Recent advances in understanding schizophrenia

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Abstract

Schizophrenia is a highly disabling disorder whose causes remain to be better understood, and treatments have to be improved. However, several recent advances have been made in diagnosis, etiopathology, and treatment. Whereas reliability of diagnosis has improved with operational criteria, including *Diagnostic and Statistical Manual of Mental Disorders*, (DSM) *Fifth Edition*, validity of the disease boundaries remains unclear because of substantive overlaps with other psychotic disorders. Recent emphasis on dimensional approaches and translational bio-behavioral research domain criteria may eventually help move toward a neuroscience-based definition of schizophrenia. The etiology of schizophrenia is now thought to be multifactorial, with multiple small-effect and fewer large-effect susceptibility genes interacting with several environmental factors. These factors may lead to developmentally mediated alterations in neuroplasticity, manifesting in a cascade of neurotransmitter and circuit dysfunctions and impaired connectivity with an onset around early adolescence. Such etiopathological understanding has motivated a renewed search for novel pharmacological as well as psychotherapeutic targets. Addressing the core features of the illness, such as cognitive deficits and negative symptoms, and developing hypothesis-driven early interventions and preventive strategies are high-priority goals for the field. Schizophrenia is a severe, chronic mental disorder and is among the most disabling disorders in all of medicine. It is estimated by the National Institute of Mental Health (NIMH) that 2.4 million people over the age of 18 in the US suffer from schizophrenia. This illness typically begins in adolescence and derails the formative goals of school, family, and work, leading to considerable suffering and disability and reduced life expectancy by about 20 years. Treatment outcomes are variable, and some people are successfully treated and reintegrated (i.e. go back to work). Despite the effort of many experts in the field, however, schizophrenia remains a chronic relapsing and remitting disorder associated with significant impairments in social and vocational functioning and a shortened lifespan. Comprehensive treatment entails a multi-modal approach, including psychopharmacology, psychosocial interventions, and assistance with housing and financial sustenance. Research to date suggests a network of genetic, neural, behavioral, and environmental factors to be responsible for its development and course. This article aims to summarize and explain recent advancements in research on schizophrenia, to suggest how these recent discoveries may lead to a better understanding and possible further development of effective therapies, and to highlight the paradigm shifts that have taken place in our understanding of the diagnosis, etiopathology, and treatment.

Historical background and diagnosis

The concept of schizophrenia as a disease entity has undergone major changes over the past century. Kraepelin distinguished chronic psychoses from functional decline, which he termed dementia praecox, and episodic psychoses, which he called the manic-depressive insanity [1]. Subsequent literature pointed to considerable symptomatic overlap between these disorders, leading to the rather loosely defined, and therefore unreliable, diagnosis of schizoaffective disorder [2]. Over the past century, these categories have—to a large extent—remained the same, as summarized in the current classificatory systems: the DSM and the International Classification of Diseases (ICD) [3].

A noteworthy recent development in psychiatry was the release of the fifth edition of the DSM in 2013. Although no major changes were made to the definitions of schizophrenia and other psychotic disorders, efforts were made to increase simplicity of diagnoses. First, the Kraepelinian subtyping of schizophrenia into paranoid, disorganized, catatonic, and undifferentiated type was eliminated because of a lack of evidence supporting the validity of these distinctions. Second, catatonia was moved to become a specifier across diagnoses rather than a schizophrenia subtype. Third, a more longitudinal approach to this diagnosis was defined. Finally, the previous emphasis on Schneider's [4] "first rank" symptoms (i.e. delusions of thought broadcast and thought insertion) and bizarre delusions was eliminated. Although all this improved the ease of use of the criteria, the validity of these boundaries remained largely in question.

Over the past two decades, it has become increasingly clear that there are neurobiological [5], genetic [6], and treatment response [7] overlaps between these disorders, bringing into question the validity of these categories [8]. A dimensional approach to psychopathology and the view that biological impairments may cut across categories have led to the recent introduction of the research domain criteria (RDoC). RDoC [9] refers to a framework of representing accruing information across molecular, cellular, circuit, and behavioral domains agnostic to symptom-based diagnoses. Although this approach is still in its infancy, it might offer a useful framework for future research that may yield a neuroscience-informed classificatory system [8].

