intervention, but a research strategy with the potential to lead to primary prevention. The strategy involves identifying, on the basis of school grades or similar measures, children in late childhood/early adolescence living in the general community, who exhibit cognitive decline relative to their peers. These children would be the target of school-based interventions. It is important to note that schizophrenia would neither be a necessary nor sole endpoint in this proposed strategy, as the intervention is likely to have an impact on a range of disorders. By taking this approach, however, we may learn how to predict and prevent schizophrenia on the basis of relative cognitive decline.

#### *What Is This Thing Called Schizophrenia?*

The proposed strategy outlined above considers cognitive decline as a closed construct within an open construct. If a putative illness, in this case schizophrenia, is an open construct, its exact features and parameters are indistinct or unknown, and the distinction between primary, secondary, and tertiary prevention is unclear. For example, if cognitive decline is understood to be an early expression of schizophrenia, interventions directed at it are, by definition, after onset, thus constituting tertiary prevention aimed at arresting further cognitive decline and/or further progress of the illness. On the other hand, if cognitive

decline is understood to be a risk factor or part of the prodrome, intervention is understood to be primary or secondary prevention. However, these are semantic distinctions. The value of identifying and responding to cognitive decline has obvious importance, regardless of whether it is a risk factor, a prodrome, or an early expression of the actual illness.

### *Specificity to Schizophrenia*

It appears that cognitive dysfunction—at least prior to psychosis onset—distinguishes schizophrenia from bipolar disorder. A consistent pattern emerging from population-based studies worldwide is that low IQ constitutes a risk factor for schizophrenia, but not for bipolar disorder or depression (Reichenberg et al. 2002; Zammit et al. 2004; Sørensen et al. 2012). Moreover, one study found that children with excellent school performance had almost four times the risk of developing bipolar illness compared to children with average grades (MacCabe et al. 2010). A number of studies have reported a decline in cognitive function prior to the onset of schizophrenia (Fuller et al. 2002; Reichenberg et al. 2010). Whether a decline in cognitive function precedes the onset of bipolar disorder has not been addressed in population-based studies. However, a study of monozygotic and dizygotic twins discordant for bipolar disorder (Van Oel et al. 2002) found, in contrast to findings from a similar study of discordant schizophrenia twins, that the twin who went on to develop bipolar disorder, compared to the unaffected co-twin, did not do worse at school and only showed a temporary decline in functioning, with no long-term underperformance (Vonk et al. 2012). Taken together, evidence strongly suggests that low IQ and cognitive underperformance during adolescence and at first presentation of psychosis differentiates schizophrenia from bipolar disorder.

### *A Research Strategy*

This strategy *aims* to identify children and adolescents in the general population who are cognitively at risk of poor future outcomes. Identification of risk should be based on cognitive decline. The assessment of outcome should not be restricted to schizophrenia: schizophrenia is a relatively rare disorder, while cognitive decline in adolescence relates to a broader risk than schizophrenia alone. Since abnormal cognitive development during adolescence may be related to other areas of dysfunction, assessment of other developmental abnormalities in this group is warranted, in particular, abnormalities in social development and the regulation of emotion. This will permit examination of the relationship between cognitive decline and other impairments, and an exploration of underlying mechanisms. It will also help to distinguish cognitive decline from normal variability in IQ that occurs during adolescence, and may

have implications for our understanding the nature of schizophrenia and its classification. At present, the direction of the relationship between cognitive decline and these other abnormalities is open. Thus, we propose that this be an area for further research. Consideration should be given to the inclusion of other assessments of at-risk status, such as the assessment of psychotic-like experiences.

The *optimal design* is the naturalistic, longitudinal study of children in early adolescence, aged 10–14 years, who are followed up prospectively over time with multiple assessments so as to permit an examination of distal outcomes for these children, including but not restricted to schizophrenia. However, a major drawback of the optimal design is the length of time required before results from such studies are available to inform intervention strategies.

An *alternative approach* to conventional longitudinal cohort studies is to use population registers to establish an “electronic” cohort. This is a particularly effective approach in jurisdictions such as Sweden, Denmark, and Western Australia, where there are networks of longstanding, whole-of-population administrative databases, including educational testing and psychiatric case registers, with linkage on the individual across registers under prescribed conditions (Morgan et al. 2011). Establishing a cohort for study based on register data offers some advantages:

- Longitudinal data collected over an extended period means that one can examine outcomes that are distal from the exposures of interest.
- Data are prospectively collected, eliminating recall bias.
- Examination of genetic influences and gene–environment interactions are possible if the registers are multigenerational and genealogies can be established.
- The size of the databases ensures sufficient power for most statistical purposes.

In Western Australia, current analysis of register data over the life course for children who develop psychotic illness includes, among others, data on familial liability, obstetric complications, intellectual disability, childhood abuse, school assessments, and mental health (Morgan et al. 2011).

The *interim design*, therefore, is based on the efficient use of extant administrative registers containing educational testing data. Employing a more interactive approach, testing data can be monitored over time to identify decline in performance, with warning thresholds set. However, work would need to be completed that would establish the best thresholds based upon empirical data. Where possible, linking nationwide standardized educational tests to data on psychiatric case registers will be particularly informative at an early stage of study, and could be used to generate hypotheses for the optimally designed longitudinal studies.

The *proposed outcome* is a research strategy that will inform intervention programs for a broad range of children experiencing cognitive decline.



Brain development is quite variable and plastic during adolescence, with brain changes directly related to IQ (Brans et al. 2010; Schnack et al., submitted). Thus, interventions that improve plasticity, such as physical activity (Pajonk et al. 2010) or cognitive interventions, could be beneficial in ameliorating or optimizing brain development during this vulnerable stage in brain maturation. Given the young age of the children, between 10 and 14 years, they are likely to be an especially good target for cognitive remediation.

### **Are There Other Targets for Primary Intervention?**

Given the likely involvement of many genes and environmental risk factors of small effect (such as infection, nutrition, urbanicity and social adversity, and the breadth and complexity of these factors), there is a paucity of clear specific targets for primary prevention of schizophrenia. Meyer-Lindenberg and Tost observe that “the scientific analysis of social environmental risk mechanisms highlights components of modifiable disease risk on the environmental level that provide entry points into both treatment, and, in some cases, prevention. Although many societal stressors such as social inequality are difficult to address, factors such as social components of urbanization may be modified through social policy, thereby enabling a truly preventative approach toward the enormous worldwide burden of mental illness” (Meyer-Lindenberg and Tost 2012:667).

Some of these targets lend themselves to population-based risk prevention programs along the lines of Head Start.<sup>1</sup> Even though the number of cases of schizophrenia prevented would be relatively low, the advantage of these programs is their benefit for many children at risk of wide-ranging adverse outcomes, encompassing psychiatric, educational, and social outcomes.

Alternatively, schizophrenia researchers could build on the mild cognitive impairment (MCI) model of dementia to identify targets for primary prevention. The MCI model identifies people at risk for dementia many years prior to the first signs of dementia through MRI scans of hippocampal volume and PET scans of the accumulation of beta-amyloid. Not everyone with MCI develops full dementia, but those with MCI are more likely to develop it than others. In schizophrenia, selection for testing could be based on the identification of evident and progressive deterioration in school performance and the assessment tools would include cognitive testing and structural MRI scans. Again, population-based selection and intervention reduces the risk of stigma attaching to people with schizophrenia and provides benefits to all who are identified.

