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SPECIAL ARTICLE

Beyond the facts in schizophrenia: closing the gaps in diagnosis, pathophysiology, and treatment

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Background. Although schizophrenia has been considered a distinct disease entity for the past century, its precise definition and etio-pathophysiology remain obscure and its treatment remains unsatisfactory. In this review, we summarize our state of knowledge about the etiology, pathophysiology, clinical features, and treatment of schizophrenia.

Methodological Issues. The inadequacy of the major conceptual models of schizophrenia is a major roadblock in providing a coherent explanation for the known facts of this illness, despite these limitations and its changing definitions, the construct of schizophrenia does convey useful information: (i) patients diagnosed as having schizophrenia do have a *real disease* – they experience both suffering and disability; (ii) a diagnosis of schizophrenia does suggest a *distinctive clinical profile* – a characteristic long-term course; an admixture of positive, negative, and cognitive symptoms; (iii) a diagnosis of schizophrenia has clear treatment and prognostic implications – likelihood of benefit from antipsychotic treatment and likelihood of incomplete recovery; and (iv) schizophrenia satisfies criteria for a valid diagnostic entity better than almost any other psychiatric diagnosis.

Discussion. On the other hand, the concept of schizophrenia has serious shortcomings. First, it is not a single disease entity – it has multiple etiological factors and pathophysiological mechanisms but common phenotypic features. Second, its clinical manifestations are so diverse that its extreme variability has been considered by some to be a core feature. Third, its boundaries remain ill defined and not clearly demarcated from other clinical entities.

Conclusions. A necessary next step is to deconstruct schizophrenia as an entity into component dimensions – endophenotypes linked to unique etiological and pathophysiological processes that may yield unique treatment targets. Innovative approaches are needed to elucidate the biological substrates of these entities because such clarity is vital for replicable research. We conclude by identifying the critical gaps in our knowledge, and unmet needs in our approaches to care, and outline steps that can move the field forward.

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Introduction

Schizophrenia is arguably one of the most challenging diseases in all of medicine. The challenge is not just in terms of the burdens of suffering and disability inflicted by this illness, the as-yet unclear nature of its causation, the complexities of diagnosis and the limits of treatment, but also its threat to our broad concepts of illness and disease. The last several decades have witnessed an impressive expansion of our knowledge base about this illness, which we summarized in a series of 'Schizophrenia – just the facts' papers recently (Tandon *et al.* 2008*a*, 2008*b*, 2009, 2010; Keshavan *et al.* 2008, 2011). In this paper, we synthesize the key points made in these papers, will attempt to identify the gaps in knowledge as well as unmet needs for each area of knowledge (Table 1), and will outline the important steps needed to move this field forward.

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Clinical features of schizophrenia

Schizophrenia is generally referred to as a major psychotic disorder; Kraepelin was more impressed by its cognitive impairment and labeled it 'dementia praecox' (Kraepelin, 1919; reprinted as Kraepelin, 1971). Bleuler was more impressed by the thought disorder (which led him to coin the term 'schizophrenia') reflecting a splitting of associations (Bleuler, 1911). He also highlighted the negative symptoms as

Table 1. *Knowledge gaps in schizophrenia: questions begging for answers*

Etiology
1. How do the genes implicated in the etiology of schizophrenia increase the risk for the illness?
2. How do the implicated environmental risk factors for schizophrenia increase the liability for the illness?
3. How do the genetic and environmental risk factors implicated in schizophrenia interact to mediate the increased illness liability?
4. How do we best define the etiology–pathophysiology–disease expression chain?
Pathophysiology
5. What are the neuropathological underpinnings of the observed structural and functional alterations?
6. Among the observed pathophysiological changes, which are the causal factors, which are the consequences, and which are the compensatory changes?
7. Which are the animal model(s) that best approximate the clinical syndrome of schizophrenia?
Clinical
8. Do any of the biomarkers validate current diagnostic constructs?
9. Are there any valid and reliable early clinical/biological predictors of later emerging illness?
10. Can dimensional approaches to diagnoses be developed in a clinically useful manner?
11. Are there any valid and reliable clinical/biological predictors of relapse/functional decline?
12. Does schizoaffective disorder represent a valid diagnostic entity, or are psychotic disorders better represented as a spectrum?
13. How can we best incorporate clinical (e.g. cognition) and biological endophenotypes (e.g. brain structure) into diagnostic guidelines?
Treatment
14. How best can we translate basic neuroscience findings into physiologically specific new treatments with a high effect size (>1) and minimal side-effects?
15. What are the best treatments to improve cognitive deficits in schizophrenia?
16. What are the best treatments to reverse the negative symptoms of schizophrenia?
17. How best can we move patients from prisons back to a clinical setting?
18. Can measurement-based care be routinely implemented in community settings?
19. What are the best ways to cost-effectively deliver evidence based treatments to the most needy patients in the community?