There has also been interest in defining schizophrenia beyond the symptoms listed in the DSM, with recent consideration of cognitive decline as a core feature with psychosis considered by some as a later development [10, 11]. Along these lines, there have also been significant efforts to better understand and characterize schizophrenia at earli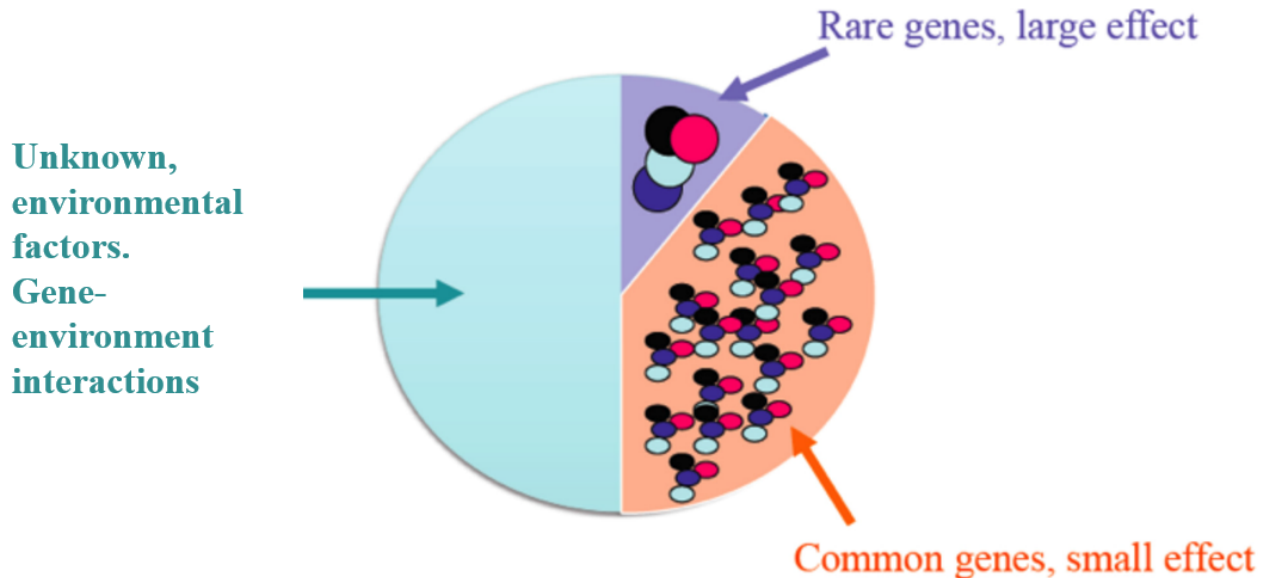er stages of the illness with the concept of schizophrenia prodome, which became of increasing clinical interest [12]. Schizophrenia prodrome, sometimes referred to as ultra-high-risk state or psychosis risk syndrome, is thought to be a spectrum of attenuated positive and negative symptoms that individuals may display several years to months before converting to schizophrenia.

Recent research has begun to elucidate risk factors for conversion to psychosis, including early impaired cognitive (e.g. inattention, concentration difficulties) and social functioning [13]. Even though not all risk factors are currently known, approximately 35% of the individuals with prodromal symptoms convert to schizophrenia [14, 15]. The North American Prodromal Longitudinal Study, a large multicenter study, has begun to demonstrate substantive neuroanatomical [16], neurophysiological [17], neurocognitive [18], and neurohormonal [19] changes during the prodromal phase that may contribute to the risk of schizophrenia [20].

Pathophysiology and etiology

Schizophrenia has a substantial genetic component, with a high heritability (up to 80%), indicating that about 80% of the variation in the trait of schizophrenia may be attributed to genetic factors [21]. Genome-wide association studies (GWASs), which compare the genomes of thousands of healthy and affected individuals, have found several genes associated with increased risk of developing schizophrenia, such as *NRGN* and *ZNF804A* [22, 23]. Recent research suggests that genetic risk for schizophrenia is composed of many common genetic alterations, each with a small effect, along with a few uncommon genetic alterations with a larger impact [24]. Additionally, genes that confer risk for schizophrenia may also be associated with bipolar disorder and other psychiatric disorders [25] (Figure 1).

