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NEW DRUG DEVELOPMENTS IN PSYCHOSIS: CHALLENGES, OPPORTUNITIES AND STRATEGIES

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Abstract

All currently approved drugs for schizophrenia work mainly by dopaminergic antagonism. While they are efficacious for psychotic symptoms, their efficacy is limited for negative symptoms and cognitive deficits which underlie the substantive disability in this illness. Recent insights into the biological basis of schizophrenia, especially in relation to non-dopaminergic mechanisms, have raised the efforts to find novel and effective drug targets, though with relatively little success thus far. Potential impediments to novel drug discovery include the continued use of symptom based disease definitions which leads to etiological and pathophysiological heterogeneity, lack of valid preclinical models for drug testing, and design limitations in clinical trials. These roadblocks can be addressed by (i) characterizing trans-diagnostic, translational pathophysiological dimensions as potential treatment targets, (ii) efficiency, accountability and , transparency in approaches to the clinical trials process, and (iii) leveraging recent advances in genetics and *in vitro* phenotypes. Accomplishing these goals is urgent given the significant unmet needs in the pharmacological treatment of schizophrenia. As this happens, it is imperative that clinicians employ optimal dosing, measurement-based care, and other best practices in utilizing existing treatments to optimize outcomes for their patients today.

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1. INTRODUCTION

Schizophrenia (SCZ) is among the most disabling illnesses in all of medicine. Until the 1950s, standard treatment for this illness consisted of custodial care, frontal lobe surgery and insulin coma therapy which, thankfully, were subsequently discredited. Despite major twenty-first century advances in neuroscience, our most effective antipsychotic drugs (APDs) are still based on chance observations from the 1950s and 1960s (Smoller, 2014). The early 1900s were marked by an emphasis on clinical observation exemplified by influential theorists like Emil Kraepelin, who in the 1920s distinguished a “dementia praecox” subset of patients with illness beginning in early adulthood and running a chronic, declining course (Kraepelin, 1971). Contemporaneously, Eugen Bleuler coined the term schizophrenia to define an illness with core features (the 4“a”s) of looseness of associations, blunted affect, autism (social withdrawal) and ambivalence (Bleuler, 1950). Treatment with APDs, beginning with chlorpromazine, was introduced in the 1950s, largely by the serendipitous observations of Jeanne Delay and Pierre Deniker (Delay and Deniker, 1955). Prior to the discovery of its antipsychotic effects, chlorpromazine was used as an antiemetic before surgery. APDs were initially termed “neuroleptics” because of their propensity to cause neurological sequelae such as extrapyramidal side effects (EPSE), including parkinsonism. Both the SCZ pathophysiology and mechanisms of action of the drug were then unknown.

It became clear by the 1970s that the mechanism of antipsychotic effects is dopaminergic receptor antagonism (Creese et al., 1976). At the same time, expert consensus-based operational criteria, i.e. Diagnostic and Statistical Manual of Mental Disorders (DSM), were being developed to critically address the issue of diagnostic reliability (American Psychiatric Association, 1978). Newer, or “second generation” APDs, which cause relatively less EPSE by their additional effects on multiple neurotransmitter systems such as serotonin, were introduced in the 1980s beginning with clozapine. However, the distinction between the so-called typical and atypical drugs remains rather blurred (Jindal and Keshavan, 2008; Tandon and Maj, 2008). Antipsychotic medications continue to be the mainstay in the psychopharmacology of SCZ; currently, three “first generation” APDs (fluphenazine, chlorpromazine, and haloperidol) are listed as Essential Medications by the World Health Organization (World Health Organization, 2010) with over 60 antipsychotic medications currently available (Bruijnzeel et al., 2014) (Table 1).

Despite a steady expansion in our knowledge of the pathophysiological and etiological underpinnings of psychotic disorders (Insel, 2010), all currently used APDs still work by reducing dopaminergic neurotransmission. Importantly, these medications have either minimal or no impact on the negative symptoms and cognitive deficits, considered to be central to the functional disability in SCZ (Keefe et al., 2007). None of the newer, atypical

antipsychotics appear to be more effective compared to the older typicals, and only clozapine has been shown to be more efficacious, (CATIE, Lieberman et al., 2005). A fair number of patients are also poorly responsive to clozapine and adjunctive electroconvulsive therapy is occasionally beneficial (Kales et al., 1999; Petrides et al., 2015). Additionally, the newer APDs are associated with significant endocrine and metabolic side-effects (Tandon and Halbreich, 2003). All of these factors underlie poor adherence. The relative lack of success with newer compounds, as well as the enormous costs of bringing drugs to the market, has led to the withdrawal of several pharmaceutical firms from this field (Muglia, 2011). Clearly, ongoing research seeks to develop more effective and better tolerated APDs based on known mechanisms, and identify new pathophysiology-based targets. Treatments that target negative symptoms and neurocognitive deficits remain an unmet need.

In this paper we first review the potential roadblocks and gaps in knowledge for identifying therapeutic targets for psychotic disorders and the challenges in moving from the “ideas to the indications” in therapeutic drug discovery. In particular, there is a need to move forward from a reliance on clinical observation and serendipity alone toward identifying pathophysiological targets and hypothesis driven drug discovery (Table 2). We then briefly review what we know of the etiopathophysiology of SCZ with a focus on putative therapeutic targets. Third, we take stock of recent efforts to develop novel therapeutic targets, as well as their promises and limitations. We conclude by identifying the needed next-step approaches to address these challenges in order to bridge the translational gaps.