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<sup>1</sup> A comprehensive U.S. health and education intervention aimed at children from low-income families; <http://www.acf.hhs.gov/programs/ohs>



### **The At-Risk State and the Prodrome as Targets for Secondary Prevention: When Do We Start, Who Do We Treat, and With What Do We Treat?**

The target for secondary prevention is the at-risk state or prodromal phase in schizophrenia, before the onset of frank psychosis. While a number of factors may influence outcome in schizophrenia, evidence of a relationship between longer duration of untreated psychosis and poorer outcomes suggests the importance of the early initiation of interventions, with recent data suggesting that the benefits of early treatment persist over time (Hegelstad et al. 2012). However, determining the critical point for early intervention to halt schizophrenia, or at least reduce its progress, is fraught with difficulty. People at risk of schizophrenia may be identified on the basis of familial risk factors or because they meet other risk criteria such as the presence of subthreshold, attenuated forms of positive psychotic symptoms, or experience a marked decline in cognitive or other functioning. To date, however, there are no accurate disease markers to indicate who among these asymptomatic or only mildly symptomatic individuals will go on to develop the disease. While early intervention is optimal for those who require it, misidentification carries the risk of stigma, potential exposure to unnecessary interventions, and other unintended consequences. As a result, treatment generally begins with the first psychotic episode, when a person is symptomatic to the point of meeting criteria for some form of psychotic disorder. This then is tertiary prevention, applied after the onset of illness according to prevailing diagnostic classifications. This may be the first entry point for pharmacological intervention in jurisdictions such as the United States, where the prodrome is not sufficient for the prescription of antipsychotic medication and a diagnosis meeting DSM criteria is required.

### **Population-Based Mental Health Promotion**

An individual's health, both physical and mental, is influenced by multiple factors. Some of these, such as sex and ethnicity, cannot be modified. Others, however, can: lifestyle risk factors, such as smoking, alcohol consumption, and poor nutrition. Health is also influenced by economic and employment status which, in turn, interact with lifestyle risk factors. In this context, the impact of poverty is notable. These latter factors not only determine an individual's health status but also determine their access to health care.

Evidence-based mental health promotion in the community provides an opportunity to address lifestyle risk factors at the population level and complements other approaches to risk reduction and illness prevention. Rather than focus on those at highest risk, in an area where there are often no clear risk factor thresholds to separate those at risk of mental illness from those not at risk, a general population approach is able to capture the many more individuals in the community at moderate risk, thereby improving the risk profile of

the entire population. This approach to mental health promotion is in keeping with the population-based approaches to primary and secondary prevention outlined above.

For example, a model of secondary intervention in the at-risk state or prodromal phase might follow the primary prevention model for cognitive decline described earlier. This could employ a targeted public health approach similar to the approach in Head Start (see above), with the intervention implemented in a normalized way to communities that include high-risk individuals. Although a “mental health for everyone” approach is possible, it runs the risk of missing the very subgroup that it aims to cover. Some interventions which lend themselves to broad implementation include physical activity programs, cognitive remediation, and nutrient supplementation (e.g., omega-3 fatty acids).

### **Focus of Treatment in Schizophrenia**

As a DSM-5 or ICD-10 disorder, schizophrenia is defined in terms of its characteristic symptoms (e.g., positive, negative, and disorganized symptoms) and impaired psychosocial functioning. Commonly associated features include other dimensions of psychopathology such as substance abuse (Mueser et al. 2000), cognitive impairment (Heaton et al. 1994), poor physical health, and premature mortality (Brown et al. 2010). Thus treatments for schizophrenia have targeted multiple domains, ranging from basic brain and cognitive functioning to psychopathology, psychosocial functioning, and physical health.

Antipsychotic medication, the most common treatment in schizophrenia, targets the positive symptoms of the disorder. The use of antipsychotic medication to manage acute symptoms and reduce hospitalization is a priority. However, these medications do not effectively reduce other deficits in schizophrenia, including negative symptoms and cognitive and psychosocial dysfunction. Moreover, through their weight-gain side-effect profile, they contribute to poor physical health in people with schizophrenia.

Although it is commonly accepted that different treatments are required to span the broad range of affected domains, there is a need to focus greater attention on the integration of treatments across domains for three practical reasons. First, different life domains impaired in schizophrenia are moderately interrelated and affect one another (Strauss and Carpenter 1972). For example, reduced cognitive functioning is strongly associated with more impaired psychosocial functioning (Green 1996), whereas a combination of psychopathology (e.g., suicide, substance abuse), unhealthy lifestyle (such as smoking, poor diet and a sedentary lifestyle), and poor management of physical illnesses can all contribute to premature mortality (Druss et al. 2001; Gale et al. 2012; Inskip et al. 1998; Kotov et al. 2010). Second, treatments targeting one domain can interact with other domains, requiring monitoring, coordination and, optimally, integration. For example, the

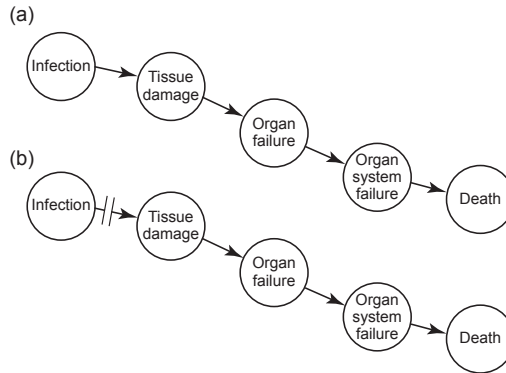
metabolic effects of antipsychotic medications can contribute to weight gain and diabetes (Meyer et al. 2008), pointing to the need for lifestyle interventions aimed at increasing activity level and weight loss (Faulkner et al. 2003; Gorczyński and Faulkner 2010). In another example, cognitive remediation has been found to be most effective at improving functional outcomes when it is paired with psychosocial rehabilitation (Wykes et al. 2011). Third, client motivation to work on one affected area of functioning may be most effectively harnessed by exploring how improvements in that area may be beneficial to the individual's personal goals in another area, suggesting a need for integration across different areas of treatment. For instance, interventions based on the principles of motivational interviewing (Miller and Rollnick 2002) have been used to instill motivation to reduce medication nonadherence and substance abuse in order to help clients achieve personally valued outcomes such as more independent living, work, and improved social relationships (Barrowclough et al. 2010).

### **Treating Proximal or Distal Outcomes?**

Although poor psychosocial functioning in schizophrenia has often been assumed to be the longer-term by-product (a distal consequence) of the more direct (proximal) effects of the disorder (such as cognitive impairments and symptoms such as psychosis), an alternative possibility is that it is more fundamental to the disorder. In other words, reduced capacity to meet social norms with respect to self-care, role functioning, and social relationships could be as proximal a consequence of schizophrenia, or even more so, as the florid psychotic symptoms or characteristic cognitive impairments often thought to be the primary cause of such impaired functioning. Problems in social and school functioning antedate the onset of psychotic symptoms in schizophrenia by many years (see Kahn, in this volume), and could reflect impairments in social drive and stamina that are associated with reduced cognitive performance, but not explained by it. This conceptualization is similar to how negative or deficit symptoms have been hypothesized to be central features of schizophrenia (Andreasen 1982; Carpenter et al. 1988), and Huber's concept of basic symptoms as reflecting core deficits in resilience, drive, and activity (Gross and Huber 2010; Schultze-Lutter 2009). The implications of this possibility is that there may be as much to learn about the nature of schizophrenia from attempts to improve psychosocial functioning as treatment efforts targeting symptoms or impaired cognitive functioning.