Various environmental factors may interact with susceptibility genes to increase the risk of schizophrenia; these interactions are the focus of an emerging area of investigation called epigenetics. One of the few replicated findings in this relatively new field is an interaction between cannabis use and the *AKT1* gene on the risk of psychosis [26, 27]. Other findings in epigenetics that have not yet been replicated include interactions between a history of fetal hypoxia and hypoxia-related genes on volume of the hippocampus [28] and interactions between childhood trauma and variants of the serotonin transporter [29] and *COMT* gene [27] on cognitive functioning. Although epigenetics research has the potential to greatly impact clinical practice, few studies have attempted to replicate findings. Among those studies attempting replication, few have been able to confirm

Figure 1. Etiology of schizophrenia

The multifactorial etiology of schizophrenia including a) rare genes that have a large effect, b) common genes that have a small effect, and c) the environmental factors and gene-environmental interactions that confer risk for schizophrenia.

previous findings, implying possible publication bias and a need for larger sample sizes in this type of research [30].

Although early neurobiological theories of schizophrenia largely focused on excessive dopamine, more recent research reflects a more nuanced role of dopamine and has pointed to the importance of other neurotransmitters such as GABA and glutamate. Recent animal models [31] and genetic studies of humans [32] suggest that hypofunction of the N-methyl-D-aspartate (NMDA) glutamatergic receptor may underlie schizophrenia. Glutamate models of schizophrenia may provide an additional explanation to the dopaminergic models for the cognitive symptoms of this illness and may ultimately yield novel pharmacological treatment approaches [33].

Neuropathology research indicates that schizophrenia is characterized by abnormal maturation of prefrontal networks during late adolescence and early adulthood, likely due to excessive pruning of synapses and dendritic spines [34, 35]. Pre- and post-synaptic abnormalities in inhibitory neurons such as the parvalbumin interneuron may disturb these critical neurodevelopmental processes [36]. Recent research using optogenetics indicates that parvalbumin interneurons may influence gamma oscillations, which in turn are associated with cognitive function [37]. Myelination (another critical neurodevelopmental process) is also abnormal in schizophrenia, as

shown by post-mortem studies demonstrating reduced expression of myelin basic protein in cortical regions [38]. Disturbances in both myelination and the inhibitory control of synaptic pruning may contribute to cognitive deficits in schizophrenia [39]. These recent advances in neuropathology build upon previous post-mortem research demonstrating reduced neuropil, but not a reduced number of neurons, in the brains of adults with schizophrenia [40].

Recent studies have shown compelling evidence that neuropathological changes in schizophrenia might set in during the critical period of adolescence, proximal to the onset of psychosis. Gray-matter declines appear to occur in the early phase of schizophrenia and may be related to poorer outcomes. The early phase of psychosis may also be associated with elevations in presynaptic dopamine turnover [41] as well as increases in glutamatergic activity [42]. These observations highlight the importance of early recognition and intervention targeted to the pathophysiological processes close to the onset of psychosis.

In the past several years, inflammation and oxidative stress have re-emerged as potentially important aspects of pathophysiology in a subset of affected individuals. Multiple studies have demonstrated elevated levels of cytokines and other signs of immune system activation in individuals with psychosis [43, 44], and genetic

studies have reported correlations between schizophrenia and genes involved in the immune response [23]. Recent rodent work has observed that exposure to infectious or inflammatory agents *in utero* can lead to behavioral and neurobiological alterations resembling those seen in schizophrenia [45]. Oxidative stress, which is associated with inflammation, may also be elevated in schizophrenia. For example, a recent meta-analysis of studies on oxidative stress markers observed reduced levels of the anti-oxidant red blood cell superoxide dismutase in schizophrenia [46].

Additionally, some recent work has focused on auto-immune dysfunction as a cause of psychosis. For example, anti-NMDA-receptor encephalitis is a potentially treatable but under-diagnosed cause of psychosis that results from the production of antibodies against NMDA receptors [47]. A number of young individuals presenting with their first episode of psychosis may have detectable auto-antibodies against this receptor or other neuronal proteins, such as voltage-gated potassium channels [48]. In addition, epidemiological data suggest a bi-directional association between psychosis and some common autoimmune diseases: individuals with one type of illness are at greater risk of developing the other type [49]. The potential therapeutic applications of these findings are being actively explored.

Various forms of imaging research have been critical in advancing our understanding of the neurobiology of schizophrenia. Studies have reported subtle structural alterations, including enlargement of the third and lateral ventricles, slight reductions in whole-brain gray matter volume, and slight reductions in the volumes of temporal, frontal, and limbic regions [50, 51]. Functional imaging studies have observed reduced activation of the dorsolateral prefrontal cortex during tasks of executive function [52] and abnormalities of limbic system activation during tasks involving emotional stimuli [53]. In addition, studies using diffusion tensor imaging, a method of visualizing white matter, have found evidence of white matter changes in frontal and temporal lobes that would imply decreased connectivity among these regions [54]. Together, these findings support the conceptualization of schizophrenia as a disorder of brain connectivity [55]. Studies in the past few years have used various forms of network analysis to uncover decreased regional connectivity in both first-episode schizophrenia [56] and the broader psychotic spectrum.