2. CHALLENGES TO IDENTIFYING NOVEL THERAPEUTIC TARGETS

2.1. Classifications are based on arbitrary symptom clusters and have little biological validity

Scientific research in SCZ continues to focus on diagnostic categories based on arbitrary collections of symptoms as described in the international classification of diseases (ICD) and DSM. While successive revisions of these classification systems have improved reliability, validity remains a question (Tandon et al., 2013). Current nosology ignores the multilevel heterogeneity—in disease etiology, pathogenesis, and clinical symptomatology—of patients who receive a given diagnosis (Nasrallah et al., 2011). Our diagnostic boundaries are limited by overlap both “within groups” and “between groups.” For example, etiological subgroups coexist within disorders, and conversely, etiologic mechanisms transcend diagnostic boundaries. There is extensive evidence of overlap in psychopathology, biological, and genetic factors between SCZ and multiple other neuropsychiatric disorders (Green et al., 2010), with associated biomarkers spanning multiple “discrete” disorders (Ethridge et al., 2012).

The importance of biomarkers in stratifying broad diagnostic categories into treatment-relevant subgroups cannot be overstated (Trusheim et al., 2007). For example, in oncologic research, the expression of human epidermal growth factor subtype 2 (HER2) receptors expression was found to predict breast cancer outcome (Slamon et al., 1987); Herceptin, a new treatment, was developed based on this (Smith et al., 2007) to specifically regulate receptor expression. This type of diagnostic subgroup stratification is becoming increasingly possible in psychiatry. For example, positron emission tomography (PET) has shown that

antipsychotic-responsive versus resistant patients can be identified by monitoring presynaptic dopamine synthesis capacity and glutamate levels using imaging (Demjaha et al., 2012); immune-related genes have been implicated in SCZ subgroups with anti-inflammatory agents proposed as potential therapeutic targets (Müller and Dursun, 2011), and acyclovir has been shown to potentially reverse cognitive deficits in herpes simplex virus 1 seropositive SCZ patients (Prasad et al., 2013). While the recent emphasis on psychopathological dimensions to characterize schizophrenia in DSM-5 is a step in the right direction (Tandon and Carpenter, 2012), the challenge of etio-pathophysiological heterogeneity remains.

2.2. Etio-Pathophysiology is complex, multi-causal and multi-final

Ever since the first systematic familial study of SCZ in the early 1900s showed disease heredity (Rüdin, 1916), the genetic etiology of SCZ has proved to be increasingly complex. Failure of genetic linkage analysis revealed the non-Mendelian nature of the disease (Smoller, 2014), and by 2006 association analysis had failed to show association of any candidate genes with SCZ (Gejman et al., 2011). Genome-wide association studies (GWAS) have allowed us to move beyond “wild guess” candidate genes to a genome-wide search for single-nucleotide polymorphisms (SNPs). The largest to-date of these studies led to the recent identification of 108 gene variants associated with SCZ (Schizophrenia Working Group 2014). Additionally, SCZ patients have an excess of copy number variants (CNVs), which represent gene deletions and duplications, which may have larger effects on the phenotypes than individual SNPs (Merikangas et al., 2009). An example of a CNV associated with SCZ is 22q11.21, a large deletion underlying velocardiofacial syndrome. . Over a third of 22qDS carriers develop psychotic disorders, 80% of whom present with SCZ (Murphy et al., 1999). The polygenic risk model posits that many small- effect genetic variants, added together, may contribute to SCZ risk (Purcell et al., 2009).

These genetic associations are complicated by the multicausality and multifinality inherent to disorders under the polygenic risk model. For example, many variables can contribute to a similar clinical endpoint, and a single genetic or environmental risk factor can have multiple different effects (also called pleiotropy). Even in familial high risk studies for psychotic disorders, no individual marker or combination of markers could accurately predict development of psychotic symptoms (Tandon et al., 2012). Conversely, patients with known genetic risk factors can range from having no pathology to general psychopathology to psychosis (Shah et al., 2013). Additionally, significant genetic overlap has been found between autism and SCZ. It is possible that these same genetic mutations are causing different symptoms in the different disease groups, or alternatively that these shared genetic loci are determining a cross-cutting symptom dimension, like psychosis in SCZ and BPD, or cognitive impairment in SCZ and autism (Schulze et al., 2006).

2.3. Lack of Satisfactory Animal Models

Good, reliable animal models have been hard to develop for neuropsychiatric disorders perhaps more than for any other type of disorder, given the inherent complexity of neurobiology and the complications posed by examination of the living human tissue (Hyman, 2014). The lack of construct, face and predictive validity among classical animal

models creates important translational road-blocks in our efforts to develop novel, effective and safe antipsychotic drugs.

Face validity, which implies that the animal model manifests behavioral, neuroanatomical, and physiological features, similar to those seen in a human disease, is limited for complex constructs like schizophrenia. First, replicating symptoms such as “delusions” in an animal model is challenging. Second, two patients with the same disease can have widely differing presentations (for example, one patient with SCZ may have delusions and hallucinations while another has mainly thought disorder symptoms.) However, cognitive impairments, which are a central aspect of SCZ, can be modelled in animals. One example is prepulse inhibition (PPI) which is easily studied in both humans and animal models. PPI is the suppression of a startle response to a strong stimulus (e.g. a loud knock on the door) by an initial, smaller stimulus (a weak knock). In rodents, PPI deficits can be induced by NMDA receptor antagonists or amphetamine or, and are reversed by APDs (Swerdlow et al., 2008), making this a popular model for preclinical testing of APDs. Deficient PPI is associated with SCZ but is non-specific and seen in several other neuropsychiatric disorders.

An example of ideal **construct validity** would be recreating in an animal the etiologic process, such as the multiple genes, underlying the risk for the disease. However, it may be unrealistic to rely on the currently reported common variants of small effect size in animal models. Even if it were known that a small effect mutation were associated with SCZ, it alone would contribute a very small increase in risk and may not result in a disease phenotype in the animal. There are also some mutations that are highly penetrant, such as the chromosome 22q11.2 microdeletion and the *Disrupted in schizophrenia-1* (Disc1) translocation. However, these mutations have both been associated with multiple disorders—velocardiofacial syndrome, SCZ and bipolar disorder in the former, and bipolar disorder, depression with psychosis, and SCZ in the latter. Since many people with the mutation are diagnosed not with SCZ but with other disorders, it is unclear which genes are actually producing which pathophysiological behaviors (Nestler and Hyman, 2010).