'fundamental', while regarding the psychotic symptoms as 'accessory'. Interestingly, Kurt Schneider who proposed the 'first-rank symptoms' of schizophrenia (Schneider, 1959) focused entirely on delusions and hallucinations and almost ignored the negative and cognitive features that are currently regarded as the main causes of functional disability in schizophrenia (Green, 1996).

The concept of schizophrenia has changed over the past half-century (Bruijnzeel & Tandon, 2011) as reflected in Diagnostic and Statistical Manual (DSM) definitions of schizophrenia from the first to the fourth revised edition (American Psychiatric Association, 1952, 2000), which reflect the evolution in our understanding of its core clinical characteristics, incorporating various symptom domains as follows (items 1–6 are core domains and the rest are additional features):

1. Positive symptoms: which comprise the psychotic symptoms of delusions and hallucinations, and agitation.
2. Disorganization of speech and behavior, including derailment of thought.
3. Negative symptoms: which include avolition, amotivation, alogia, and inappropriate affect (from flat and blunted to incongruous) (Andreasen, 1982).
4. Cognitive deficits: which include severe impairments in memory, executive functions, and learning (Saykin *et al.* 1991; Keefe, 2005).
5. Mood symptom: including depression and suicidal urges as well as hostility, aggression, and homicidal urges (Yung & McGorry, 1996; Hafner & an der Heiden, 1999).
6. Neuromotor symptoms: which include varying degrees of catatonia, stereotypic movements, dystonia, akathisia, hypokinesia, and dyskinesia (all in the drug-naïve phase, not secondary to medications) (Honer *et al.* 2005; Morrens *et al.* 2007).
7. Disorders of self-integrity, which includes loss of self/non-self-boundaries, depersonalization, de-realization, and lack of a sense of urgency or insight (Raballo *et al.* 2011).
8. Minor physical anomalies: including a furrowed tongue, high-arched palate and abnormal dermatoglyphics (Compton *et al.* 2007).
9. Soft neurological signs: including right–left confusion, mirroring, dysiodokinesia, clumsiness,

perseveration/repetitive movements (Nasrallah *et al.* 1982; Heinrichs & Buchanan, 1988).
10. Psychiatric comorbidities: both axes I and II including depression, anxiety, OCD, eating disorders, sexual disorders, and sleeping disorders as well as mental retardation, schizoid or paranoid or schizotypal personality disorder (Braga *et al.* 2004), substance abuse is a very common comorbidity condition (Lubman *et al.* 2010).
11. Medical comorbidities: including metabolic disorders such as diabetes, dyslipidemia, and hypertension, which can become worse with some antipsychotic medication (McEvoy *et al.* 2005).

Schizophrenia is now recognized to be a lifetime disorder starting from birth and manifesting throughout life with different manifestations and stages (Tandon *et al.* 2009) including the following:

1. Infancy: erratic developmental milestones often delayed (such as walking), as well as neurological soft signs and dysregulation (Fish, 1957; Fish *et al.* 1968).
2. Childhood: social anxiety, shallow affect, neuromotor abnormalities, lack of friends, and a decline in school performance between age 8 and 11 (Done *et al.* 1994).
3. Prodromal phase: in early to mid teens characterized by a variety of non-psychotic symptoms and attenuated psychotic symptoms as well as various negative symptoms and cognitive decline (McGorry *et al.* 2006).
4. First-episode psychosis: the emergence of psychotic symptoms usually occurs between age 17 and 25 in males and somewhat later (20–30) in females. Delusions, hallucinations, bizarre behavior, and severe thought disorders appear during this first episode along with prominent negative symptoms and substantial cognitive decline. Response to antipsychotic treatment in patients with first episode is usually faster and more favorable than in their more chronic counterparts (Weiden *et al.* 2007).
5. Recurrent psychotic episodes with deterioration: this phase is usually triggered with poor adherence to medications, resulting in repeated re-emergence of psychotic symptoms, less optimal response to antipsychotic medication, and the increasing prominence of negative symptoms and cognitive impairments. Suicide risk is high during this phase.
6. Residual phase: after several years of recurrent psychotic episodes, the patient settles into a chronic state of unremitting positive, negative, and cognitive symptoms, severe social and vocational dysfunction (McGlashan & Fenton, 1993).

