Review

Illness Phase as a Key Assessment and Intervention Window for Psychosis

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ABSTRACT

The phenotype of schizophrenia, regardless of etiology, represents the most studied psychotic disorder with respect to neurobiology and distinct phases of illness. The early phase of illness represents a unique opportunity to provide effective and individualized interventions that can alter illness trajectories. Developmental age and illness stage, including temporal variation in neurobiology, can be targeted to develop phase-specific clinical assessment, biomarkers, and interventions. We review an earlier model whereby an initial glutamate signaling deficit progresses through different phases of allostatic adaptation, moving from potentially reversible functional abnormalities associated with early psychosis and working memory dysfunction, and ending with difficult-to-reverse structural changes after chronic illness. We integrate this model with evidence of dopaminergic abnormalities, including cortical D_1 dysfunction, which develop during adolescence. We discuss how this model and a focus on a potential critical window of intervention in the early stages of schizophrenia impact the approach to research design and clinical care. This impact includes stage-specific considerations for symptom assessment as well as genetic, cognitive, and neurophysiological biomarkers. We examine how phase-specific biomarkers of illness phase and brain development can be incorporated into current strategies for large-scale research and clinical programs implementing coordinated specialty care. We highlight working memory and D_1 dysfunction as early treatment targets that can substantially affect functional outcome.

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NEURODEVELOPMENT OF PSYCHOTIC DISORDERS

In the late 20th century, phenomenological descriptions of young persons characterized behavioral, motoric, and cognitive alterations as antecedents of later development of psychosis (1–3). While nonspecific, findings offered indirect evidence of altered neurodevelopment in those at risk for psychosis, in line with a neurodevelopmental model of schizophrenia (SZ) (4–6). Psychosis, as a syndrome, is characterized by symptoms including hallucinations, delusions, and changes in behavior and communication; these can be present in different disorders. However, the SZ phenotype, as a disorder, is viewed as the representative psychotic disorder. We acknowledge that the diagnosis of SZ is based on expression of a common phenotypic pathway arising from various possible genetic and environmental interactions. The recent National Institute of Mental Health Research Domain Criteria emphasis on dimensional biological and cognitive processes that lead to mental health and illness does not result in diagnostic classifications, which in the past have posed limitations in elucidating neurobiology associated with psychiatric symptoms. Indeed, there have been ongoing considerations regarding alternatives to the SZ construct that may lead to new nomenclature and novel phenotypic classifications

(7). To accommodate the evolving shift away from viewing SZ as a distinct disorder with unitary causality, we will refer to the phenotype of SZ in this article. This phenotype of SZ has provided the opportunity to study genetics and environment, biomarkers, and phases of illness in an enriched sample. Family studies led to the discovery of heritable markers of brain processing associated with the SZ phenotype, for example, smooth pursuit eye movement dysfunction (8,9), sensory gating deficits (10), and certain cognitive deficits, such as working memory (WM) (11,12), associated with familial vulnerability for psychosis. Potential risk genes, such as single nucleotide polymorphisms, copy number variants, and de novo mutations, were associated with later development of psychosis (13). A recently updated large genome-wide association study (14) in SZ phenotype cases and controls identified 270 risk loci. The role of environmental factors in psychosis risk is also critical, including numerous nonspecific influences during prenatal, perinatal, early childhood, and adolescent development (15). In the diathesis–stress model, genetic risk interacts with environmental influences to result in altered brain development. According to this concept, transition to psychosis and subsequent chronic illness relates to neurodevelopment mediated by common and/or rare gene

alterations in interaction with various adverse environmental influences at any time during brain development, starting in utero up to close to onset of illness (16). Thus, early environmental influences (e.g., infections, nutritional deficiency, and neglect during intrauterine to early childhood period) may exert influences that can alter neurodevelopment directly, or indirectly through gene expression. Later events (e.g., drugs, brain injury) more proximal to the onset of psychosis may disrupt dopaminergic homeostasis. This model is neither unitary nor discrete, and a person may undergo exposure to multiple risk factors. This developmental perspective promotes understanding of how distinct phases in the pathophysiology of the phenotype of SZ deviate from neurotypical brain development spanning the prenatal period through adulthood.