Predictive validity questions whether an animal model responds to a therapeutic intervention the way that a human patient would. However, pathophysiologic mechanisms of SCZ remain unclear, and manipulating a particular molecular target or evoking a certain behavior in animals may not produce an analogous/associated behavior in humans. Historically, new APDs have been tested based on similarity of their behavioral effects to those evoked by dopamine antagonists like chlorpromazine. For example, animals were given apomorphine (a dopamine agonist) which induced cage climbing and catalepsy. New potential APDs were then tested to see if they could reverse these effects. It is now believed, however, that the behavioral changes seen after drug administration were in fact due to Parkinson-like side effects of the APDs, rather than demonstrative of antipsychotic efficacy (Nestler and Hyman, 2010).

2.4. Lack of actionable biomarkers

Expanding knowledge about the biological basis of psychotic disorders has generated optimism for biomarkers that can generate integrative, predictable model for diagnosis, selection of treatment and disease course monitoring. However, few laboratory tests exist in

psychiatry other than those used to exclude underlying medical illnesses (hypothyroidism in depression, brain tumors in psychosis) (Kapur et al., 2012). Another example is the use of EEG to rule out epilepsy, and sleep studies to rule out sleep apnea or narcolepsy and sleep polysomnography to assess comorbid causative disorders such as sleep apnea and narcolepsy. PET biomarkers such as estimation of D2 receptor binding have clinical potential and are well validated, but are not being routinely used, at least in part because of their invasive nature and cost. Future technological advances may allow less invasive, and inexpensive markers of neuropharmacological effects for routine clinical use.. Genetic diagnostic markers such as copy number variants, chromosomal translocations, and SNPS are objective and reliable but have low applicability to clinical use given their small individual effect size and low prevalence. Imaging biomarkers such as hippocampal and ventricle volume as well as hypofrontality have shown some promise, but replicability and accuracy remain unclear (Prata et al., 2014). PET biomarkers such as estimation of D2 binding as an index of antipsychotic benefits and side effects are well validated and have therapeutic potential, but are not routinely used, perhaps because of cost and safety issues. Future technological renovations and reimbursement improvements might allow such tests to be used in standard clinical care.

Multiple issues have been posited as contributing to this paucity of biomarkers. First, there is the relative inaccessibility of brain tissue for study, as the living brain cannot be biopsied in most cases. Additionally, unlike other diseases like cancer, most brain disorders are localizable to networks of cells rather than to single cells, making analysis difficult even when tissue can be procured (Hyman, 2014). The symptom-based approach to disease nosology has also been counterproductive for research purposes, with increasing fractionation of disorders into strict DSM diagnostic boundaries (Kapur et al., 2012; Prata et al., 2014). The small effect size of genetic and biological findings in SCZ has been problematic making replications difficult (Ioannidis, 2008). This may also result from underpowered studies in genetically complex disorders, small sample sizes, and subjective outcomes (Mitchell, 2012). An additional factor is publication bias for findings related to diagnostic rather than outcome biomarkers; the latter may be more attuned to clinician needs, may be more cost-effective, and more impactful to the patient's well-being than the former (Andre et al., 2011). Research has instead focused on developing biomarkers to cross-sectionally distinguish patients from matched controls. While this has led to a better understanding of psychosis, it has not led to outcome and/ or treatment response predictors, which require a longitudinal design. In terms of controls, patients are commonly matched with healthy volunteers based on extraneous variables with no mention of how these variables relate to the biomarker or the clinical endpoint. Finally, inconsistent reporting in terms of type of biomarker that is being tested (for diagnosis, versus treatment response or disease progression, etc), has decreased the clinical utility of these studies (Prata et al., 2014).

2.5. Design and regulatory road-blocks to clinical trials

Controlled clinical trials to investigate experimental drugs is a key translational process to develop new medications for psychotic (and other CNS) disorders. The paradigm of designing, conducting and analyzing the data from placebo-controlled clinical trials is a

highly complex enterprise whose many interlocking components can lead to many potential confounds, pitfalls and challenges. Yet, when successful, the data of large, controlled clinical trials are immediately elevated to the status of “evidence-based medicine”, and are subsequently included in meta-analytic studies that influence clinical guidelines and future research strategies. The following challenges in the design, the conduct, reliability, and validity and lead to multiple sources of error in the clinical trials of schizophrenia:

1. The parameters of the clinical trials are imposed and constrained by rather rigid regulatory policies. That includes the inclusion/exclusion criteria, the choice of measurement instrument (rating scale), the trial duration, the use of placebo vs. active comparator, and the metrics for acceptable safety and tolerability. The result is a “clean” sample of patients (with no substance use, no serious medical problems, no history of suboptimal response, etc.) all of which renders the study sample very different from “real-world” patients for whom the drug will be prescribed.
2. The assumption that an experimental drug must be significantly better than placebo for the entire sample regrettably misses the opportunity of identifying biologically different subgroups within the overall sample, which may demonstrate excellent, partial or poor response to agent being tested. It is baffling that illness heterogeneity is conveniently ignored when analyzing clinical trial data. Many experimental drugs were discarded because they failed to improve the majority of study subjects.
3. The “placebo response” problem has escalated dramatically in recent years (Kemp et al, 2010) dooming the outcomes of new drugs, especially in U.S. clinical trials and less so in non-U.S. trials. The reasons are multifactorial and include: a) the dramatic shift from academic sites with no profit motive to for-profit private sites who benefit greatly from high enrollment that may compromise diagnostic rigor b) recycling of “professional patients” who eagerly participate in one trial after another and “please the investigator” by claiming symptomatic improvement when they are scored on a rating scale c) disparate levels of experience and intra-and inter-rater reliability at various sites d) “bending” the inclusion/exclusion criteria to increase the sample size. Attempts to address the high placebo response have yet to achieve the desired outcome.
4. Uncertain adherence to study medication in the outpatient phase of a clinic trial is a confounding issue in ascertaining the efficacy of a drug. Poor adherence is well documented in the management of schizophrenia in clinical setting, and the same factors (substance use, negative symptoms, and cognitive deficits) may lead to erratic and partial adherence to study medications in outpatient trials.
5. The rigid regulatory policy of testing a drug for a specific diagnostic category, rather than a specific symptom, is a hurdle to drug development for psychiatric disorders, many of which share several key symptoms such as depression, impulsivity, agitation or delusional ideas. Given that 80% of DSM diagnostic categories have no approved treatment (Devulapalli and Nasrallah, 2009), it is not surprising that there is a massive amount of off-label prescribing in