### **A Biosystemic Perspective on Treatment**

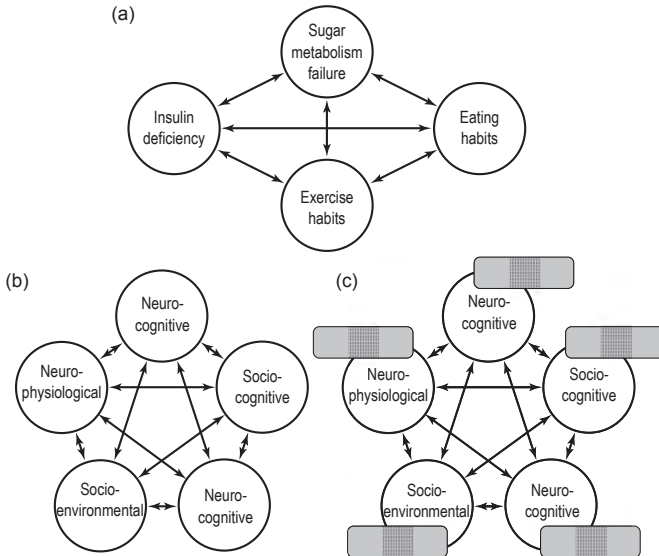
According to a traditional view of etiology and treatment (Figure 17.1), disease is a linear cascade that emanates from a unitary source. Treatment is only palliative when it targets the source of the cascade, invoking the allopathic



**Figure 17.1** A traditional view of etiology and treatment (after Spaulding et al. 2003). (a) In catastrophic disorders, casual cascades are the rule. (b) Catastrophic diseases are effectively treated by disrupting a cascade at a key point.

ideal of a “magic bullet” or ideal therapeutic agent proximal to the cause, that prevents distal consequences.

However, some illnesses, such as diabetes, are systemic (Figure 17.2). A systemic illness has no distinct origin: an ill system is in a state of negative



**Figure 17.2** A systemic view of etiology and treatment (after Spaulding et al. 2003). (a) In systemic disorders (e.g., diabetes, psychiatric disorders), stable dysregulation (homeorhesis) is the rule. (b) Systemic disorders (e.g., psychiatric disorders) often involve multiple levels of functioning and impairment. (c) Systemic disorders (e.g., psychiatric disorders) must often be addressed at multiple levels simultaneously.

homeorhesis; functional decline is gradual as consequences of impairments radiate throughout the system. Schizophrenia is a systemic condition; impairments interact reciprocally across multiple levels of organismic functioning, from neurophysiological to environmental (Figure 17.2). Treatment at any given point is usually insufficient, even though benefits are also distributed throughout the system. Success is determined not by proximity to a causal origin, but by the multiplicity of interventions at all accessible points. The allopathic imagery of a high-potency bullet gives way to the less appealing but more realistic imagery of multiple low-potency Band-Aids. The idea of being proximal or distal to the source of illness loses its meaning.

### **Managing Physical Health Outcomes**

It is well established that physical morbidity, especially cardiometabolic disease, and mortality are elevated in people with schizophrenia. In schizophrenia, life expectancy is reduced by 18.7 years for men and 16.3 years for women, compared to the general population, with diseases of the circulatory system impacting on life expectancy more than death from external causes (Laursen 2011). A recent national representative survey found 55% of people with schizophrenia aged 18–64 years met the criteria for metabolic syndrome (Morgan et al. 2012). Poor physical health is associated with weight gain as a result of antipsychotic medication use, lifestyle risk factors including high rates of smoking and alcohol consumption, poor nutrition, and low levels of physical activity; recent evidence also points to underlying genetic vulnerability to metabolic disturbance for some (van Winkel et al. 2010). Critically, people with schizophrenia are less likely than the general population to receive appropriate interventions for their physical health conditions, further increasing rates of morbidity and associated mortality (Lawrence et al. 2003).

Improving access to appropriate physical health care is a matter for clinical intervention. From a service perspective, it is essential to address fragmented service delivery across mental and physical health domains. In addition, consideration among medical and mental health practitioners must be given to attitudinal factors that lead to the neglect of the physical health needs of their patients. This includes stigma, which may lead to an under-recognition of physical health issues in people with severe mental illness, as well as a belief that lifestyle change is not possible for this group (Lawn 2012). Regular screening for metabolic syndrome and prescription of medication for those with disease or who are at risk is part of frontline management of physical health for these people. As important is the need to motivate people with schizophrenia to modify lifestyle risk factors. Excess rates of lifestyle risk factors are well documented, and intervention studies support the effectiveness of lifestyle interventions that focus on physical activity and nutrition (Verhaeghe et al. 2011). Nonetheless, little is known about how best to

promote the uptake of lifestyle changes in these individuals and to help them self-manage their physical health. Moreover, the quality of existing guidelines is variable; De Hert et al.'s review (2011) identified only four quality guidelines out of 18 published between 2000 and 2010. Many are poorly evaluated, and their implementation is suboptimal (De Hert et al. 2012). Moreover, the guidelines tend to focus on how to measure (screen and monitor) risk, rather than how to modify risk.

As risk may be associated with poor psychosocial function, cognitive remediation may improve functioning and indirectly increase motivation to maintain or regain good health. Increasing their physical health awareness may be another strategy: a person struck by severe schizophrenia in their twenties may miss out on important health promotion messages that their peers are internalizing at the same age.

Benefits of lifestyle risk management extend to mental health. There are interactions between physical health and brain pathology. Physical exercise improves hippocampal neurogenesis (Erickson et al. 2011) while diet impacts on neural growth (Stangl and Thuret 2009). There is a growing literature on the association between physical activity and mental well-being. At the same time, clinicians need to consider the impact of pathology on risk behaviors. Abnormalities in the brain reward system lead to increased risk of smoking addiction in people with schizophrenia, making modification of the reward system a target for intervention. The differential impact of specific antipsychotic medications on smoking behavior needs to be factored into prescribing practices (Montoya and Vocci 2007). In the meantime, much more needs to be understood about genotypes associated with excessive weight gain.

## Suicide

In addition to high rates of mortality due to physical morbidity, rates of suicide are also high in this population. It is estimated that 5–13% of people diagnosed with schizophrenia die as a result of suicide (Pompili et al. 2007). Suicide rates peak within a short time of discharge from hospital, making this a critical period for screening and intervention (Lawrence et al. 2001). The range of risk factors include youth, being male, substance abuse, hopelessness, social isolation, deteriorating health after a high level of premorbid functioning, fear of further deterioration, recent loss or rejection, limited external support, and family stress or instability, as well as the experience of either excessive treatment dependence or loss of faith in treatment (Pompili et al. 2007). Nonetheless, what is known about suicide risk is yet to be integrated into effective risk assessment guidelines that enable clinicians to monitor suicide risk in people with schizophrenia and intervene in a timely fashion.

## Issues in the Development of Successful Treatments

Over the past two to four years, drug discovery and development for novel therapeutic agents to treat schizophrenia suffered a major setback when several major pharmaceutical companies abruptly abandoned efforts on schizophrenia drug discovery (Abbott 2010; Miller 2010; Nutt and Goodwin 2011). Their reasoning was that (a) CNS drugs take the longest time from discovery to approval, (b) CNS drugs have one of the highest failure rates, (c) neuropsychiatric diseases are heterogeneous, making it difficult to target treatment to the right patient groups, and (d) animal and tissue culture models have shown poor translation into human efficacy (Kaitin and DiMasi 2011; Kaitin and Milne 2011). Economic pressures, patent expirations, uncertainties in the changing health care political environment, and regulatory challenges played an important role in these decisions.

What can the schizophrenia community do to help reinvigorate such vitally important efforts that impact on a large segment of society? How can the process of drug development be restructured to help reenergize the involvement of the pharmaceutical and biotechnology industries?

We believe that there are near-term opportunities for building on what we know today. Ongoing drug development programs with a variety of experimental therapeutic agents have shown positive results.<sup>2</sup> Several programs which focus on negative symptoms and cognitive impairment are at advanced stages of drug development.<sup>3</sup> Given that there are no approved drug treatments for these fundamental components of schizophrenia, support and promotion of these programs is of great importance to the treatment of people with schizophrenia. Surrogate endpoints such as neuroimaging, genetic background, and other biomarkers have the potential to be of great value in refining treatment signal detection. The involvement of regulators will help forward research in this area so that, as this clinical science develops, there is agreement and full acceptance of these endpoints. Meta-analytic techniques have been applied in depression studies (Kirsch et al. 2008) and may also be used to determine the potential benefit of surrogate endpoints in schizophrenia trials.