EARLY PHASE OF ILLNESS

Alterations in behavior across various dimensions, lasting from weeks to years, prior to emergence of psychosis have been described. Nonspecific at-risk symptoms in childhood and adolescence may include anxiety, depression, reduced emotional experience, cognitive difficulties, and social withdrawal (17). Specific syndromes identifying psychosis prodrome are embodied in clinical high-risk (CHR) (18) and ultra high-risk (UHR) (19,20) constructs. CHR/UHR classifications are primarily based on acute or increasing subthreshold positive symptoms, including unusual thought content, perceptual anomalies, and disordered thinking/speech, with relatively intact reality testing. In individuals identified as experiencing attenuated psychosis syndrome (APS), transition to threshold psychosis occurs in an estimated 20% to 35% within 2 to 3 years (21). Young persons who do not transition may experience persistent symptoms, in some cases consistent with schizotypy or another nonpsychotic disorder, or may experience symptom resolution. Innovative transdiagnostic clinical staging models developed in recent years aim to provide conceptual frameworks for characterizing risk, development, and progression of a broad array of youth mental health outcomes (22–26). Risk calculator (27–32) and machine learning (33,34) approaches, which incorporate an array of risk factors, have been developed to predict progression to first-episode psychosis (FEP). Thus, the FEP outcome is inherently probabilistic rather than determined (24), as delineated in a growing literature supporting the construct of transdiagnostic pluripotential risk (35).

The emergence of FEP is often associated with changes in mood, anxiety, cognition, and substance use problems resulting in uncertain/inconsistent endorsement of target symptoms, phenomenological heterogeneity, and diagnostic uncertainty. Yet as the clinical course evolves over time, eventual clinical diagnosis in FEP becomes evident and remains relatively stable for SZ (36). In the United States, about 100,000 young people experience FEP annually, with a lifetime prevalence of 3%. About one-third of those with FEP develop the phenotype of SZ; the remainder are diagnosed with a range of nonaffective, affective, and substance-induced psychoses. Traditionally, SZ has been viewed as an illness with limited recovery rates, high disability-adjusted life years, and a 20% reduction in

average life expectancy, which underscores the need for more effective interventions.

IMPORTANCE OF EARLY INTERVENTION

Intervention programs in young persons at CHR have been implemented in numerous countries and aim to attenuate or possibly prevent progression to psychosis, mostly through nonspecific treatments and education (37). In FEP, early intervention can preserve or improve functional abilities (38–40) and potentially alter neurobiological progression of untreated illness. Educational and social developments proceed rapidly during adolescence and young adulthood, and even brief disruption can produce enduring consequences for attaining important maturational milestones. These, in turn, lead to challenges for young persons and their supports, most commonly their family. Consequently, individuals may experience emotional distress, social alienation, and stigma (41). It has been postulated, although with inconsistent empirical support, that the duration of untreated psychosis (DUP) appears to exert adverse or toxic effects on brain functioning (42). DUP has been associated with poorer outcome (43), even years later (44), leading the World Health Organization to recommend constraining DUP to <3 months. Long mean DUP of several years in the representative North American FEP trial (45) illustrates how far the field is from attaining the goal of early intervention, particularly in community settings in the United States. This critical delay is due to multiple contributors, including limited mental health literacy in the general public, absence of universal screening and mobile detection strategies, limited access to dedicated care, and societal stigma. In addition, lack of significant improvement within a few months to years after onset is associated with limited long-term recovery (46,47). These harsh findings highlight the pressing need to invest in effective prevention and early intervention approaches to reduce rates of outcome and disability that have not changed significantly in many years despite novel antipsychotics and other treatment modalities.

Typical FEP treatment in general psychiatric settings makes little differentiation between illness phases, and young persons with FEP may receive similar treatment as individuals with chronic illness. Consequently, individuals with FEP are particularly sensitive to both therapeutic and side effects of medications (48). They can easily experience excessive exposure to antipsychotics and a failure to implement recovery-oriented interventions. For young patients, traditional intervention approaches in settings serving more chronically ill persons can contribute to resistance to illness acceptance and proposed treatment, demoralization, and enforced stigma of serious mental illness, leading to poor outcome.