psychiatric disorders. If drugs are approved for a major clinical symptom, rather than for a diagnostic “construct” arbitrarily defined by a DSM committee, the problem of off-label prescribing would be resolved. This would help in the partial treatment of dozens of psychiatric disorders, for whom drug indication is decades away.

3. PUTATIVE THERAPEUTIC TARGETS IN SCHIZOPHRENIA

Numerous theories have been advanced about the etiopathology of SCZ, leading to varying interpretations of the illness; this has been likened to the tale of six blind Indian men who come up with different conclusions while groping different parts of the same elephant (Keshavan et al., 2011, Figure 1). Precisely what the core symptoms of this illness continues to be debated. Therapeutic interventions can potentially target several aspects of etiology and pathophysiology (Figure 2), and are briefly outlined here.

3.1. Dopamine

Dopamine plays key roles in motivation, salience, reward and motor control. Increased dopaminergic function as a pathophysiological theory of SCZ has held sway over half a century. (A. Carlsson, 1978) (Van Rossum, 1966). Much of the evidence for the dopamine theory has been indirect, i.e. the fact that all antipsychotics block dopaminergic receptors (mainly D₂ receptors, but possibly effects on other receptors, D₁, D₃₋₅), and that dopamine agonists such as amphetamine trigger psychosis (Guillin et al., 2007). However, there is incremental direct evidence in recent years. Acute psychosis has been shown to be associated with increased amphetamine induced dopamine release in the striatum (Laruelle and Abi, 1996) Increased D₂ receptor binding in the brains of patients with SCZ has been seen in post-mortem and PET studies with a mean effect size of about 1.5, though this is likely to be secondary to antipsychotic effects (Erritzoe et al., 2003)(Laruelle, 1998). Meta-analyses have pointed to evidence of increased striatal presynaptic DA synthesis, but no change in density of striatal dopamine terminals or of dopamine transporter (Fusar-Poli, 2013; 2012). More recent evidence suggests increased presynaptic dopamine function in prodromal individuals leading up to early psychosis (Bonoldi and Howes, 2012).

Weinberger (Weinberger, 1987) has attributed the cognitive deficits seen in SCZ to impaired prefrontal dopaminergic function. The impaired working memory in SCZ has been thought to be related to altered D₁ function in the prefrontal cortex (Abi, 2002). It has been suggested that a deficit in mesocortical dopaminergic system may underlie negative and cognitive symptoms, and that a mesolimbic dopaminergic overactivity, or disinhibition may lead to positive symptoms (Davis et al., 1991). Grace (Grace, 1991). has proposed SCZ may be related to reduced tonic dopaminergic activity (causing negative and cognitive symptoms) and exaggerated phasic responses to stimuli such as stress (causing psychosis). Drawing upon neurochemical imaging, and animal model data, it has been recently suggested that dopaminergic abnormalities might reflect a final common pathway for manifestations of psychosis (Howes and Kapur, 2009). All current treatments work by addressing this downstream link in the pathophysiological chain, and the more upstream processes need to be investigated for novel treatment development.

3.2. Glutamate

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system. Early observations of decreased glutamate levels in the cerebrospinal fluid in schizophrenia patients (Kim et al., 1980), though inconsistent (Perry, 1982), led to the initial glutamate hypothesis of SCZ. . A widely held view is that glutamate mediated excitatory neurotransmission via N-methyl D-aspartate (NMDA) receptors (Moghaddam, 2003; Olney et al., 1999) may be deficient in SCZ. This view is consistent with observations of psychotic symptoms induced by phencyclidine (PCP) and Ketamine which are NMDA antagonists. (Javitt and Zukin, 1991). Post-mortem studies suggest reduced NMDA receptor expression in a variety of brain regions, such as the hippocampus and the prefrontal cortex. However, the literature is inconsistent in this regard (Lewis and Gonzalez, 2006).

A consequence of reduced NMDA receptor activity in the inhibitory GABAergic neurons may be the disinhibition of cortical pyramidal glutamatergic neurons (leads to Figure 2). Metabotropic glutamate group 2/3 receptor agonists can serve to normalize such excessive glutamatergic neurotransmission and can potentially improve positive, cognitive and negative symptoms (Moghaddam et al., 2012). NMDA receptors bind glutamate as well as its co-agonists glycine or D-serine; both of these offer additional therapeutic targets.

3.3. Gamma Amino Butyric Acid (GABA)

There is consistent post-mortem evidence for decreased prefrontal GABA expression in SCZ as measured by mRNA levels of Glutamic acid decarboxylase, a key enzyme involved in GABA Synthesis (Lewis et al., 2005). There is also post-mortem evidence for reduced interneuron number, gene and protein expression in the hippocampus (Heckers et al., 2014). There is also evidence for upregulation of GABA_A receptors perhaps suggesting a compensatory response to decreased GABA (Jarskog et al., 2007). The chandelier subtype of parvalbumin positive GABA neurons may be particularly affected . These changes may be disease specific (Benes et al., 2007); it has been suggested that GABA abnormalities may underlie the alterations in neural synchrony, indexed by abnormal gamma oscillations, and the working memory impairments observed in SCZ (Lewis and Gonzalez, 2006).