The course of schizophrenia is usually a deteriorative one in over 80% of patients (Tsuang *et al.* 1979). Recovery has been documented in about 20% of patients with reliably diagnosed schizophrenia. Mortality is high in schizophrenia from all causes (Brown *et al.* 2000). About 5–10% of patients with schizophrenia will die of suicide (Pompili *et al.* 2008) and another 2–5% may commit a violent or homicidal act (Large & Nielssen, 2011). Most of the deaths in schizophrenia are due to cardiovascular disease, which is inadequately treated in a majority of patients due to lack of treatment and disparity of care (Nasrallah *et al.* 2006). Finally, with the wholesale closure of state psychiatric facilities around the country during the deinstitutionalization period (1970–1990), a substantial number of persons with schizophrenia are currently incarcerated in jails and prisons that have become the new 'asylums' but with a criminal not a medical context, which is deplored by many psychiatrists, advocates, and observers.

The conceptualization of schizophrenia has evolved substantially over the past century (Tandon & Maj, 2008), but especially over the past three decades with the acceleration of neuroscience research and the increasing sophistication of research methods. The thrust of the investigation leads to several broad and important models of the clinical concept of schizophrenia, especially the extensive heterogeneity of the illness in symptoms, course, and outcome (Keshavan *et al.* 2011). The clinical studies of first-degree relatives of schizophrenia also point to the heritability of several biological, cognitive, and behavioral features of the illness, leading to the concept of endophenotypes (Gottesman & Gould, 2003; Braff *et al.* 2007). This has spurred extensive research into the genetic and environmental factors in schizophrenia, as discussed in the epidemiology section of this article.

There are many questions waiting to be answered and gaps of knowledge that need to be filled about the exact clinical nature of schizophrenia (Table 1). These include the lack of biomarkers to validate the clinical construct of schizophrenia as currently diagnosed by DSM IV-TR (American Psychiatric Association, 2000). There are also very few clues to confirm early predictors of schizophrenia during the age of risk or to identify who is at risk to develop the illness. Valid and reliable clinicobiological predictors of psychotic relapse are also lacking in patients who have already begun their illness. There still does not exists a valid approach to differentiating schizophrenia from closely related disorders such as schizoaffective disorder, delusional disorder, or psychotic bipolar disorder (Tandon & Maj, 2008). The veritable surge of molecular biology and genetic findings has yet to be translated into a form that has clinical utility. Finally, there is an urgent need to translate biological

endophenotypes into the diagnostic subtyping of schizophrenia.

Epidemiology

The annual incidence of schizophrenia averages 15 per 100 000, the point prevalence averages approximately 4.5 per population of 1000, and the risk of developing the illness over one's lifetime averages 0.6% (McGrath *et al.* 2004; Saha *et al.* 2005). Schizophrenia runs in families and there are significant variations in the incidence of schizophrenia, with urbanicity (Kirkbride *et al.* 2006), male gender (Aleman *et al.* 2003), and a history of migration (Cantor-Graae & Selten, 2005) being associated with a higher risk for developing the illness. The fairly consistent relative risk of urban *v*. rural birth (2.4) across studies and the finding of a dose–response relationship between degree of urbanicity and risk of schizophrenia (Pedersen & Mortensen, 2001) support the proposition that some factor associated with urbanicity is causally related to schizophrenia. What that specific risk-modifying factor linked to urbanicity might be, however, is unclear (Cantor-Graae, 2007). The relative risk of developing schizophrenia is greater than double for immigrants than for residents. Although the association between migration and increased risk of developing schizophrenia provides the most compelling evidence supporting a role for social factors in the etiology of schizophrenia; the specific risk-mediating factor (social or biological), however, remains to be elucidated (Cantor-Graae, 2007).