The next major challenge is to translate neuroimaging findings into the clinical setting. Consequently, recent research has started to integrate various imaging modalities with genetic, electrophysiological, and clinical data to identify biomarkers, which may eventually be relevant for clinical diagnosis and management.

Pharmacological treatments in schizophrenia

Antipsychotic drugs have been the mainstay of schizophrenia treatment since the introduction of chlorpromazine, focusing on decreasing the frequency and severity of psychotic episodes as well as improving the functional capacity of individuals with schizophrenia [57]. However, adverse effects and suboptimal outcomes associated with first-generation antipsychotics (FGAs) led to the development of second-generation antipsychotics (SGAs), which due to their 5HT-2A antagonism are generally associated with reduced extrapyramidal symptoms (EPSs) as compared with FGAs [58]. However, there is controversy concerning the categorization of FGA and SGAs; some literature differentiates them based on their ability to cause EPSs, whereas other studies base it on their antagonism of the dopamine D-2 receptors [59, 60]. The first and most efficacious SGA for the treatment of refractory schizophrenia, clozapine, is limited by the risk of agranulocytosis, which necessitates the use of periodic monitoring of blood cell counts. EPSs are lowest with clozapine and highest with haloperidol. All drugs except haloperidol, ziprasidone, and lurasidone produce more weight gain, with olanzapine and clozapine producing the greatest weight gain. Prolactin elevation is highest with risperidone and paliperidone. All drugs, except for amisulpride, paliperidone, sertindole, and iloperidone, are significantly more sedating than placebo [61].

Several large-scale investigations suggest no clear superiority of SGAs over FGAs among first-episode patients [62] or chronic patients [63] in regard to positive, cognitive or social outcomes [64]. Furthermore, both FGAs and SGAs do not sufficiently target negative symptoms (with only olanzapine and asenapine showing moderate effects [65-67]) and sometimes insufficiently treat positive symptoms [68, 69]. Clozapine seems to be the most effective medicine, whereas the effectiveness of olanzapine and risperidone over other antipsychotics remains controversial [61, 70-72]. In terms of relapse prevention, SGAs have a modest benefit compared with FGAs [73]. Newer antipsychotics such as asenapine, iloperidone, lurasidone, and paliperidone do not seem to be significantly better than haloperidol [61], and for the treatment of refractory schizophrenia, clozapine has been shown to be significantly more efficacious than other agents [74-78]. However, several studies suggest that olanzapine and risperidone have greater efficacy over other antipsychotics, but this remains controversial and more research is necessary in this area. Additionally, amisulpride, olanzapine, clozapine, paliperidone, and risperidone show significantly lower all-cause discontinuation than several other agents [61, 79-81].

The Schizophrenia Patient Outcome Research Team (PORT) summarized strong empirical support for both FGAs and SGAs in acute and maintenance treatment of schizophrenia and for the use of clozapine for treatment-resistant positive symptoms, hostility, and suicidal behaviors [82].

Research over the past decade further investigated agents that stimulate the NMDA glutamate receptor, including partial and full agonists at the glycine site and glutamate 2/3 receptor agonists, and found that they may ameliorate negative symptoms with some success if used in conjunction with antipsychotics [83]. The PORT concludes, however, that there is still limited information on the use of adjunctive pharmacological agents as well as the treatment of co-occurring substance abuse [82]. None of the pharmacological agents to date effectively ameliorate cognitive deficits, which are a core feature of schizophrenia; larger and more rigorous studies are needed to examine the potential pro-cognitive effects of medications that impact dopaminergic, nicotinergic, glutamatergic, GABAergic, and other novel targets [84].

Long-acting injectable antipsychotics are helpful in treating patients with poor medication adherence and have more controlled distributions in the body; for these reasons, they are superior to oral antipsychotics in preventing hospitalizations [85] and may foster a better therapeutic alliance. Both FGA (haloperidol and fluphenazine) and SGA (risperidone, paliperidone, olanzapine, and aripiprazole) medications are now available as long-acting preparations. Recent preliminary investigations suggest a therapeutically beneficial response to dose reduction and alternate day dosing [86] in the early stages of remitted first-episode psychosis. However, more research is needed to confirm these observations [87].