FEP-specific interventions in dedicated settings were developed in Australia and Europe in the past 3 decades and have been more widely implemented in the United States since 2015 through support of the Substance Abuse and Mental Health Services Administration. FEP-specific interventions are provided by a dedicated team of coordinated specialty care (CSC), including case management, psychotherapy, medication management, supported employment and education, and family support and education. A recent meta-analysis (49) of 10 randomized controlled trials in FEP provides empirical support

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for improved outcomes in individuals engaged in 6 to 24 months of early intervention services, compared with treatment as usual. However, 10-year outcome data from the OPUS trial did not support sustained clinical and functional improvements in individuals with CSC compared with usual care, highlighting the need for additional longer-term outcome studies (50). CSC programs in the United States remain scarce in many regions (51) and are thus inaccessible to many individuals experiencing FEP.

NEURODEVELOPMENTAL MECHANISMS

Prior Phase-Specific Model of SZ Pathophysiology

Individuals with FEP are more sensitive to standard D_2 receptor (D2R)–blocking antipsychotics compared with those with chronic illness (52,53). Similar early-stage sensitivity was recently noted with respect to novel glutamatergic interventions (54). Thus, treatment response appears greater in early stages, suggesting that pathophysiology of illness differs according to illness stage. Krystal and Anticevic (55) previously outlined a model of stage-specific pathophysiology and its dynamic evolution over time. In this model, the earliest illness stage (predrome) is marked by minimally symptomatic glutamatergic hypofunction. Allostatic adaptations to this initial excitatory deficit, particularly reduced GABA (gamma-aminobutyric acidergic) signaling, lead to cortical disinhibition/overexcitation during the prodromal phase. This, in turn, causes abnormalities in neural tuning, oscillations, and functional hyperconnectivity, which produce frank psychotic symptoms, and cognitive impairment including WM dysfunction. Further adaptations to hyperexcitation and hyperconnectivity, such as accelerated synaptic pruning, cause atrophy and worsening neural circuit dysfunction over time, producing worsening psychosis and potentially irreversible structural changes. One limitation of this exciting model is that it addressed dopaminergic systems only in passing. Here, we expand this model (Figure 1) to incorporate literature on developmental and phase-specific changes in dopaminergic function, with a particular focus on dopamine D1Rs in the prefrontal cortex (PFC).

Normal and Abnormal Development, Focusing on PFC Dopamine D_1 System

The Krystal and Anticevic (55) model coheres with earlier suggestions that SZ pathophysiology reflects abnormal early neurodevelopmental vulnerability, with frank illness only manifesting in the context of further adolescent brain development (56,57). Adolescence is marked by profound normative changes in dopaminergic innervation, receptor levels, and signaling, and behavioral responses to dopaminergic agents (e.g., stimulants) peak during adolescence (56–59). This contributes to broader maturation of the PFC, which involves synaptic pruning and myelination continuing well into the third decade in humans (60,61). Indeed, adolescence has been proposed as a neurodevelopmental critical window of heightened plasticity for PFC and its functions, including WM (58).
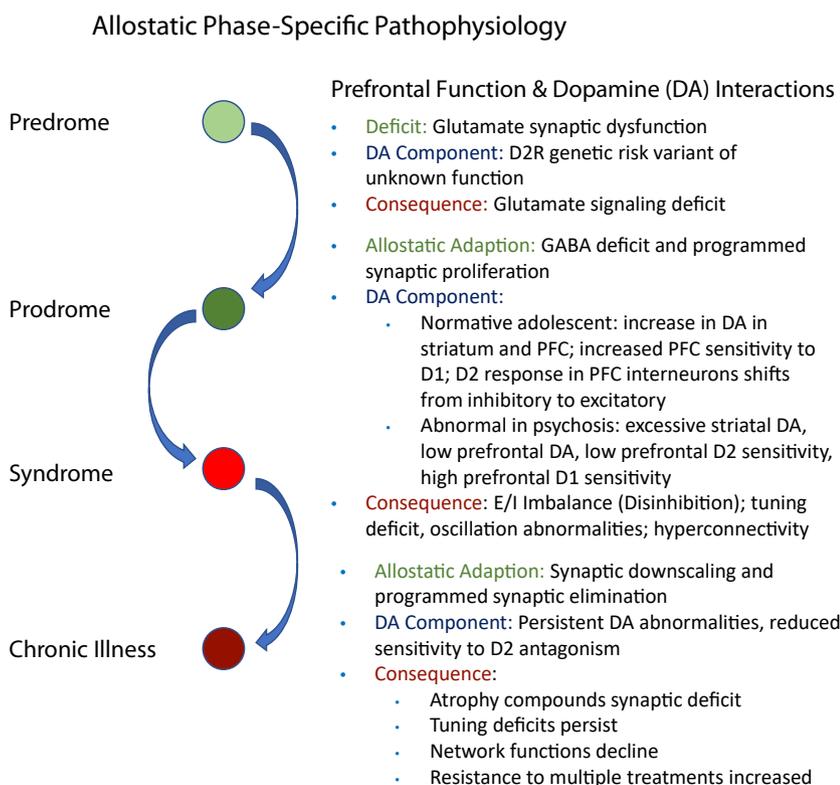
Allostatic Phase-Specific Pathophysiology