3.4. Acetylcholine

Smoking is widely prevalent in SCZ, and has been thought to reflect the patients' effort to overcome a deficit in nicotinic cholinergic receptors. Several lines of evidence suggest altered CNS muscarinic activity in SCZ (Tandon, 1999; Raedler et al., 2007). There is 1 postmortem evidence for regionally specific reductions in selective muscarinic receptors in the brains of SCZ subjects.. SCZ patients fail to inhibit their P50 evoked responses to repeated auditory stimuli (paired clicks), which may reflect impaired sensory gating. This observation may have a genetic basis, and has been associated with the chromosome 15q14 locus of the alpha-7-nicotinic receptor gene (Freedman et al., 2003). These observations have motivated studies of pro-muscarinic agents such as alpha7 nicotinic agonists in treating certain symptoms of SCZ (Olincy and Stevens, 2007).

3.5. Serotonin

Observations psychotogenic effects of LSD as well as of the antipsychotic effects of serotonin-dopamine antagonists such as such as clozapine and risperidone have led to increased interest in the interaction between these two neurotransmitter systems as a possible pathophysiological target in SCZ (Kapur and Remington, 1996). It is well known that serotonin antagonists ameliorate the extrapyramidal effects of antipsychotics. However, there is still no direct evidence of serotonergic dysfunction in the pathogenesis of SCZ; specific serotonin receptors continue to be a focus of interest (particularly 5HT-3 and 5HT-6) in SCZ (AbiDargham, 2007).

3.6. Inflammation

In recent years, there has been an increasing interest in the role of inflammation and oxidative stress in the pathophysiology of SCZ (Feigensohn et al., 2014; Na et al., 2014). There is evidence that *in utero* exposure to infectious or inflammatory agents in rodents can cause behavioral and brain changes similar to those seen in SCZ. Alterations in the complement system, which mediate innate immunity, have been implicated in SCZ, with observations of increases in C1, C3 and C4 complement protein activity (Mayilyan et al 2008; Sekar et al 2016). Complement proteins may “tag” synapses for phagocytosis by activated microglia, leading to accelerated pruning of synapses (Sasaki et al 2014; Stephan et al 2012).

An example of an inflammatory model of psychotic disorders is the NMDA encephalitis syndrome which has been recently described. In this syndrome, schizophrenia like features, including catatonic symptoms and autonomic dysfunction may be combined with elevations in NMDA autoantibodies; immunotherapy is helpful in treatment (Dalmau et al 2008).. Another treatable immune model of schizophrenia is gluten sensitivity, and some reports suggest elevation of transglutaminase antibodies; such patients may benefit from gluten-free diets (Jackson et al 2012).

3.7. Oxidative stress

Oxidative stress, which reflects an excess of metabolic byproducts involving oxidant molecules that may be toxic to cells, has been implicated in SCZ (Yao and Keshavan 2011). The balance between prooxidants and antioxidants (such as certain vitamins, enzymes) may be altered in SCZ. A recent meta-analysis showed reduced levels of the anti-oxidants such as red blood cell superoxide dismutase in SCZ. These observations have potential therapeutic applications worthy of further studies (Bitanirwe et al., 2011). Deficits in an endogenous antioxidant, glutathione, has been implicated in schizophrenia, and may cause impairments in white matter integrity (Monin et al 2014).

3.8. Summary

In summary, the core pathophysiology of schizophrenia might involve anomalies of GABA, glutamatergic and dopaminergic alterations leading to aberrant functioning of interneurons and pyramidal neurons which manifest as cognitive, behavioral and social dysfunction via altered functioning of a broad range of macro- and microcircuits. Genetic and early-life environmental risk factors and their interactions could contribute to these abnormalities.

Taken together, all these alterations may together explain the phenotypical manifestations of what we call schizophrenia (Figure 1), though it is by no means clear that this is one disease entity (Keshavan et al 2011). It has been suggested that oxidative balance, immune, and glutamatergic systems may represent multiple interlocking nodes in a central hub; imbalance within any of these nodes might affect the entire system (Steullet et al 2014). Likewise, reversing anomalous activity in any of the nodes, or any combinations thereof, might have beneficial effects on the entire system.

4. NOVEL THERAPEUTIC TARGETS AND EMERGING TREATMENT STRATEGIES

Our increasing ability to link neurobiological findings to clinical expression in schizophrenia (Dawson et al., 2015; Horvath and Mimics, 2015; Padmanabhan et al., 2015) and recognition of the need to unravel the pathophysiology of schizophrenia in a developmental context enables us to more efficiently develop drug treatments addressing distinct phases of the illness. Our improved understanding of the etio-pathology of the schizophrenias enables us to more systematically define potential therapeutic targets (Bernstein et al., 2015; Feigenson et al., 2014; Hall et al., 2015; Na et al., 2014), harness more valid animal models (del Rio et al., 2014) and utilize more actionable biomarkers (Pickard, 2015). In the context of the incredible heterogeneity of etio-pathology and treatment response, genetic advances provide us with necessary tools to better personalize treatments for individuals with SCZ. We herein review that status of each of these therapeutic approaches.

4.1. Targeting Dimensions of Psychopathology

Antipsychotic treatment development has thus far generally depended on a unitary pathology with the hope of identifying disease-specific medications that might address multiple symptom domains. However, current antipsychotics work better for positive disorganization symptoms than negative symptoms or cognitive deficits (Tandon et al., 2010 and 2013). Specific pharmacological strategies directed at each of these non-psychotic symptom domains are therefore critically needed. These agents are being evaluated both as add-on treatments to existing antipsychotic medications and stand-alone treatments.