The genetic basis for schizophrenia

Genetic factors contribute about 80% of the liability for developing schizophrenia and a number of chromosomal regions have been 'linked' to the risk of developing the disease (Sullivan *et al.* 2003; Tandon *et al.* 2008*b*). Environmental factors linked to a higher likelihood of developing schizophrenia include cannabis and other substance use, a history of obstetric and perinatal complications, and a history of winter birth; the exact relevance or nature of these contributions are unclear (Tandon *et al.* 2008*b*). Genetic and environmental factors need to be considered together because both are important in the etiology of schizophrenia and neither operates in isolation (van Os, 2008). How various genetic and environmental factors interact to cause schizophrenia and via which precise neurobiological mechanisms they mediate this effect is not understood.

It is well known that schizophrenia aggregates in families (Gottesman *et al.* 1987). Although over two-thirds of the new cases of schizophrenia occur sporadically, having an affected family member substantially increases the risk of developing schizophrenia. This risk increases as the degree of genetic affinity with the affected family member increases. Recent advances in the technology and science of molecular biology have substantially driven developments over the past decade and four broad approaches and combinations thereof have been utilized to elucidate the nature of genetic contributions to the etiology of schizophrenia (Gejman *et al.* 2011; Kim *et al.* 2011). Linkage studies attempt to identify chromosomal regions that are linked to differences in liability for schizophrenia. Candidate gene studies assess the association between variations in specific genes of interest and risk for schizophrenia; positional candidate gene studies combine the above two approaches. Mapping of the human genome has enabled large-scale genome-wide association studies (GWAS). What specific brain processes may be affected by such genetic variations and how this may result in schizophrenia constitutes the fourth approach to elucidating the genetic basis of schizophrenia.

What is the status of our understanding of the nature of genetic contributions to the etio-pathogenesis of schizophrenia in 2011? This is what we do know:

(i) Heritability is high and genetic factors contribute about 80% of the liability for the illness.
(ii) There is no major gene locus and a large number of susceptibility genes, each of small effect, contribute to the liability for the illness. No single genetic variation likely more than doubles the risk of developing schizophrenia across the population at large.
(iii) No gene yet appears to be sufficient or necessary for the development of schizophrenia.
(iv) Molecular genetic studies have identified multiple chromosomal regions and variations in several positional candidate genes to be linked to differential risk for developing the illness. Multiple chromosomal regions across the genome have been linked to transmission of schizophrenia and variations in several specific genes (many located in the 'linked' chromosomal regions) have been found to be associated with differences in liability for developing schizophrenia (Purcell *et al.* 2009; Stefansson *et al.* 2009).
(v) Rare copy number variations may account for a proportion of individuals with phenotypic manifestations of schizophrenia (Bassett *et al.* 2010).
(vi) GWAS confirm the association of specific alleles in chromosomal regions such as 2q32.1, 6p22-21, and 18q21.2 with schizophrenia risk, but these alleles collectively explain less than 5% of the overall liability

for schizophrenia (Psychiatric GWAS Consortium, 2009; Nieratschker *et al.* 2010; Sullivan, 2010). GWAS also show an overlap in the genetic basis of schizophrenia with autism and bipolar disorder.

Currently, the predominant genetic view of schizophrenia is that it is a heterogeneous, polygenic disease with multiple genes of small effect that are shared across populations worldwide. This 'common disease–common alleles with multiple genes of small effect' model of schizophrenia is the basis for the large-scale genetic association studies being conducted around the world in the past decade. An alternate genetic model for schizophrenia proposes that schizophrenia is better conceptualized as a highly heterogeneous genetic entity caused by multiple, highly penetrant, and individually very rare mutations of large effect that may be specific to single cases or individual families. Results of GWAS provide support for this model. A third genetic model proposed for schizophrenia is that it is not DNA sequence variation but heritable changes in gene expression (epigenetic factors) that explain its genetic origins. It is conceivable that all the above mechanisms might partially explain the genetic basis of schizophrenia.

Environmental risk factors

A variety of specific environmental exposures have been implicated in the etiology of schizophrenia. These include both biological and psychosocial risk factors during the antenatal and perinatal periods, early and late childhood, adolescence, and early adulthood. In the antenatal period, maternal infections and nutritional deficiency during the first and early second trimesters of pregnancy have been linked to an increased liability for developing schizophrenia (Penner & Brown, 2007). Although *maternal* risk factors for schizophrenia during the prenatal–perinatal period receive the most attention, older paternal age at conception has been linked to an approximate doubling of the risk for developing schizophrenia (Malaspina *et al.* 2001). Urbanicity during the childhood years and migration are important risk factors for schizophrenia, although how these effects are mediated is not completely understood. Childhood trauma and abuse (Read *et al.* 2005) and parental separation or death during childhood or early adolescence has also been linked to an increased liability for developing schizophrenia. During adolescence, cannabis use has been linked to an increased risk of developing schizophrenia. Social adversity and stressful life events have long been linked to the precipitation of schizophrenia and might also increase the liability for developing the illness.