There are ongoing clinical studies using device-type interventions, such as computer-based cognitive exercises for cognitive remediation. In addition, deep brain stimulation as well as transcranial magnetic stimulation have been

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<sup>2</sup> Dana Hilt, Herbert Meltzer, Maria Gawry, Susan Ward, Nancy Dgetluck, Chaya Bhuvaneshwaran, Gerhard Koenig, Michael Palfreyman. EVP-6124, an Alpha-7 Nicotinic Partial Agonist, produces Positive Effects on Cognition, Clinical Function, and Negative Symptoms in Patients with Chronic Schizophrenia on Stable Antipsychotic Therapy. Presented at the annual meeting of the American College of Neuropsychopharmacology, Kona, Hawaii, December, 2011.

<sup>3</sup> Daniel Umbricht. Effects of the Glycine Transporter Typ1 Inhibitor RG1678 in Schizophrenic Patients with Predominant Negative Symptoms. Presented at the annual meeting of the American College of Neuropsychopharmacology, Miami, December, 2011.



used for the treatment of drug-resistant depression (Cusin and Dougherty 2012; Downar and Daskalakis 2013). These interventions have demonstrated medium effect sizes across a large range of studies and methods (Wykes et al. 2011).

In the mid to long term, better, more effective translation is needed. Delineation of pathomechanisms, next-generation low-cost sequencing, and many other recent techniques will provide high-resolution guidance for genetics to help determine predisposition, susceptibility, and vulnerability genes. Better and more appropriate animal models are needed. In this light, it is worth mentioning that, in addition to existing pharmacological and genetic models, circuit-modulatory models are being developed using optogenetics (Deisseroth 2012). This unique ability to generate switchable phenotypes and symptoms that approximate human symptoms has created a new ability to screen for and test existing drugs. Induced pluripotent stem cells and other cell-based models (Brennan et al. 2011; Dolmetsch and Geschwind 2011) are making important contributions to the understanding of pathomechanisms. We need to accept that we are treating symptoms and this is a viable option when disease-modifying treatments have been elusive.

### **The Clinical Trial: Learning from Failure**

As discussed by Mitchell et al. (this volume), the relevance of current animal models for treatment development has been questioned, although innovative work is underway or has been proposed. One of the greatest gaps in drug development research has been progress from phase 1 studies of healthy humans to phase 2a and 2b, where the efficacy of novel compounds is tested. Results at these early stages are often proprietary and, in some cases, are not made available. Only phase 3 data are made available and, since many drug development programs are abandoned before this stage, the information streams that can facilitate drug development are weak.

Research to enable a “go/no-go” decision at the early phase of drug development will reduce costs and enable a greater number of compounds to be studied, thereby increasing the possibility of bringing effective drugs to market. Several initiatives to meet these goals are underway, including the NIMH “Fast-Fail” Trials (Yan 2013).

The methodologies of phase 3 trials in patients with schizophrenia are a source of constant refinement. Work on several specific issues is underway by international groups of experts (e.g., the International Society for CNS Clinical Trials and Methodology). In multisite trials, the greater the number of sites, the greater the risk of a negative results (Mallinckrodt et al. 2011). Normally, this challenge is met by increasing sample sizes. However, more rational approaches are needed as well as work that addresses site heterogeneity and improves inter-site reliability. Personalized medicine approaches using genetic

and other biomarkers, described later in this chapter, may reduce heterogeneity across patients.

Neuroimaging techniques offer the potential to increase signal intensity, allowing for smaller samples in early phase treatment studies. However, few studies have empirically demonstrated that these technological advances surpass conventional clinical tools, such as rating scales and cognitive performance measures. Further, there are few standard activation paradigms that can compare results across trials. Currently, work is in progress to map systematically brain activation responses to cognitive activation tasks in controls, providing normative data that can be used in patient populations on standard protocols.

The cost of phase 2 clinical trials may be reduced by shortening the length of trials. Recent work suggests that treatment efficacy can be established earlier in the course of a clinical trial than is traditionally accepted. For example, the period of greatest sensitivity of antipsychotic efficacy may occur in the first two weeks of treatment, and the traditional endpoint of antipsychotic trials of 8–12 weeks may actually reduce the effect size of new treatments due to patient drop out (Agid et al. 2003; Kapur et al. 2005).

#### *A Conundrum: Sample Homogeneity versus Heterogeneity*

A number of schizophrenia trials failed because of challenging patient cohorts, geographic and cultural differences, and inclusion and exclusion criteria that are too broad or poorly defined. In the clinical trial, two principles drive the need for sample homogeneity: (a) an ethical imperative, with safety given precedence over efficacy and (b) the scientific need for homogeneity to maximize signal detection, particularly in trials involving biomarkers, to allow precise estimation of treatment effects. Unfortunately, the need for homogeneity can result in narrowly constrained clinical trial samples that are not representative of the heterogeneous community of treatment users. Thus, a major challenge in schizophrenia clinical trials methodology is to identify patient cohorts that are refined enough to permit the detection of a true treatment signal, yet broad enough to enable treatment efficacy to be generalized to the schizophrenia patient population at large.

#### **New Models and Alternative Approaches**

Numerous innovative strategies for testing the safety and efficacy of new treatments for schizophrenia are currently under development. Given the current conservatism in clinical trials, driven in part by the fiscal challenges in industry and academia alike, many of these innovations remain untested. We review a few of these here.

Due partially to the professional and disciplinary separation of investigators from pharmacologic and behavioral traditions as well as the cost of such

studies, very few studies have examined the synergistic or complementary effects of behavioral treatments and drug treatments. However, such studies hold much promise and have been effective in other psychiatric conditions (Barr et al. 2008). Analogous to the obvious need for physical exercise when an individual takes steroids to increase muscle mass (Keefe et al. 2011b), behavioral interventions may be included as a platform for all patients receiving a new drug when compared to placebo to enhance the potency of the compound, especially in cognitive paradigms that may require an enriched environment before pharmacologic treatments can become effective.

A less costly approach would be to examine retrospectively the relative efficacy of different treatment designs using existing databases, some of which have tremendous statistical power to address important questions. A recent stroke study with a very large sample used a naturalistic, retrospective design that relied on hospital records and patient retrospective recall. In addition, the South London Case Register Interactive Search system collects data that will allow retrospective study.

Other innovations that have not been sufficiently utilized are virtual reality outcomes and interventions, and adaptive trial designs. Several different research groups are focusing on the use of virtual reality environments as interventions for the treatment of symptoms (Freeman 2008) and cognitive deficits (Spieker et al. 2012), or as outcome measures in clinical trials (Harvey and Keefe 2012). Additional validation work, however, needs to be done on these methods before they will be accepted into later phase trials. One approach would be to include such measures as exploratory outcomes in studies using conventional outcomes as primary endpoints. With regard to adaptive designs, despite encouragement from regulatory agencies, such as the U.S. Food and Drug Administration (Wang et al. 2011), pharmaceutical companies have been hesitant to utilize these approaches.

### **Other Bases for Therapeutic Intervention in Schizophrenia**

On the level of differential psychopathology, there appear to be few new leads. Elaborate systems, such as the Kleist–Leonhardt classification, have not been shown to have therapeutic relevance, and other subdivisions, such as the concept of brief reactive psychosis, may have merit but are well treated with current approaches. On the level of neuropsychology or psychosocial function, no commonly used test or scale has been shown to have clear differential therapeutic relevance; although poor cognition predicts worse treatment response, moving this forward into differential treatment would require a new generation of cognitive interventions.