Recent advances in the understanding of schizophrenia have restored interest in inflammatory and oxidative stress pathways as the pathogenesis for a subset of patients. Research on human and animal models supports this new insight [88-93]. In a review by Sommer *et al.*, 26 double-blind randomized controlled trials reported on the efficacy of anti-inflammatory agents such as aspirin, celecoxib, davunetide, fatty acids (eicosapentaenoic acids and docosahexaenoic acids), estrogens, minocycline, and antioxidants such as *N*-acetylcysteine (NAC) as treatment augmentation for schizophrenia [94]. Aspirin, estrogens, and NAC showed significant effects; in contrast, celecoxib, minocycline, davunetide, and fatty acids showed no significant difference [95]. Whereas more research is needed to investigate the therapeutic effects of both current and novel anti-inflammatory agents, current evidence does suggest a benefit in treating inflammation.

Pharmacogenomics is a growing field in the treatment of schizophrenia and can bring the field of psychiatry closer to achieving evidence-based personalized medicine with the goals of predicting better treatment response and reducing medication-induced side effects. For example, polymorphisms in the serotonergic system are associated with the efficacy of clozapine and risperidone, dopamine D_3 receptor polymorphisms are associated with response to clozapine and olanzapine, and D_2 variants are associated with the efficacy of risperidone [96]. As for side effects, the serotonergic system (HTR2C) and hypothalamic leptin-melanocortin genes (MC4R) can predict antipsychotic-induced weight gain [97, 98], cytochrome P450 (CYP2D6) and dopamine receptor variants are associated with tardive dyskinesia [96, 99], and major histocompatibility complex (human leukocyte antigen [HLA]) markers have been consistently found to be associated with clozapine-induced agranulocytosis. However, despite progress made in pharmacogenomics, the field has encountered obstacles such as replication inconsistencies, small study sizes, and lack of randomized control trials.

Psychosocial treatments

Antipsychotic medications are a necessary but not sufficient treatment for schizophrenia. The broad objectives of treatment should be reducing the frequency and severity of episodes of psychotic exacerbation as well as improving the functional capacity and quality of lives of the individuals afflicted with the illness. Thus, in tandem with research over the past decades, the urgently needed multimodal care has continued to evolve. Psychoanalytic treatments beginning in the early 20th century seemed to insufficiently address the burden caused by the illness. In the early '60s, major role therapy and family psychoeducation were introduced based on the interpersonal and family theories of psychosis. With further research in the field and increased knowledge about the nature of the specific deficits (cognitive, social, and affective), more disease-specific psychotherapies started to develop in the '80s and '90s. These therapies target both pathophysiology and other core manifestations of the disease.

The PORT recently provided an extensive summary of the current evidence-based psychosocial treatment [100]. Cognitive behavioral therapy (CBT) is based on the theory that the way we interpret events has cognitive, emotional, and behavioral consequences, which lead to the creation and maintenance of unhelpful responses. CBT has been a successful approach for other mental illnesses such as depression [101] and anxiety [102]. More recently, CBT has been applied to the treatment of positive as well as negative symptoms. Research shows that CBT can improve positive symptoms [103, 104] but is less consistent with the improvement of negative symptoms [105, 106].

A recent review shows that CBT may mostly be efficient in the short term (i.e. more than 12 months) [107].

Social skills training (SST) is based on a behavioral model that targets the improvement of a person's ability to function skillfully in social situations (i.e. interactions). SST has emerged among the possible treatments for schizophrenia [108] to address social skill deficits primary to developmental derailments but also secondary due to both positive and negative symptoms [109]. SST has been found to improve both positive and negative symptoms [106], and some of the improvements may persist at follow-up [110].

Family therapy is based on a model that suggests that problematic behaviors are maintained and created by patterns in systems (i.e. proximal or distal family) [111]. System theory underlies the multifamily treatment approach that includes coping recommendations, problem solving, crisis intervention, reduction of pathogenic interactions such as high "expressed emotions" (e.g. criticism, hostility), and (in its core) psychoeducation. Psychoeducation enables not only the patient but also the family and others to recognize early warning signs, which is particularly important in an illness that shows such high vulnerability to stress.

Assertive community treatment (ACT) offers a multidisciplinary approach that is usually combined with SST, CBT, or any personal support. Teams include peer support specialists and practitioners with expertise in psychiatry, substance abuse treatment, and employment. Although ACT reduces time in the hospital for mental illnesses in general [112], it seems specifically to improve housing stability [113] and reduce hospitalization rates, especially in patients with higher baseline hospitalization rates [113].