Predrome

Prodrome

Syndrome

Chronic Illness

Prefrontal Function & Dopamine (DA) Interactions

- Deficit: Glutamate synaptic dysfunction
- DA Component: D2R genetic risk variant of unknown function
- Consequence: Glutamate signaling deficit

- Allostatic Adaption: GABA deficit and programmed synaptic proliferation
- DA Component:
  - Normative adolescent: increase in DA in striatum and PFC; increased PFC sensitivity to D1; D2 response in PFC interneurons shifts from inhibitory to excitatory
  - Abnormal in psychosis: excessive striatal DA, low prefrontal DA, low prefrontal D2 sensitivity, high prefrontal D1 sensitivity
- Consequence: E/I Imbalance (Disinhibition); tuning deficit, oscillation abnormalities; hyperconnectivity

- Allostatic Adaption: Synaptic downscaling and programmed synaptic elimination
- DA Component: Persistent DA abnormalities, reduced sensitivity to D2 antagonism
- Consequence:
  - Atrophy compounds synaptic deficit
  - Tuning deficits persist
  - Network functions decline
  - Resistance to multiple treatments increased

Figure 1. Developmental schema for neurobiological progression of schizophrenia, adapted from Krystal and Anticevic (55) by incorporating dopaminergic components. D2R, D_2 receptor; DA, dopamine; E:I, excitatory-to-inhibitory balance; GABA, gamma-aminobutyric acid; PFC, prefrontal cortex.

Dopaminergic midbrain neurons continue to arborize into the nucleus accumbens as well as into the PFC across adolescence. While these changes affect the entire PFC, dopaminergic innervation is particularly increased during adolescence in cortical layer 3 of the dorsolateral PFC, which is strongly implicated both in WM and SZ phenotype pathophysiology (59,62,63). Human postmortem data indicate that D1R levels increase from infancy through adulthood, while D2R levels decrease (64). Response to dopamine receptor stimulation in the PFC also changes dramatically during adolescence. Dopamine effects on PFC neurons are complex, with a mix of excitatory and inhibitory impacts varying across cell types, subcellular components, and developmental stages. D1R signaling at low levels directly increases PFC pyramidal neuronal firing by enhancing NMDA response, while at higher dopamine levels, the D1R has a net inhibitory effect on pyramidal cells via modulation of dendritic potassium channels (63,65) as well as through excitation of interneurons, particularly parvalbumin-positive fast-spiking interneurons (FSNs) (63,66,67). D1R responsivity in PFC neurons generally increases across adolescence (68–70). D1R and D2R signaling have a complex interaction in PFC, with some similar and some opposing effects (69,71). This interaction varies according to basal dopamine levels, which can shift the direction of D1R effects, contributing to inhibitory tuning (63). The interaction also varies dramatically across adolescence, as D2R effects change direction from inhibitory to excitatory on FSNs during this period (thereby increasing cortical inhibition) (56). FSNs, implicated in WM and in SZ pathophysiology, show progressive increases in synaptogenesis throughout primate development, including adolescence, and are also particularly sensitive to dopamine modulation compared with other interneurons (62,65). Dopamine also directly accelerates the development of FSNs and their synapses (72). Dopaminergic maturation in the PFC thus interacts with the maturing GABAergic system, contributing to increased inhibition and reduced excitatory-to-inhibitory balance across adolescence (62,69). Developmental dopamine dysregulation can be impacted by abnormalities of perineuronal nets, extracellular matrix structures that increase across adolescence and protect parvalbumin interneurons from damage while also reducing their plasticity and more broadly contributing to closure of developmental critical windows (73,74).