There may be more promise for the concept of dimensional psychopathology. In particular, diagnoses-transcending dimensions such as depressive symptoms may prompt appropriate adjunctive treatment including antidepressant prescription. Extending the dimensional concept to neuropsychology leads

to the National Institute of Mental Health's concept of the Research Domain Criteria (RdOC) (Cuthbert and Insel 2010). Going further, it has been proposed that the most useful defining entities of such dimensions may be neural systems (Buckholtz and Meyer-Lindenberg 2012).

Further down the translational chain, there are few genetic or genomic markers for treatment response available. However, important advances are being made in genetic predictors of side effects, such as metabolic syndrome or tardive dyskinesia, that may be important for therapy. The therapeutic predictive value of environmental risk factors, such as childhood abuse or urbanicity, is almost unexplored and should be investigated. The same goes for epigenetic markers from blood or cerebrospinal fluid. Diagnostic blood markers through proteomics are being marketed (rules-based medicine), but it is currently unclear whether these will be useful to guide therapy under real-world conditions.

New tools may offer novel avenues to enhance treatment prediction. Momentary assessment technologies may give a more comprehensive view of hour-to-hour, day-to-day fluctuations in mood, symptoms, salience processing, and stress. Virtual reality techniques may allow better assessment of social function under controlled circumstances. Investigation of social media activity may show changes or abnormalities in web-based interactions. Eye movements can be tracked naturalistically using a new generation of glasses or using lasers from a distance.

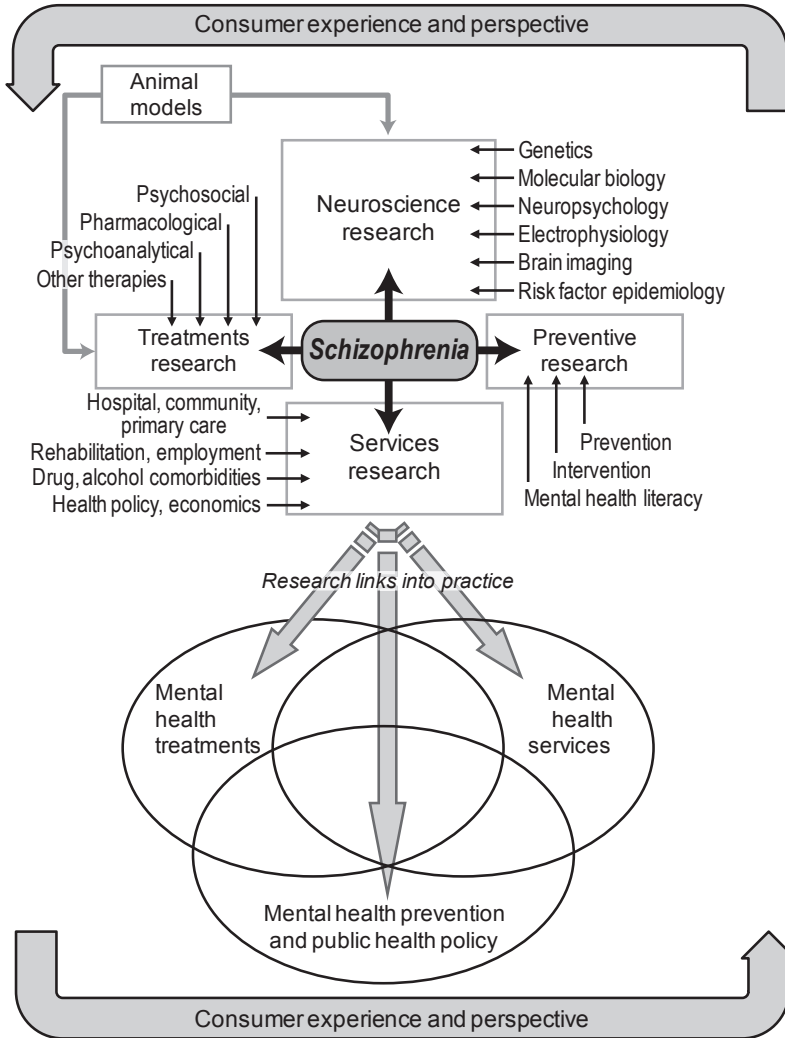
Given the neurodevelopmental nature of the illness, measuring performance during the second decade of life may better define early intervention points, for example, by using and linking school performance and testing data as well as data on social interactions, where these are readily available.

In moving the field forward, a dialectical process between defining intervention points and new therapies is expected. Without differentially effective therapeutics, early intervention has little consequence. Conversely, by understanding the processes early in the illness, especially the pre-psychotic state, new treatment targets are expected to come into focus.

## **A Framework for Treatment Development**

Treatments for schizophrenia cover psychosocial treatments and other therapies, as well as biological treatments. While discussion in this section has focused primarily on new developments within biological treatments, throughout this chapter we stress the key role played by psychosocial interventions and the importance of their integration with biological approaches to treatment.

Finally, it is important to recognize that treatment development does not take place in isolation from other areas of schizophrenia research. These areas are multidisciplinary and include work on animal models, neuroscience research, preventive research, and services research (Figure 17.3). Integration across modalities is an essential ingredient of the development of new paradigms. In addition, to ensure its effectiveness, research needs to link into practice to



**Figure 17.3** A multidimensional, translational treatment model (after Morgan et al. 2006).

inform mental health policy development and service delivery. Critically, we note that the consumer experience and perspective is the fundamental context in which both research and practice occur (Morgan et al. 2006).

**Personalized Treatment: Tailoring Treatment to Individual Needs**

To explore personalized treatment, we begin with two definitional approaches: (a) a bottom-up approach which starts with the identification of predictors of

response that may apply to any patient; and (b) a top-down approach which begins with the patient and assesses what is available for tailoring treatment to that patient's specific needs. Whereas the first approach is generally associated with a broad, biological perspective and the second with an individualized, psychosocial perspective, these associations are not immutable. Ideally, the two approaches converge. These two approaches are then framed by a patient's perspective set within a collaborative model of care.

### **Personalized Medicine from a Broad, Biological Perspective**

The conventional definition of personalized medicine encompasses the idea of predicting a priori response to antipsychotic drugs. Predictors of response include demographic factors (age, age of onset), clinical factors (neurocognitive function), or neurobiological factors, including brain imaging phenotypes or molecular genetic sequence variation. Phenotypes for examination commonly utilize broad clinical response parameters based on drug efficacy but have also focused on side effects of treatment, such as clozapine-induced agranulocytosis.

To date, much of the neurobiological prediction of drug response research has utilized the pharmacogenetics approach. Advantages of this approach are the relative ease of access to DNA, the immutability of genotype, and the increasing ability to interrogate entire genomes in a cost-effective manner. Work on pharmacogenetics of efficacy has, however, not led to clinically actionable results, although this may be secondary to methodological issues pertaining to these studies. For example, most studies have utilized convenience samples derived from clinical trials designed to compare antipsychotics. This serves to diminish power due to multiple treatment arms and incomplete DNA collection, and phenotypes under examination may not be maximally informative for identifying the effects of subtle DNA sequence variation. Finally, it should be recognized that the genetic architecture of clinical treatment response may be complex, and perhaps no simpler than that of disease susceptibility, which has hampered genetic studies aimed at identification of common variation.

Studies of side effects have been more successful, in part because of the increased power due to the decreased measurement error of these phenotypes. Recently, the human leukocyte antigen system has been linked to clozapine-induced agranulocytosis and weight gain with a melanocortin receptor genotype. These studies require follow-up, and clinical trials based on these genotypes are being planned. At the same time, we need better studies of side-effect *burden* if we are to improve patient adherence to medication. Many studies are limited to measuring frequency and severity, without assessing more subjective side effects such as dysphoria or considering the trade-off of side-effect burden against symptom reduction.