Although a range of environmental risk exposures have been linked to liability to develop schizophrenia, none appears to be sufficient or necessary. Precisely how these factors might interact with one another and with genetic risk factors to cause schizophrenia and exactly what neurobiological processes mediate these effects remain as major 'knowledge gaps' in schizophrenia, and are key priorities for research (Table 1).

Pathophysiology of schizophrenia

Investigating the neurobiological basis of schizophrenia is critical for establishing its diagnostic validity, predicting outcome, delineating causative mechanisms and identifying targets for treatment research. As discussed earlier, in our recent 'facts' series of papers (Tandon *et al.* 2008a; Keshavan *et al.* 2011), we reviewed what is known about schizophrenia to date, and identified a limited number of key clinical facts of this illness: persistent cognitive deficits, positive and negative symptoms typically beginning in adolescence or young adulthood, premorbid alterations, and functional declines early illness in a substantive proportion of the afflicted individuals. What are the neurobiological facts that may underlie these clinical facts?

Advances in this field have occurred, largely via developments in neuroimaging, electrophysiological and neuropathological approaches. Several neurobiological alterations in domains of brain structure, physiology and neurochemistry have been documented which may reflect diverse pathophysiological pathways from the 'genome to the phenome'. A large body of literature has accumulated showing brain structural alterations in a substantial proportion of patients, including reduced volumes of gray matter in a wide range of brain regions that subserve cognitive, thought and affective processes, notably prefrontal, superior and medial temporal, inferior parietal, thalamic and striatal regions, and impaired white matter integrity as evidenced by reduced fractional anisotropy in critical white matter (WM) pathways in diffusion tensor imaging (DTI) studies (Prasad & Keshavan, 2008; Shenton *et al.* 2010). There is increasing evidence for functional brain alterations such as reduced prefrontal efficiency while performing executive function tasks (Minzenberg *et al.* 2009) and hippocampal alterations while performing declarative memory tasks (Heckers & Konradi, 2010), neurophysiological alterations include reduced amplitude of P300 evoked response potentials, abnormal smooth pursuit with eye movement studies (Thaker, 2008), and reduced gamma oscillations in response to cognitive tasks (Uhlhaas & Singer, 2010). Neurochemical alterations include dopaminergic

(Howes & Kapur, 2009), glutamatergic (Kantrowitz & Javitt, 2010), and GABAergic dysregulation (Gonzalez-Burgos & Lewis, 2008). At a neuropathological level, there is a consistent evidence of reduced dendrite density, largely due to loss of excitatory glutamatergic synapses, and decreased neuronal somal size as well as glial numbers but normal or increased neuronal density, and reductions in functional activity and expression of GABAergic interneurons (Sweet *et al.* 2010; Beneyto & Lewis, 2011).

While none of the observed pathophysiological abnormalities are likely to qualify as diagnostic markers at this time, many can serve as potential biomarkers for elucidating causal factors including genes, and as targets for therapeutic discovery. The substantial phenotypic, pathophysiologic, etiological heterogeneity of schizophrenia, technological limitations, and the less than ideal animal models limit progress in this area. A major constraint to progress in unraveling the biology of schizophrenia is the fact that the concept of schizophrenia as a unitary disease entity remains poorly defined. However, several promising models of schizophrenia are emerging. An important example is that of a neurodevelopmentally mediated imbalance in excitatory/inhibitory neural systems (i.e. glutamatergic and GABAergic) leading to impaired neural plasticity (leading to premorbid and persistent negative and cognitive symptoms), downstream tonic, and phasic dopaminergic alterations leading to psychosis. Such an imbalance could result from genetic, epigenetic, and environmental causes, as well as infections/inflammation and oxidative stress (Keshavan *et al.* 2011). Several key steps are needed to move the field forward: (a) more neuroscience-based phenotype definitions; (b) cross-diagnostic dimensional and a staging approach to psychopathology; (c) elucidating genomic and environmental factors and their interactions; (d) separating causes from consequences and compensatory phenomena; and (e) formulating refutable predictions and developing animal models close to biological phenotypes. Hopefully all these steps will help redefine schizophrenia and move the field beyond the current conceptual impasse.