In addition to indirect effects via GABAergic interneurons, dopamine's direct effects on glutamatergic neurons also change across adolescence. In particular, the excitatory component of D1R signaling on PFC pyramidal neurons increases across adolescence, partly through alterations in NMDA receptor function (56,69,75,76).

While we focus on the PFC here, PFC dopaminergic systems also interact with striatal dopamine systems and related limbic circuitry (57,77). Activity of the striatal dopamine system peaks during adolescence (78,79), and striatal hyperdopaminergia is strongly associated with psychosis (80). In contrast, PFC dopamine is abnormally low in SZ (77,81). Dopamine systems in the PFC and accumbens can have reciprocal or antagonistic effects (82,83), and this interaction changes dynamically across adolescence (84–86). Striatal dopamine is already elevated in the prodromal phase, increasing further with progression to frank psychosis (87).

Beyond direct corticostriatal interactions, the hippocampus and amygdala also participate in circuits linking to the PFC as well as the ventral striatum, and are likely to be important in neurodevelopmental risks for psychosis. Early developmental injury to the hippocampus recapitulates features of SZ in animal models in part through dysregulation of the PFC, and disruption of the PFC may, in turn, cause dysregulated hippocampal and amygdala function, particularly in the context of elevated stress (57). Disturbance of PFC maturation may thus contribute to progression of the striatal dopamine and limbic dysfunction component of pathophysiology, and vice versa.

Adolescent neurodevelopmental vulnerabilities can be exacerbated by adverse environments that produce anxiety and stress. In animal models, nondopaminergic agents including GABAergic modulators used clinically as anti-anxiety medications, as well as metabotropic glutamate modulators, demonstrate the ability to prevent development of hyperdopaminergic states (57,88). Such mechanisms may have important interactions with environmental risk and resilience factors—environmental enrichment also blocks development of hyperdopaminergia (89), and adverse environmental effects on psychosis risk are likely mediated at least in part by the increase in anxiety and stress they cause (90–92).

Updated Model Incorporating Dopamine Systems

While many details remain unknown, the above literature points to the need to incorporate dopaminergic systems into the prior model of allostatic phase-specific pathophysiology. Dopaminergic maturation in adolescence and early adulthood represents a key illness phase vulnerability point in SZ pathophysiology, and PFC dopamine abnormalities contribute to a disinhibited and hyperconnected PFC associated with WM impairment (57,93). In models of SZ, the PFC dopamine system appears to be shifted toward greater D1R sensitivity and reduced D2R sensitivity. Reduced D2R sensitivity directly impacts interneuron activity, leading to pyramidal disinhibition. This disinhibition likely drives the PFC hyperglutamatergia and hyperconnectivity found using magnetic resonance imaging (MRI) in early-stage but not later-stage illness, perhaps owing to progressive synaptic loss (94–96); D1R agonism reduces PFC pyramidal cell hyperconnectivity in primates (97). The impact of increased D1R sensitivity may depend on basal dopamine levels, as D1R is more excitatory for pyramidal cells when dopamine levels are low but is more inhibitory when dopamine levels are high; the weight of the evidence indicates that dopamine levels are low in the PFC in SZ. These dopamine effects are likely to be greatest during adolescence and young adulthood, although dopamine abnormalities may also impact earlier stages of pathophysiology.

Application of the Developmental Model to Illness Phase and Potential Interventions

This updated model integrates glutamatergic and dopaminergic abnormalities into a dynamic model of pathophysiology that can guide biomarker development and therapeutic development specific to illness phase and brain development. An implication is that dopamine modulators other than D2R-blocking antipsychotics should be considered in early illness and for symptoms outside the positive symptom domain. The

combination of abnormally low dopamine, increased D1R sensitivity, and reduced D2R sensitivity points to potential benefits of a D1R agonist, which in the low-dopamine regime would be expected to bring pyramidal neuronal firing into a more optimal range, improving inhibitory tuning and reducing hyperconnectivity. Given the inverted-U effects of D1R on PFC physiology and WM (63,77), a partial D1R agonist would be expected to have a similar effect but with reduced risk of overshooting the optimal range, compared with a full D1R agonist. Challenges of effective PFC D1R stimulation and selection of a novel partial D1R agonist as a candidate to improve WM have been described (77).