New study designs may need to be considered (Malhotra et al. 2012), including the study of alternative phenotypes. For example, brain imaging measures utilized shortly after drug administration may provide novel information more closely linked to the sites of gene action. Focus on more homogeneous patient populations, use of earlier phase patients, and minimization of prior drug treatment may also provide benefit.

### **Personalized Medicine from an Individualized, Psychosocial Perspective**

The idea of personalized medicine converges with related ideas about individualizing treatment that evolved in psychiatric rehabilitation. Broadening the focus from psychopharmacotherapy to include psychosocial treatment addresses multiple levels of functioning, including neurophysiological, neuropsychological, sociocognitive, behavioral, and socioenvironmental processes. These are no longer seen as competing paradigms: they reflect distinct levels of analysis and action within a unified biosystemic understanding of mental illness.

In severe mental illness, measurable impairments are observed at all of these levels and are a source of heterogeneity in schizophrenia, occurring in constellations that differ from one person to the next. While effective pharmacological treatment may resolve acute psychosis or eliminate symptoms, impairments remain in cognition, self-care, interpersonal effectiveness, and social role performance. There is a rapidly growing armamentarium of psychosocial treatment modalities to address specific deficits across levels of functioning. For example, modalities like cognitive remediation act primarily at the neuropsychological level. Cognitive behavioral therapy and related behavioral treatments act at sociocognitive and behavioral levels. Behavioral family therapy extends to the socioenvironmental level. To treat individual constellations of impairments optimally, we must select and apply the respective treatments that correspond to those individual constellations. As with personalized medicine, this creates an assessment burden that may limit complete individualization of multimodal treatment regimens. However, for more severe illness, resulting in more pervasive distribution of impairments across levels of functioning and more severe disability, comprehensive and integrated treatments are necessary. The level of severity and/or pervasiveness at which this type of individualization becomes cost-effective can, in principle, be empirically determined, but as assessment and treatment technologies advance, one would expect the threshold level to become lower.

Coordinated treatment of multiple, functionally independent but interrelated impairments across levels of functioning is problematic in diagnosis-driven clinical decision making and is better accommodated by broader problem-solving approaches. These are familiar to clinicians and have even been canonized in American medical records standards as Problem-Oriented Medical Information Systems (PROMIS). A similar approach, termed case formulation,



has evolved within the methodology of cognitive behavioral therapy. With some further formalization and structure, a clinical problem-solving approach can effectively guide multimodal treatment of heterogeneous conditions like schizophrenia.

In clinical problem solving, the unit of analysis is not diagnosis but “problem type.” Problem types are jointly defined by types of impairment at the various levels of functioning and by technologies currently available to measure and treat those impairments. For example, psychopharmacology and the neurophysiological impairments it treats is usefully categorized under a “CNS dysregulation” problem type. Measureable deficits in interpersonal functioning that can be effectively reduced by social skills training are usefully categorized under a “social skills deficit” problem type. Failure to recognize one’s illness and therefore to adhere to needed treatments can be effectively addressed with psychoeducational interventions, and is usefully categorized as an “illness management deficit” problem type. A problem type reflects what we know from science about the links between the problem and its effective solution, and thus provides a logical justification for treatment selections. An integrated, individualized treatment regimen is achieved with a complete inventory of the person’s problem types and a plan for systematically addressing them with evidence-based treatments.

Contextual factors (e.g., patient’s perspective, neuropsychological status, developmental and environmental factors) as well as the nature of the treatments drive clinical decisions about how to prioritize or sequence treatment, and determine what configuration of pharmacological and psychosocial approaches works best on a case-by-case basis. For example, the time frame in which the effects of drug treatment can be evaluated is much shorter than that for evaluating skill-training interventions. It is more practical to determine what interpersonal deficits persist after effective drug treatment than what psychotic symptoms persist following social skills training. Similarly, drug treatment of an acute CNS dysregulation may be prerequisite to social skills training in some cases whereas in others, the potential for medication nonadherence must be addressed either before or in the context of providing pharmacotherapy. In the foreseeable future, advances in clinical psychopharmacology may provide additional reasons to prioritize, sequence, coordinate, and integrate treatment of problem types across levels of functioning, for example, the possibility that short-term effects of oxytocin might improve engagement in psychosocial treatments, or that cognitive therapy is necessary to consolidate the effects of deep brain stimulation.

A crucial element in this approach is for treatment to proceed as a quasi-experimental hypothetico-deductive process, wherein the effects of specific interventions are reliably evaluated and reevaluated in iterative cycles. This is how we determine that, for any one person, specific additional problems remain to be treated after maximum pharmacotherapeutic benefit has been achieved. No scientific breakthrough is likely to change this clinical reality.

### **Personalized Medicine from a Patient's Perspective Set within a Collaborative Model of Care**

An additional perspective on personalized treatment is that of the patient. This perspective is framed in a collaborative model of care where the patient is an active participant involved in shared decision making in the treatment process. The relationship between patient and therapist in mental health care is one of the most important factors in successful treatment. It is a reliable predictor of treatment outcome, regardless of diagnosis, setting, or type of therapy. Shared decision making builds on a trustful therapeutic relationship, incorporating concepts such as recovery, empowerment, and self-esteem. It takes into account not only a person's individual circumstances, but also their preferences for outcomes they most value. For practitioners, personalized treatment within a collaborative framework requires that they:

- Determine the problems to be treated.
- Identify the available treatments.
- Recognize individual differences in a patient's psychological, biological, and social makeup.
- Consider the patient's desires.

It is important to note that in a biosystemic view of human functioning, the patient's perspective, beliefs, attitudes, and values are important elements, shaped by social cognition. Sometimes addressing and influencing those elements is beneficial to the patient's recovery. For example, a belief that no better life is possible and all effort will be punished is a frequently encountered perspective; changing that perspective may promote recovery. We have effective methods for facilitating such changes (e.g., cognitive behavioral therapy and motivational interviewing). We can therefore identify self-defeating beliefs as a specific problem type in an integrated and individualized treatment plan, treat it with cognitive behavioral therapy and related methods, and measure the success of the treatment.

However, there is danger in treating perspectives as targets for change. For example, a person's perspective on adherence to treatment may be detrimental to symptomatic recovery, but people often make different choices across treatment options. Historically, we have erred much more on the side of not respecting patients' perspectives than on missing treatment opportunities. Practitioners need to know and understand their patients' perspectives, and some of these perspectives may also be a target of treatment. To this end, respect for patient decision making needs to rest on a foundation of mutual understanding of the nature of the disorder, to the extent that this is possible, and the patients' goals for treatment. In the end, how and where we draw the distinction between perspectives to treat versus perspectives to respect will be settled by social consensus, not science. The recovery movement has contributed importantly to the broader discourse on the roles of perspective,

attitudes, and values in psychiatric treatment and rehabilitation, but a working consensus will require participation of all quarters of the mental health community.

### **Optimizing Service Delivery**

Although current treatments for schizophrenia are still far from optimal, there is a reasonable evidence base to inform the clinician as to what works and when. These evidence-based interventions, however, are not implemented systematically, if at all. Pharmacological treatment of positive symptoms is the basis of most treatment regimes, yet patient adherence to treatment is generally poor, and the prescription of depot medication and clozapine is suboptimal. The use of nonpharmacological treatments targeting other aspects of the illness is low, with these other treatment modalities poorly integrated into mainstream treatment regimes. What is needed is a strategic way of refocusing or fine tuning treatment goals, bearing the individual patient in mind. This includes careful management of the balance between pharmacological and psychotherapeutic interventions, with a view to optimizing treatment response across modalities, increasing quality of life, and preventing psychosis relapse.