Treatment

The treatment of schizophrenia has come a long way from its primitive roots to the current approaches. However, the current standard treatments, both pharmacological and psychosocial, remain limited and inadequate as evidenced by partial response and functional disability in the majority of patients at this time (Tandon *et al.* 2010).

For centuries, insanity (the term used prior to the early 20th century when Bleuler coined the term schizophrenia) was completely mysterious, misunderstood or attributed to evil spirits, leading to mistreatment and persecution rather than any medical treatment. In the 18th century, the institutionalization movement began as a humane treatment extending for 200 years until the early 1950s. Futile treatments such as hydrotherapy, rotating chairs, insulin coma, psychotherapy, electroconvulsive therapy, and even the extremely harmful prefrontal lobotomy were all used to no avail to reduce the psychotic or violence symptoms (Valenstein, 1997).

Finally, the serendipitous discovery of chlorpromazine in 1952 was a dramatic turning point in the treatment of psychotic symptoms, eventually leading to the hurried emptying of mental institutions and the rise of homelessness and incarceration of patients with schizophrenia. The limitations of chlorpromazine, other phenothiazines, and the other various neuroleptic classes that were manufactured were numerous including:

1. Serious neurological side effects that were intolerable, leading to ubiquitous non-adherence rate, and frequent rehospitalization (instigating the term 'revolving door syndrome'). For four decades, it was not known that psychotic relapses are associated with progressive brain atrophy, drug resistance, and functional deterioration. Recent studies report that the antipsychotic drugs themselves may be associated with some brain tissue loss as well (Ho *et al.* 2011).
2. The patients remained disabled despite the improvement in psychotic symptoms like delusions and hallucinations. In the 1980s, researchers began to recognize that schizophrenia is associated with negative symptoms that were unresponsive to neuroleptics and were even worsened by excessive dopamine blockade of antipsychotic drugs (Carpenter & Koenig, 2008).
3. In the 1990s, another clinical domain of schizophrenia, cognitive dysfunction, was recognized as not responsive to dopamine-blocking agents and was often worsened by high doses of neuroleptics and the anticholinergic (memory impairing) drugs added to mitigate the Parkinsonian side effects of excessive dopamine blockade (Nasrallah & Smeltzer, 2011). Cognitive deficits, especially poor memory and impaired executive functions, were soon established to be another cause of disability (Green, 1996). Impaired social cognition (misreading cues, dysfunctional theory of mind, poor social skills, and attributional bias) also contribute to social dysfunction and was not responsive to available antipsychotic agents.

The accidental discovery of the first atypical antipsychotic clozapine, which does not cause any neurological movement disorders, led to the development of the second-generation antipsychotic (SGA) class in the mid 1990s, now consisting of 15 agents, all of whom block dopamine but have a stronger antagonism to the serotonin 2A receptors (5-HT2A) and a lower movement disorders profile (Tandon *et al.* 2008*c*; Nasrallah & Smeltzer, 2011). Over the past 15 years, the SGA class has become the main staple of schizophrenia, but was soon found to cause significant weight gain, hyperglycemia, and hyperlipidemia (Newcomer & Haupt, 2006). Large-scale effectiveness studies such as the CATIE trial confirmed those metabolic adverse events of the SGAs but found that their effectiveness (measured by all-cause discontinuation) was similar to the first generation drugs. A United Kingdom study (CUtLASS) (Jones *et al.* 2006) and a European study (EUFEST) (Kahn *et al.* 2008) reached similar conclusions, casting doubts about the SGA class. Furthermore, initial claims of efficacy on the primary negative and cognitive symptoms were not validated. Thus, the current status of pharmacologic treatment of schizophrenia is at a stalemate with a strong recognition of the huge unmet needs in schizophrenia. The efficacy of clozapine in patients with refractory psychotic symptoms or suicidal risk is considered the only bright spot but the metabolic side effects of clozapine and the need for close monitoring of white blood cell counts for possible agranulocytosis, tempers the enthusiasm for a large-scale use of clozapine.