(A) Specific Treatments for Negative Symptoms—A major reason for functional disability in schizophrenia is persistent negative symptoms; few current treatments have efficacy in this domain (Kirkpatrick et al., 2006). Several novel strategies are now being evaluated (Davis et al., 2014). Studies targeting glutamatergic receptors with glycine transporter inhibitors (eg., bitopertin, Umbricht et al., 2014) and metabotropic M2/M3 agonists (eg., pomeglumetad methionil, Stauffer et al., 2013) initially yielded positive results which were not confirmed in subsequent studies. In addition to agents directed at the glutamatergic system, treatments that specifically target negative symptoms include nicotinic and muscarinic cholinergic agents (Jones et al., 2012; Raedler et al., 2007), antibiotics (eg., minocycline, Chaudhry et al., 2012), and hormones (eg., oxytocin, Modabbernia et al., 2013; estrogen receptor modulator raloxifene, Usall et al., 2011; pregnenolone, Marx et al., 2011). Results thus far remain inconsistent at best.

(B) Specific Treatments for Cognitive Deficits—Cognitive dysfunction is with a strong predictor of social and vocational disability in schizophrenia. While several pathophysiological mechanisms have been postulated to underlie cognitive impairments in SCZ, few can be considered as being established. Several pharmacological targets are currently being investigated, and will be reviewed in section 4.3. (Ibrahim and Tamminga, 2012; Rowe et al., 2015; Tandon et al., 2010). Thus far, no consistent benefits of any of these strategies have been demonstrated.

4.2. Targeting the phase of the illness

Pathophysiological processes may vary across different stages of schizophrenia, but current pharmacological treatment is typically not different during the course of the illness. It is clear that while the diagnosis of SCZ is first made in adolescence or early adulthood, its pathology originates much earlier in aberrant neurodevelopmental processes eventually leading to deviant brain structure and function (Keshavan et al., 2008). Several risk factors contribute to the clinical manifestations of the illness, acting individually, in combination or by interaction with each other. Approaches towards prevention are focused on early identification of those at risk and development of safe and effective interventions that can eliminate the specific risks (Ammeringer et al., 2010; Tsuang et al., 2013). Treatments which can potentially prevent deteriorative brain processes and approaches to reverse them are being assessed (Dodd et al., 2013).

4.3 Targeting specific etiology and pathophysiology

(A) Dopaminergic antagonists and stabilizers—All current antipsychotic therapies have been developed their purported mechanism of antagonism of dopaminergic receptors. Recent trials with selective dopamine D3 and D4 antagonists have not led to promising results. An exception is the recent introduction of pimavanserin as an antipsychotic in parkinson's disease (Cummings et al 2014). Dopamine "stabilizers" include D2/D3 partial agonists such as the currently available aripiprazole, and the recently approved brexpiprazole and cariprazine. Dopamine-1 receptor agonists are being evaluated to treat cognitive deficits, but rapid development of behavioral tolerance and adverse effects such as hypotension and risk of seizures are challenges yet to be overcome. Newer preparations of long acting antipsychotics are also being developed, including the tripartite formulation of paliperidone palmitate and the aripiprazole lauroxil which can be given every 4-6 weeks. These incremental advances raise the hope of addressing the frequent problem of non-adherence which is a significant road-block for recovery in many patients with schizophrenia.

Serotonin agents—While the serotonin-dopamine antagonism provided by the atypical antipsychotics offers some protection against extrapyramidal symptoms, these agents other than clozapine do not provide additional efficacy relative to the first generation antipsychotics (Tandon et al., 2010). Alternative 5HT approaches in SCZ under investigation include the use of 5HT1A agonists, 5HT reuptake inhibitors, 5HT2C antagonists and agonists, 5HT3 antagonists, 5HT6 antagonists, and 5HT7 antagonists either individually or in combination with D2 antagonism and/or 5HT2A antagonism. While agents with D2/5HT2A antagonism and 5HT1A partial agonism are currently available, efforts to

develop agents with more potent 5HT1A activity (targeting negative and cognitive symptoms) with better tolerability are ongoing. While there are compelling preclinical data supporting the potential utility of 5HT2C agonists and 5HT6 antagonists in the treatment of schizophrenia, development of such agents for use in the clinical setting is still in its early stages. After a relative hiatus, there is renewed interest in the development of 5HT3 antagonists as adjunctive agents for negative and cognitive symptoms (Ellenbroek and Prinssen, 2015). Lurasidone, the most recently introduced SGA, has potent 5HT7 antagonism but no clinical implications of this property have been demonstrated thus far.

(B) Glutamatergic Agents: NMDA receptor, AMPA receptor, metabotropic receptors—

With the strong implication of glutamatergic dysfunction as a pathophysiological mechanism in schizophrenia, there has been increasing focus on targeting this system. Recognizing the breadth and complexity of glutamatergic neurotransmission, a range of therapeutic approaches is being evaluated in schizophrenia. Because of the glutamatergic model of schizophrenia as discussed earlier, agents stimulating the NMDA receptor have received the greatest attention. Since direct NMDA agonists are neurotoxic, efforts to stimulate the NMDA receptor indirectly by glycinergic agents (eg., serine and cycloserine) and glycine transport (GlyT1) inhibitors (eg., bitopertin) have been extensively studied. Glycine and D-serine bind to the NMDA receptor site as co-agonists; thus, increasing glycine availability by Gly-T1 inhibitors is expected to produce therapeutic benefit. While demonstrating modest benefits on a range of schizophrenia symptoms in initial studies (eg., Umbricht et al., 2014), later clinical trials have not confirmed such efficacy. While some GlyT1 inhibitors continue to be investigated, development of bitopertin has since been discontinued.