Another critical implication is that biomarker and treatment studies should stratify according to illness phase, and further work is needed to identify appropriate definitions of illness and brain development phases. Initially, specific age or DUP cut-offs may be selected, but eventually, biomarker-based staging may specify an individual's neurodevelopmental phase and illness phase, providing more accurate stratification. The critical window hypothesis suggests that adolescence and early adulthood represent a period in which treatments work differentially and that aberrant plasticity developed may get cemented once this window closes. This highlights the urgency of implementing treatments specifically effective during this critical window to prevent illness progression or even reverse it. A more speculative implication of the critical window concept is that treatments that reopen this window of neuro-plasticity (for example, histone deacetylases) could potentially reinstate sensitivity even during the chronic phase of illness (92). Interventions to prolong neuroplasticity could be combined with other treatments to normalize circuit functioning.

Advances in phase-specific treatment will depend critically on biomarker development. These could include measures that more precisely capture an individual's developmental stage and illness phase and/or different components of the patho-physiological model and its behavioral sequelae, including prefrontal dopamine levels, D1R sensitivity, prefrontal tuning, and WM. These considerations have driven the design of the TRANSCENDS (Translational Neuroscience Computational Evaluation of a D1R Partial Agonist for Schizophrenia) study including D1R intervention and a WM biomarker (77).

UNIQUE CHALLENGES AND OPPORTUNITIES IN EARLY PSYCHOSIS ASSESSMENT AND TREATMENT

Stage-Specific Screening, Assessment, and Ttreatment

Warning signs of early psychosis (EP) may arise in nonclinical settings (e.g., school or work) or clinical settings without proper recognition, and the condition often goes unaddressed, contributing to DUP. Interventions for CHR/UHR persons include different, mostly nonpharmacological, modalities and may protect against transition to psychosis, which occurs in a minority of persons. Reasons for nontransition remain to be better elucidated (98) and may include protective behavioral, environmental, and genetic factors. Young persons with FEP commonly endorse changes in mood, anxiety, and cognition, and may use substances, contributing to phenomenological heterogeneity and delayed identification of psychosis. The

clinician needs to be comfortable with diagnostic uncertainty in FEP (99,100). Initial diagnoses of affective psychosis (i.e., major depressive or bipolar disorder) may change to non-affective psychotic disorders and (less commonly) vice versa. Over time, considering clinical course, resolution of symptoms, relapse, or chronic illness, the clinical diagnosis becomes evident and remains relatively stable for SZ (36). Conveying diagnostic fluidity to the person with EP and their family members protects them from confusion and potential stigma associated with premature diagnosis and allows treatment to remain symptom focused.

Over the past 20 years, the psychiatric field has moved toward implementation of CSC in persons with EP. Here, a small interactive team of providers offers multiple treatment components in settings dedicated to young persons. Longi-tudinal assessment of psychosis and nonpsychosis symptom domains represent an important component of CSC and al-lows for more accurate eventual diagnosis. Stage-specific assessments of core psychosis symptoms include brief screeners (101–103) and structured assessments (18,104) for CHR and FEP (105,106). Other important EP assessments include mood, anxiety, cognition, substance use, and devel-opmental disorders (e.g., attention-deficit/hyperactivity disor-der, autism spectrum). Assessment of functional (role/social) capacity informs an individualized treatment plan across CSC components, minimizing disruption of the expected develop-mental trajectory in this vital developmental period. For FEP, the Early Psychosis Intervention Network Core Assessment Battery (107) was specifically developed, incorporating vali-dated and widely used instruments.

Increasingly, psychiatry has moved away from placing undue emphasis on a single intervention in FEP (i.e., antipsychotic monotherapy), instead embracing combination treatments of mostly pharmacological interventions with different behavioral modalities. CSC effectiveness and its longer-term effects beyond CSC (108) may result from synchronized delivery of multiple treatment components by a small team, albeit early benefits may not be sustained (50). In the United States, FEP services are modeled after the RAISE (Recovery After an Initial Schizophrenia Episode) trial (45) and longstanding EP services in other countries. Many young persons with EP make their own treatment decisions but remain dependent on logistical, finan-cial, and emotional support from their families. Including families in formulating an individualized treatment plan can increase implementation of services and potentially improve outcomes. While we do not want to overstate the benefits of CSC, the dedicated setting and treatment team are best positioned to adopt new approaches.