The main thrust of research efforts to advance the pharmacological treatment of schizophrenia now focuses on the following targets:

1. A shift to a glutamate-modulating class of antipsychotic agents. A large body of evidence over the past two decades suggests a hypofunction of the *N*-methyl-D-aspartate (NMDA) receptor in schizophrenia. Such a hypofunction can in fact lead to dysregulation of dopamine pathways (which are stimulated by the excitatory neurotransmitter glutamate). Activity of the mesolimbic dopamine rises and the activity of the mesocortical dopamine pathway declines. This produces positive symptoms and negative/cognitive deficits, respectively. There are currently several strategies to enhance the activity of the NMDA by enhancing the levels of the co-neurotransmitter glycine at the glutamate receptor site. Early results are encouraging but nothing has been approved for use yet.
2. A concerted effort to improve negative symptoms is another ongoing research effort to overcome the apathy, avolition, impoverished thinking, and affective blunting or incongruity in schizophrenia. Nothing is yet approved or close to approval by the FDA.
3. An organized program to develop cognition-enhancing drugs has been developed as a partnership between NIMH, pharmaceutical industry, and academia. The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) has focused mainly on memory as a cognitive target deficit. Several mechanisms of action were prioritized and a number of trials are currently underway.

In summary, there is a tremendous unmet need in the pharmacotherapy of schizophrenia including a safer and more effective treatment for positive symptoms, a treatment for negative symptoms, and a treatment for cognitive deficits. Theoretically, a glutamate-modulating agent may accomplish all the above but the possibility of a combination therapy for schizophrenia is quite likely as well. There is growing interest in exploring agents (or non-pharmacotherapy approaches such as neurostimulation) that have the following neuroprotective properties:

1. Enhance neuroplasticity (to regenerate the lost neuropil in schizophrenia) as well as,
2. anti-inflammatory agents (to counteract putative inflammatory processes that underlie the elevated cytokines in schizophrenia) and,
3. drugs that stimulate the production of neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (which decline severely during psychotic episodes) may all be parts of a future treatment model in schizophrenia to address both the structural and neurochemical pathologies in schizophrenia.

In addition to pharmacotherapy, non-pharmacological treatments for schizophrenia have always been a key component of long-term management and rehabilitation. In addition to the basic supportive therapy, social skills training, family intervention, environmental support, cognitive behavioral therapy, group therapy, illness self-management training, and vocational rehabilitation, all are being used to varying degrees in treatment settings.

Unfortunately, learning is impaired in schizophrenia and that may undermine the outcomes of some psychosocial interventions in schizophrenia, and the positive but not the negative findings tend to be published in the literature. One encouraging treatment, cognitive remediation therapy, appears to be a promising new approach to improving the core cognitive deficits in schizophrenia. One study even found an increase in cortical tissue following cognitive remediation (Eack *et al.* 2010). If replicated, it

may indicate that non-pharmacological approach may do what pharmacotherapy is yet to do. However, much remains to be done to improve clinical, cognitive, social, and vocational outcomes in schizophrenia.

Conclusions: Filling the gaps in schizophrenia

Although we know a great deal about schizophrenia, significant challenges remain to close the numerous clinical, etiological, and treatment of this disabling and heterogeneous brain syndrome with many overlapping genotypes and phenotypes. These challenges will require innovative approaches to research and investigators need to unshackle themselves from the traditional concept of schizophrenia and untether themselves from the simplistic notions about a highly complex clinical entity. Research into schizophrenia must espouse an agnostic stance towards diagnosis in order to make major breakthroughs and to glean new insights. As van Os (2011) suggested, researchers must transcend existing facts to explore and define 'metafacts' about schizophrenia. A potential source of inspiration for future researchers is the dozens of neglected facts and discarded hypotheses of the past that may have some nuggets of truth in them, although they have been relegated to the trash heap of unproven or untested theories. An example is the observation of reduced flush response to nicotinamide in schizophrenia (Horrobin, 1980), which led to the prostaglandin hypothesis of this illness. This replicable observation is in search for alternative hypotheses (Lin & Hudson, 1996). Most importantly, entirely new and novel paradigms must be introduced and employed to discover both the numerous genetic, environmental and epigenetic factors as well as to design more effective treatments that are disease modifiers not simply symptom modulators. The ultimate goal for a radically creative approach to the study of schizophrenia and filling its gaps is to develop a personalized medicine approach where each patient receives the most accurate diagnostic formulation and treatment intervention.

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