In terms of optimizing delivery, there are two issues: one for research funders and one for health care providers. First, we need to consider what are the service configurations that will provide the most benefit—this is a research question. The second concerns the translation of current findings into practice. This is not an easy issue to address as it is not clear how individual and effective therapies may best be implemented into “normal” services. Dissemination science or implementation science takes into account social and organizational psychology approaches to drive the implementation. Its outputs can act as a template for translation of therapies into clinical practice.

The arguments made for change will differ according to different groups but perhaps the overarching argument needs to be made in terms of net benefit. This can be defined in different ways. For example, it may be defined as cost savings for some service providers, a political argument necessary for some potential investors. For others, it may need to be defined as a benefit in cost utility; that is, it achieves a desired outcome such as people attending services, which increases the immediate cost in the hope that improvements in functional or other outcomes will result in the future. Net benefit is also a way of costing the outcome. For example, people are more content, have more friends, and rely less on family support.

### **Impediments to the Implementation of Evidence-Based Treatments**

The evidence base supporting the efficacy of specific psychosocial interventions for schizophrenia has grown steadily over the past several decades.

Despite this growth, there continues to be a significant lag, possibly growing, between the science of treatment and the implementation of empirically supported interventions. At least three broad factors can be identified, each of which contributes to this gap in knowledge and implementation.

First, practical knowledge about how to implement and sustain individual practices in routine treatment settings is needed. For example, the successful adoption of an intervention requires attention to the science of implementation. This involves consideration of factors traditionally studied under the purview of organizational psychology. These include structural aspects of a human service organization, distribution and sharing of power and decision making, openness to change and innovation, and access to critical resources such as training and consultation expertise. Attention to these issues is critical both to understanding how to implement a specific practice and to appreciating organizational characteristics and needs in ways that will facilitate broad-scale adoption of the practice. Variables which may have an impact on implementation are: training, supervision, and collaboration among service providers; the attitudes, beliefs, and practices of treatment staff; time allotted to staff to provide services; and the skill of those individuals responsible for overseeing and supervising the practice.

Second, and related to the first point, psychiatric rehabilitation programs based on social learning in institutional and hospital settings are generally understood to have features that are inconsistent or even incompatible with the conventional “medical model” of administrative and clinical practices that predominate in such settings (Paul and Lentz 1977; Liberman 1979; Silverstein et al. 2006a; Tarasenko et al. 2012). These features include:

- The need to supervise direct care staff closely, to ensure high fidelity to procedure manuals which require behavioral responses by staff that are sometimes counterintuitive and/or contradictory to conventional nursing or medical practice.
- Administrative control over direct care staff by a program director, who is directly accountable for treatment fidelity and outcome, rather than indirect control of direct care staff by an administrative supervisor, such as a director of nursing, who is not directly accountable for program operation.
- Psychiatric staff who have a “consultant” role with focused responsibility for pharmacological dimensions of treatment, rather than superordinate authority and accountability for all patient care.
- Individualized treatment prescribed and directed according to a treatment plan that is constructed by an interdisciplinary treatment team rather than through physicians’ orders.

These incompatibilities may also apply in community-based service systems outside institutions and hospitals.

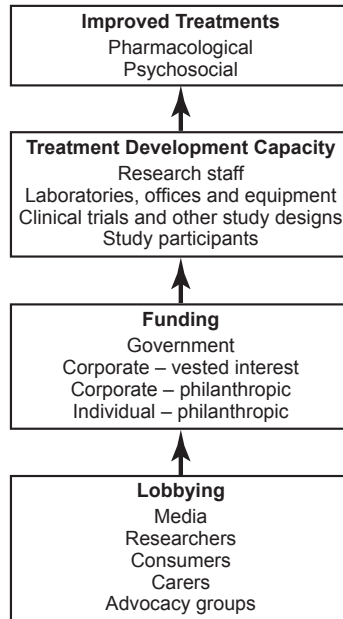
Finally, training and mental health policy issues need to be addressed to improve the uptake of these evidence-based practices. All mental health professionals should understand and be competent to provide high-quality, effective treatments for people with schizophrenia. This should happen as part of basic training, further supplemented by continuing practice development as novel and effective treatments emerge. Mental health service providers and purchasers need to incorporate sufficient incentives and accountability for providing such efficacious treatments, not only ensuring they are carried out as prescribed in the evidence but also checking to see that outcomes are in the expected direction and at the expected level.

### **A Business Model of Service Delivery**

For the many reasons discussed above, the effective and individualized use of pharmacological and psychosocial therapeutic options has been limited, despite their availability. One means of overcoming problems with current mental health service delivery is to operate a free market model for some of its components. This type of business model, operating across public and private sectors, would approach patients as “purchasers” and mental health services as “products.” In this context, shared decision making and patient education would increase the market for mental health services. Increased demand, in turn, could motivate private companies to invest in treatment development, the training of specialized professionals, and the establishment of quality standards, thereby optimizing quality, diversity, and costs of services—especially psychosocial therapies which are more expensive in the short term than pharmacological interventions, and more difficult to standardize. At the same time, investors may be motivated to increase their market hold and consumer retention through investments in innovative services which target patients’ special needs. One example would be the establishment of e-health systems using smartphones to navigate the use of treatments. Recently, investigators in the Netherlands and Great Britain have started to test the principles of the free market in the context of mental health service provision by examining which services are accessed, and how frequently, when patients are allowed to manage their own therapeutic budget. However, much more research is needed to ensure that such a business model would be viable, effective, affordable, and equitable.

### **Promoting Greater Investment in Treatment Development**

Greater investment in treatment development is essential. This should involve multiple stakeholders to fund or to act in concert to promote the research agenda (see Figure 17.4). In addition to scientific peers, these stakeholders include research funders, service users and carers (family and friends),



**Figure 17.4** Engaging stakeholders in treatment development (after Morgan et al. 2006).

pharmaceutical and other commercial interests (e.g., biotechnology companies), and health care providers (both public and private). Despite a shared vision on what investments are needed, dialog with each of the stakeholders needs to be tailored to their specific needs and a format and language that is familiar to them needs to be employed. One key emphasis is the benefit that can result from such investments; these can be described in the vocabulary of health economics as cost benefit, cost utility, and cost effectiveness. There is current evidence that investment in mental health care can result in substantial benefits and impacts. A review of mental health research investment by the Academy of Medical Sciences in the U.K. found that for every one pound invested in mental health research, there was a return of 37 pence each year in perpetuity. Thus, after three years, the investment has been repaid and the following years actually produce a profit in terms of health care savings and reduced disability.

Engaging the media to promote information on research attainments is critical. Closer ties with science journalists are vital, so that they can better appreciate current scientific breakthroughs and grasp where we want to go next. Likewise, background and news briefings will generate greater media coverage of mental health issues and provide key science and health reporters in national news with more in-depth understanding. This is not only important for promoting investment in treatment research but also has benefits

for all key stakeholders and goes hand in hand with the suggestions we make at the end of this chapter for improving the social context for people with schizophrenia. In sum, the general benefits of a media-based program include its potential to:

- Raise public awareness of issues in mental health research.
- Decrease stigma through reporting of incremental changes in understanding causation and treatment developments.
- Increase public understanding of mental ill health (the science press seems to do this better than the health press).
- Increase hope and optimism for people with mental health problems (and their families) by publicizing incremental changes.
- Increase the public profile of charities who can comment on the work being published. We know that when a charity comments on a mental health issue that it is more likely to be given a public profile report on the BBC website. This, of course, increases the visibility of the charity to potential donors. This same argument can be put to public funders who need a media profile to support future funding from national governments.

In addition, specific approaches need to be made to public investors. Research funders need to be aware of the particular areas that have been agreed as vital for improving the understanding and treatment of schizophrenia. For example, naturalistic studies that examine heterogeneous samples are not funded by the pharmaceutical industry; this raises the possibility of public investors funding these types of studies.