Potential Role of Biomarkers in EP Assessment

For many years, the field has explored potential biomarkers associated with psychosis. Biomarkers can improve our un-derstanding of neuropathological mechanisms involved in development of psychosis and assist in illness staging by contrasting the clinical phenotype against static or illness-phase dynamic biological markers, resulting in improved diagnosis and prediction of clinical course. Biomarkers could potentially be targeted for individualized treatment or serve as endpoints in treatment studies. Candidates for biomarkers are

derived from findings in genetics, electrophysiology, neuro-imaging, neurocognition, inflammation, and neuroendocri-nology (109). For example, in 40 individuals with CHR (110), conversion to psychosis was predicted with high accuracy by combining demographic and clinical data with blood bio-markers and quantitative electroencephalography (EEG). Similarly, a baseline panel of 15 serum analytes modulating immune system function, hypothalamic-pituitary function, and oxidative stress differentiated CHR persons who developed psychosis from unaffected individuals with high predictive validity (111). While promising, larger-scale and adequately powered studies are necessary to explore the role of bio-markers in psychosis detection and how they can inform treatment course.

Cognition represents a strong predictor of functional outcome and quality of life in SZ (112). The illness is associated with dysfunction in multiple domains, including attention, WM, semantic memory, executive functioning, and social cognition. Cognitive difficulties may present in the predromal phase, can worsen during prodomal and FEP phases, and respond poorly to existing interventions. Even in EP patients whose positive psychotic symptoms are effectively treated, cognitive diffi-culties (113), particularly in WM, significantly affect indepen-dent daily functioning and scholastic and occupational advancement. PFC-dependent WM impairment (77) presents an endophenotypic marker of psychosis, given its occurrence irrespective of clinical acuity (114–116) and in unaffected first-degree family members (117,118). In fact, WM may differen-tiate between those who do versus do not transition to psy-chosis (119). Thus, WM represents a highly suitable candidate as a biomarker and target of novel interventions in EP. The recently established Accelerating Medicines Partnership-Schizophrenia represents a ground-breaking new phase in EP research (120). The Accelerating Medicines Partnership–Schizophrenia is a global partnership among the National In-stitutes of Health, the U.S. Food and Drug Administration, and multiple public and private organizations. The Accelerating Medicines Partnership–Schizophrenia focuses specifically on CHR to identify promising biological targets and biomarkers and build an infrastructure for testing CHR-specific treatments in over 2000 youths. Over 2 years, participants will undergo clinical and biomarker assessments, including psychopathol-ogy, cognition, genetics, behavior, language analysis, and brain structure and function, to evaluate whether biomarkers can predict individual clinical trajectories. The Early Psychosis Intervention Network (121), through eight regional hubs including over 100 FEP clinics in 17 states, represents a similar but more intervention-oriented initiative to develop improved CSC models.

Implementing Biomarkers Into CSC for EP and Potential Novel Compounds

Large-scale networks focused on phenotyping EP provide a promising platform to investigate specific and individualized treatments, based on both conceptual models of neuro-developmental staging and empirical findings provided by biomarkers. During this stage of neurodevelopment and early illness, a time-limited window of opportunity exists to change the curve from poor outcome and prognosis commonly associated with more chronic illness. This assertion is sup-ported by neuroplasticity during brain development in adolescence and early adulthood, which diminishes with aging and illness chronicity. Higher rates of treatment response and remission in EP (52) support temporary potential reversibility of neurochemical brain changes associated with psychosis.