Similarly, metabotropic 2 and 3 (mGlu2/3) receptor agonists (eg., pomuglumetad methionil) that attenuate excessive glutamate release have also received much attention. Similar to the experience with bitopertin, initial studies with pomuglumetad methionil were positive (Patil et al., 2007), other studies have not confirmed efficacy (Kinon et al., 2011; Stauffer et al., 2013). It is possible that these agents might only be effective in the earlier stages of schizophrenia (Goff, 2015), or that they might be effective in individuals selected by specific genetic polymorphisms such as neuregulin (Liu et al 2012), but these hypotheses remain to be firmly tested. Strategies targeting the AMPA glutamate receptor have also not demonstrated any consistent benefits. At this time, selective positive allosteric modulators of NMDA receptor subunits and mGlu5 receptors are eliciting the greatest interest. Of note, mGlu5 receptors are co-localized with NMDA receptors and also modulate microglia activation (Byrnes et al., 2009), relevant to inflammatory mechanisms in schizophrenia (Bernstein et al., 2015).

(C) GABA allosteric modulators—Despite the longstanding interest in the GABA alterations as pathophysiological mechanisms of schizophrenia, understanding was limited until the past 20 years when clear GABA deficits began being demonstrated. Benzodiazepines (that work on GABA_A receptor allosteric sites) have long been utilized along with antipsychotic medications in schizophrenia. Selective GABA_A agonists and

GABA_B antagonists and more recently allosteric modulators at GABA_A receptor subtypes (alpha 1, 2, 3, and 5) are being evaluated in the treatment of schizophrenia.

(D) Cholinergic Agonists (Alpha7 Nicotinic, Muscarinic M1)—The cholinergic system has long been of interest in the pathophysiology of schizophrenia and both muscarinic and nicotinic receptors have been targeted in the therapy of schizophrenia (Tandon et al., 1992; Raedler et al., 2007; Freedman, 2014). This approach has face validity, given the clinical observations that nicotine smoking, which the majority of schizophrenia patients are exposed to, has pro-cognitive effects. While several agents targeting these receptors are currently in various stages of study, alpha-7 nicotinic and M-1 muscarinic agonists and positive allosteric modulators are of greatest interest (Dineley et al., 2015; Felder et al., 2012). Whereas nicotinic agonists principally target cognitive symptoms (Rowe et al., 2015), muscarinic agonists appear to show promise in addressing positive symptoms (Tandon et al., 1999). Encenicline, an Alpha7 Nicotinic receptor agonist, which had shown promise in early phase trials, has not shown efficacy in phase 3 studies..

(E) Neuropeptides: Cholecystokinin, Neurokinin, Cannabinoid, Neurotensin—In view of the significant interactions between a range of the neuropeptide family of receptors with dopaminergic and glutamatergic systems, drugs for several of these targets have been studied. Cholecystokinin (CCK) agonists were among the earliest to be evaluated but results have been equivocal (Montgomery and Green, 1988). Because of the implication of cannabinoid (CB) mechanisms in schizophrenia (Müller-Vahl et al., 2008), the cannabinoid receptor subfamily has received considerable attention as a potential antipsychotic target with CB1 antagonists being of greatest interest. Results thus far have been inconclusive. Neurokinin 3 receptors have broad modulatory effects on several neurotransmitter systems (including dopamine and GABA); preclinical data with NK3 receptor antagonists has suggested potential efficacy across several symptom dimensions in schizophrenia. Agents such as osanetant and talnetant were promising in early clinical studies but subsequent evaluations yielded negative results leading to discontinuation of their development as therapeutic agents in schizophrenia. Similarly despite studies pointing to a role for neurotensin (NT) in the pathophysiology of schizophrenia (Cáceda et al., 2006), there is controversy about which NT receptor to target and how best to do so.

(F) Phosphodiesterase Inhibitors—Phosphodiesterase is a family of enzymes responsible for the degradation of the intracellular signaling pathways such as cyclic AMP and cyclic GMP, which mediate function of neurotransmitters such as dopamine. Data from several lines of research implicate phosphodiesterases (PDEs) in the pathophysiology of schizophrenia. Consequently phosphodiesterase inhibitors have generated great interest as a therapeutic strategy to address positive, negative, and cognitive symptoms of SCZ.. PDE4 inhibitors (such as rolipram) and PDE10A inhibitors have been investigated, although results thus far have not been promising (Dunlop and Brandon, 2015).

(G) Kynurenine aminotransferase (KAT II) inhibitors—Kynurenic acid is an antagonist at the NMDA glutamate and alpha-7 nicotinic cholinergic receptors and behavioral studies suggest a potential link between elevated kynurenic acid levels and

cognitive deficits in schizophrenia. Kynurenine aminotransferase (KAT) is the proximal enzyme in the synthesis of kynurenic acid, making it a potential therapeutic target for addressing cognitive deficits in schizophrenia (Wonodi and Schwarcz, 2010). While there is interest in evaluating the utility of KAT II inhibitors in treating cognitive deficits in schizophrenia, studies are in their early stages.

(H) Anti-inflammatory approaches—A large number of epidemiological, experimental, and clinical studies demonstrate significant associations between schizophrenia and inflammatory conditions (Feigenson et al., 2014). A broad range of anti-inflammatory strategies has been evaluated in schizophrenia, but results have been inconsistent (Na et al., 2014). It appears that anti-inflammatory approaches might be most effective early in the illness (Kenk et al., 2015; Müller et al., 2010). Targeted immune interventions may also be utilized for etiologically specific syndromes whenever they can be identified, e.g. NMDA encephalitis, and gluten encephalopathy as mentioned earlier.

(I) Anti-oxidants—Pre-clinical studies point to the potential benefit of using antioxidants compounds, which may enhance neuroprotection as adjunctive therapy in schizophrenia. Mice with glutathione (GSH) deficit show several behavioral features linked to schizophrenia : altered prepulse inhibition, increased reactivity to stress, stimulant-induced motor hyperactivity, N-methyl-D-aspartate receptor hypofunction, altered GABA function, altered dopamine function, aberrant neuronal synchrony, and deficient myelination. A recent systematic review suggested favorable evidence for the use of N-acetyl cysteine, which increases tissue levels of GSH, in several psychiatric disorders including SCZ (Slattery et al., 2015). However, clinical evidence for efficacy is modest., for other antioxidants such as vitamin C and vitamin E.