Finally, academic outputs can be harnessed to build a program of research that would benefit from larger-scale future investment. The leverage of larger investment will require specific approaches to foundations as they may become the change managers or charismatic leaders for such philanthropy.

Ultimately, promoting greater investment in treatment research involves a concerted effort to strengthen the nexus between lobbyists, funders, and researchers.

### **The Role of Social Context in Improving Treatment Outcomes**

Here, we consider social context on three levels. The macro level addresses broad societal aspects that impact on people with schizophrenia. The meso level is concerned with the social networks, including family and other caregivers, within which people with schizophrenia find themselves. The micro level operates at the level of the individual: a person with schizophrenia may be designated variously as an affected person, patient, client, consumer, and so forth, with each designation implying a different perspective (Pescosolido et al. 2008).



### Social Context at the Macro Level

One of the major impediments to the treatment and care of patients with schizophrenia is the stigma associated with the disorder. Stigma is a general term that describes the process of assigning a certain characteristic to a person (e.g., dangerousness), independent of the person him- or herself. Prejudice characterizes the affective component of assigning the negative characteristic (e.g., being afraid of and avoiding a person with mental illness because of his or her assumed dangerousness). Discrimination relates to the behavioral component of stigma that typically reduces opportunities of the person to gain access to resources that others in society can generally tap (Link and Phelan 2001). Examples include attempting to prevent a person with mental illness from renting a nearby apartment, obtaining a job, voting, or getting health services.

These socially constructed labels have important consequences for people with schizophrenia. In particular, labeling theory provides a useful framework for understanding their impact. Labeling theory, centered on the social construction of deviant behavior, evolved in the 1960s (Goffman 1963). The sociologist Thomas Scheff applied the theory to people with a mental illness, arguing that mental illness is a social construction and questioning its existence (Scheff 1966). In the 1980s, Link et al. (1989) presented a modified form of labeling theory that did not question the existence of mental illness. In a series of empirical studies, they described how the process of labeling people with a mental illness has a negative impact on their lives and leads to a cycle of social rejection and isolation. Today, labeling theory, as outlined by Link, is widely accepted in social psychiatric research.

Numerous studies have examined stigma in mental illness, particularly schizophrenia. In recent years, there has been an accumulation of empirical evidence of the negative consequences of labeling and perceived stigmatization. These include demoralization, low quality of life, unemployment, and reduced social networks (Graf et al. 2004). Affected individuals, once they have been labeled as having a mental illness and become aware of the related negative stereotypes, expect to be rejected, devaluated, and discriminated against. Such individuals often incorporate these negative stereotypes into their own self-perceptions (called *self-stigma*), with associated problems of demoralization, avoidance, and a pervasive sense of hopelessness. This vicious cycle decreases the chance of recovery and normal life.

Successful initiatives make clear that efforts to reintegrate persons with serious mental illness into community life must be accompanied by measures on the societal level. On the basis of comprehensive research over the past decade, several strategies have been developed to fight the stigma and discrimination suffered by this group. Contact with mentally ill people reduces social distance, with those in contact often having a more positive attitude toward people with mental illness: this is a strong argument in favor of community psychiatry. Social distance from mental illness also decreases, and stigma is

reduced, if mental disorders are presented as a life crisis, not as a brain disease (Lauber et al. 2004b). In addition, some research centers have developed destigmatization interventions directed at relevant target groups (e.g., students or police officers).

Social policy also needs to recognize that stigma operates at an intrapersonal as well as interpersonal level, often to the detriment of individual patients. As previously mentioned, individuals in stigmatized groups sometimes incorporate stigmatizing into their own beliefs. Self-stigmatization is a personal perspective, but also a social cognitive process, subject to therapeutic change with cognitive behavioral therapy and related methods (Link et al. 1991). For example, skillful assertiveness is an important determinant of self-esteem, self-worth, and other perspectives incompatible with stigmatization. Social policy needs to promote inclusion of these treatment resources in service systems as yet another way of combating stigmatization.

### **Social Context at the Meso Level**

#### *Wider Social Networks*

The beneficial effects of work for a person's mental health have been known for centuries. Vocational rehabilitation has been a core element of psychiatric rehabilitation since its beginning. Employment is seen as a step toward independence and integration into society. Vocational rehabilitation is based on the assumption that work not only improves activity, financial standing, social contacts, and so forth, it also promotes gains in related areas such as self-esteem and quality of life. Enhanced self-esteem, in turn, improves adherence to rehabilitation in individuals with impaired insight (Rössler 2006).

Today, the most empirically supported vocational rehabilitation model is supported employment. In supported employment, persons with a disability are given assistance to find competitive employment based on their preferences as soon as possible, and they receive the support needed to maintain their jobs. Participation in supported employment programs is associated with greater success in finding and keeping work than other approaches to vocational rehabilitation (Burns et al. 2007). Positive relationships have been found between obtaining competitive work and nonvocational outcomes (e.g., improved self-esteem, reduced symptoms, social integration and relationships, improved cognition, quality of life).

Although findings regarding supported employment are encouraging, some critical questions remain. Many individuals in supported employment obtain unskilled part-time jobs. Thus, further research is needed into the role of supported education and career development as strategies for helping patients obtain higher paying and more interesting jobs. In addition, since most studies evaluate only short (12–18 months) follow-up periods, long-term impact remains unclear. Currently we do not know which individuals benefit from

supported employment and which do not. It is important to realize that integration into the labor market depends not only on the ability of the persons affected to fulfill a work role and on the provision of sophisticated vocational training and support techniques, but also on the willingness of society to integrate its most disabled members (Rössler 2006). One indicator of such willingness is the enactment of laws prohibiting discrimination against people with a mental illness in obtaining work.

### *Family and Caregiver Relationship*

As a consequence of deinstitutionalization, the burden of care has increasingly fallen on the relatives of the mentally ill (Schulze and Rössler 2005): 50–90% of people with a disability live with their relatives following acute psychiatric treatment. This is a task many families do not choose voluntarily. Caregiving may impose a significant strain on families (Lauber et al. 2003). Those providing informal care face considerable adverse health effects, including higher levels of stress and depression, and lower levels of subjective well-being, physical health, and self-efficacy. In addition, not all families are equally capable of giving full support to their disabled member or are willing to be a substitute for an insufficient health care system.

Still, families are an often untapped resource in the treatment of schizophrenia. They represent support systems that provide natural settings for context-dependent learning, which is important for recovery of functioning. Therefore, since the beginning of care reforms, there has been a growing interest in supporting affected families. Family intervention programs have produced promising results. Family interventions are effective in lowering relapse rates and also in improving outcomes (e.g., psychosocial functioning). Furthermore, treatment gains are fairly stable (Pilling et al. 2002). However, more data are needed to clarify the effective components of different models, which may differ in content, frequency, and length of treatment (Barbato and D'Avanzo 2000).

### **Social Context at the Micro Level**

In some parts of the world in recent years, social skills training in psychiatric rehabilitation has become very popular and has been widely promulgated. Social skills training programs focus on areas such as medication management, symptom management, substance abuse management, basic conversational skills, interpersonal problem solving, friendship and intimacy, recreation and leisure, workplace fundamentals, community (re-)entry, and family involvement (Lieberman and Kopelowicz 2002).

The results of multiple controlled studies suggest that individuals with schizophrenia can be taught a wide range of social skills (Kern et al. 2009). Social and community functioning improve when these skills are relevant for the patient's daily life, and changes in behavior are recognized and reinforced.

Unlike medication effects, benefits from skills training occur more slowly. Furthermore, long-term training has to be provided for positive effects. Overall, however, social skills training has been shown to be effective in the acquisition and maintenance of skills and their transfer to community life and improvement of psychosocial functioning (Kurtz and Mueser 2008).