Recent biomarker studies in EP, including neuroanatomy (122,123), neurochemistry (124,125), EEG (126), peripheral in-flammatory markers (126–128), and oxidative stress (129), were found to relate to conversion to psychosis (123), anti-psychotic response (124,127), and functional outcome (122,128–130). Current advances of in-depth phenotyping in EP combining demographic, clinical, and stage-specific biomarker findings offer the exciting potential for earlier detection and more targeted treatment options improving clinical and functional outcome. Potential biomarkers in EP settings include digital phenotyping, serum analytes, genetic markers, cognitive functioning, EEG, and MRI. Digital pheno-typing in behavioral science (131) is rapidly expanding and has been implemented in persons with psychosis (132), in partic-ular actigraphy (133) and ecological momentary assessment (134), to monitor mood and activity. Serum analytes can include markers of stress, inflammation, and oxidative stress (135). Molecular genetic studies (13,136) have identified vari-ations in neurotrophic, serotonin, cell adhesion, and sodium-channel systems and their association with neurocognition and social cognition in SZ. Last, commercial pharmacogenetic testing is rapidly expanding and provides information about medication metabolism to tailor medication choices to in-dividuals (137).

Cognitive testing, EEG, and MRI can monitor possible bio-markers but are more labor intensive and costly, requiring access to suitable equipment. Cognitive batteries exist in pa-per and computerized format that can be administered online. The MATRICS Consensus Cognitive Battery (138) has been widely implemented in SZ. The PhenX Toolkit, a Web-based catalogue of high-priority assessment measures (139) for close to 1000 conditions, also includes neurocognition (140). Promising biomarker paradigms in EEG include mismatch negativity (141), steady-state responses (142), and resting EEG (143). Structural brain MRI can reveal minor developmental abnormalities or, rarely, clinically significant abnormalities; multivariate patterns of subtle structural changes can help predict psychosis transition risk and functional outcomes in CHR (33). Potential utilization of biomarkers, either alone or in combination, in identifying illness, monitoring progression, and governing treatment choices remains a promising concept.

An area of particular promise is the incorporation of bio-markers into interventional studies. Past studies have shown that antipsychotics do not prevent psychosis (144), but mod-ulation of the dopaminergic system remains a focus of psy-chosis intervention. For example, as outlined above, selective enhancement of prefrontal D1R signaling may enhance pre-frontal cortical activity and downregulate mesolimbic hyper-activity associated with psychosis symptoms. Over the past 20 years, multiple efforts have attempted to augment cortical glutamate functioning based on the NMDA hypothesis in SZ (145). While exploration of NMDA receptor hypofunctioning has informed our understanding of SZ pathophysiology, modulation of NMDA activity has produced variable success

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using glycine, D-serine, and cycloserine (146) or allosteric metabotropic glutamate receptor (147) agonists. Other potential agents exist for addressing cortical excitatory-to-inhibitory balance imbalance proposed by the model put forth by Krystal and Anticevic (55) and warrant further investigation. These include GABA agonists, N-acetylcysteine, α7 nicotinic acetylcholine receptor agonists, and D-amino acid oxidase inhibitors. Potential candidate interventions via non-dopaminergic mechanisms include fatty acids, modulation of serotoninergic or cannabinoid systems, and immunomodulators (e.g., nonsteroidal anti-inflammatory medications, antioxidants, nutrients, vitamins, and anti-inflammatory herbal products). Beyond pharmacological approaches, cognitive and neuromodulatory interventions, either alone or in combination, also hold promise and may benefit from incorporation of phase-specific biomarkers.

CONCLUSIONS

Development and dissemination of standardized CSC in EP has been a fairly recent development. CSC care, providing an individualized multimodal approach, represents our best option to retain patients in treatment and can be further enhanced through implementation of biomarkers. Early years of illness represent a critical and narrow window for potential recovery or significant clinical improvement. CSC programs also offer ideal settings to explore novel interventions in EP. In concert with biomarkers, employing pharmacological or behavioral interventions in EP before progression to more chronic or relapsing illness offers the opportunity to stabilize or reverse the proposed dynamically developing cortical dysfunction. WM functions mediated by prefrontal physiology hold particular promise as an early biomarker with a strong relationship to outcome (77). Based on our conceptual model, WM provides a promising target of specific interventions in early illness, before PFC maturation is completed, and this impairment becomes more difficult to modulate. Rapidly developing knowledge regarding potential mechanistic biomarkers, linked with new large-scale efforts toward standardized assessment in CHR/UHR and EP, positions the field to discover developmentally informed phase-specific interventions that are both standardized and personalized. These efforts should ultimately encompass a broad array of options for prevention and treatment, including medications, neuromodulation, psychotherapy, and cognitive remediation, to improve long-term outcomes.

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