Personal therapy was developed by Hogarty *et al.* [114] on the basis of supportive psychotherapy. It is one of the few approaches that was designed specifically for people suffering from schizophrenia and combines SST with some common elements of CBT. Personal therapy is modeled to the phases of recovery; thus, it is a long-term endeavor and seems to decrease the probability of relapse [115].

Cognitive remediation therapy (CRT) is a computer-based intervention that was originally designed to improve deficient cognitive abilities (e.g. attention, memory, and executive function) in people with traumatic brain injury [116] but since has proven to help in people with depression [117], eating disorders [118], and schizophrenia [117]. Whereas CRT by itself has no effect on improving negative symptoms [119], the combination of CRT with SST, groups, and problem solving has been found to be promising [120]. Although preliminary results showed improvements in speed of processing, attention, working memory, executive function, and social cognition in a cognitive enhancement therapy (CET) compared with a personal therapy group, rigorous validation is needed, and the durability of these improvements remains to be investigated.

For many patients the ability to resume work or school is the ultimate goal. Thus, supported employment interventions are of significant importance – the most commonly studied being the Individual Placement and Support (IPS) [121] model. An important principle of the IPS model is that minimal pre-vocational training is provided, and the job itself becomes the primary training environment. There is clear evidence that supported employment strategies help return people with schizophrenia to work [122], even for young people with their first episode of psychosis [123]. A recent meta-analysis of a total of 11 studies found that competitive employment rates were 61% for patients and 23% for controls and that about 30% out of the 61% worked more than 20 hours weekly. Supported employment further increased the duration of employment (47% of the 52-week year) and the time of onset of employment (approximately 10 weeks earlier than controls). In conclusion, the effect sizes support the effectiveness of evidence-based supported employment as one of the most robust interventions.

Given the clinical heterogeneity of schizophrenia, it is important to choose the right treatment for the right patient; thus, although supportive treatment might benefit all symptom domains, CBT may be particularly beneficial for those with residual psychotic symptoms and cognitive remediation, SST for those with cognitive or social cognition deficits or both, and ACT for those at risk for frequent hospitalizations or those who have had recent homelessness. There is increasing emphasis on tailoring psychotherapeutic interventions to the phase of the illness (e.g. personal therapy), since the primary goals of intervention might vary across phases. More research is needed, however, to examine active ingredients of the therapeutic modalities that work and to identify the synergistic effects of combinations of interventions that are hypothesis-driven and cost-effective.

Conclusions and Future directions
In summary, although our understanding of the causes and treatments of schizophrenia remains limited, several important paradigm shifts have occurred. The diagnosis of schizophrenia is still symptom-based, but increasing amounts of data point to the large genetic and neurobiological overlaps between psychotic, affective, and

developmental disorders, suggesting that future classifications of these illnesses need to move toward more evidence-based, valid, and biologically based categories and dimensions. Pathophysiology is now seen as developmentally mediated alterations in neuroplasticity, manifesting in a cascade of neurotransmitter and circuit dysfunctions setting in around adolescence. Etiology is now seen as an interaction between multiple genes of small-effect and some rare large-effect genes and unknown environmental factors. These observations may help therapeutic interventions move beyond the current sole focus on dopamine toward novel therapeutic targets such as glutamate, GABA, and calcium channels. The focus of intervention has expanded beyond relief of psychotic symptoms alone toward restoring functionality by targeting dimensions such as cognitive deficits and negative symptoms. Research is intensifying on the possible utility of several evidence-based psychotherapy modalities in combination with pharmacological approaches. Treatments are still based on serendipitous discoveries from decades ago, and the urgent need is to discover novel interventions based on etiopathology. Finally, recent incremental advances in understanding the etiopathology have motivated vigorous prevention approaches in early phases of the illness and early interventions with novel pharmacological targets and plasticity-based treatments such as cognitive remediation.

Abbreviations

ACT, assertive community treatment; CBT, cognitive behavioral therapy; CRT, cognitive remediation therapy; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; EPS, extrapyramidal symptom; FGA, first-generation antipsychotic; IPS, Individual Placement and Support; NAC, *N*-acetylcysteine; NMDA, N-methyl-D-aspartate; PORT, Schizophrenia Patient Outcome Research Team; RDoC, research domain criteria; SGA, second-generation antipsychotic; SST, social skills training.

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