(J) Epigenetic strategies—Several epigenetic abnormalities have been described in schizophrenia. While earlier studies principally documented abnormally condensed chromatin, recent data indicate that epigenetic abnormalities in the disorder are more complex and include a combination of both restrictive and open chromatin and dysfunctional communication between various epigenetic mediators leading to faulty regulation (Gavin and Floreani, 2014; Guidotti et al., 2011). Epigenetic factors can account for both genetic and environmental risk and their interactions in the pathogenesis of SCZ.. Furthermore, epigenetic factors are modifiable and a multitude of epigenetic pharmacological treatments are already available or in development for nonpsychiatric disorders (Ivanov et al., 2014). While none of these treatments have yet been properly investigated in schizophrenia, necessary clinical trials are underway (Millan, 2013).

4.4. Towards Personalized Therapy

Individuals with schizophrenia exhibit marked variations in their response to different therapeutic interventions. This heterogeneity in treatment response is influenced by a range of factors including age, gender, race, and genetic factors. Our current inability to prospectively predict individual response to specific treatments leads to a trial-and-error therapeutic strategy. Advances in pharmacogenomics (the study of genetic determinants of drug response) generate optimism about applying these strategies to the treatment of

schizophrenia (Arranz and Kapur, 2008; Hamilton, 2015). As we better understand the clinical moderators of treatment response (Fleeman et al., 2010) in schizophrenia, we will be better able to individualize treatment. A recent example of personalized medicine in SCZ is the ongoing work by Levy (Levy DL, personal communication, also see <http://www.nimh.nih.gov/about/director/2014/celebrating-science.shtml>). Two family members, one with schizophrenia and another with bipolar disorder, were identified to have a CNV in chromosome 9 with a duplication of the gene, which codes for glycine decarboxylase; overactivity of this enzyme leads to low glycine levels. Glycine supplementation replicably (within the same individuals) improved psychosis or mood symptoms in these patients. Another example is gluten sensitivity, which can potentially be treated by gluten-free diet, as discussed earlier.

4.5. Summary

Over 100 compounds directed at a broad range of targets in schizophrenia are currently in various stages of drug development (Table 3). Although recent results with some of the most novel drug candidates has been disappointing (Dunlop and Brandon, 2015), the recent robust genetic findings in schizophrenia generate optimism about developing more effective and specific treatments for the disorder (Hall et al., 2015). To translate these opportunities into reality, however, generation of truly testable hypotheses and their rigorous testing will be essential (Schubert et al., 2014).

At this time, it is unclear which of the current pharmacological treatment strategies will become clinically viable. What generates optimism about the likely success of one or more of these approaches is the fact that they are based on our current understanding of the biology and clinical expression of the disorder. Genomics research is leading to the delineation of converging pathways that are potential medication targets. Recent insights into the causes and mechanisms of schizophrenia offer promising cellular and molecular targets. Elucidation of distinct dimensions of schizophrenia psychopathology also allows us to develop different domain-specific treatments rather than a single treatment for all the disparate symptoms. Our recent advances in understanding the neurobiology and clinical expression of the schizophrenias generate optimism about the likelihood of important breakthroughs in the near future. How rapidly these efforts result in disease modification and improve the quality of lives of SCZ persons remain to be seen.

5. WHERE DO WE GO FROM HERE?

Several aspects of the discovery process will have to be considered in understanding the current impasse in developing newer treatments for schizophrenia. These are outlined in figure 3; we discuss the potential opportunities and next steps below.

5.1. Deconstruction of translational domains of pathophysiology

Symptom-based diagnostic categories have repeatedly shown a lack of parallel with genetic and neurobiological observations across psychiatric disorders. The National Institute of Mental Health (NIMH) has introduced the Research Domain Criteria (RDoC) project, which aims to incorporate genetic and neuroscientific data into a dimensional rather than

categorical diagnostic approach. RDoC criteria rests on the three distinct assumptions. The first assumption is that psychiatric disorders are brain circuit aberrations, rather than other neurological disorders with identifiable lesions. Second, it assumes that neural circuit dysfunction can be identified with tools such as electrophysiology, functional neuroimaging, and other new methods for establishing connections in vivo. The third assumption is that genetic and neurobiological investigations will yield “biosignatures” that will provide value for clinical decision making. Using the neural circuit as a compass, analysis will proceed both upward to variation amongst circuits, as well as downward to genetic and molecular functions that ultimately impact the circuit.

A key point is that future research will be chosen based on the broad domains of function that are controlled by these brain circuits, rather than on specific DSM diagnoses or diagnostic criteria. It has been shown that broad realms of behavior, such as fear/extinction, arousal, reward sensitivity, salience, executive function, and impulse control, rather than specific disease diagnoses, map onto these circuits. These broad domains of function may meet the criteria for endophenotypes—i.e. are quantifiable, heritable, measures of brain function that are believed to co-segregate with the illness in families, and may be expressed in unaffected family members. It is believed that these endophenotypes may be more closely associated with underlying genetic etiology than are our current complex clinical syndromes.

While RDoC offers a way to deconstruct diseases into their translational units of analyses, they many not easily led themselves into pragmatic categories that clinicians need. An agnostic re-categorization of disease entities based on biological signatures may be useful (Keshavan et al., 2013). Using data from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP), three biological subtypes of psychoses have been identified, which appear to be validated by biological measures that were not included in such classification (Clementz et al., 2016).

5.2. Translational biomarkers

Efforts to develop effective cognition enhancers will require characterization of clinical populations that are informed by cognitive neuroscience constructs that have analogous processes and neural circuits in animal models. The Cognitive Neuroscience Informed Research to Improve Cognition in SCZ (CNTRICS) group has been proposing several such assays for cognitive processes (Nuechterlein et al 2009). An example is the 5-choice serial reaction time task for visuospatial attention in rodents; this has similarities to the human continuous performance test (CPT). These tasks, in both humans and in animals, activate the prefrontal cortex and the thalamus. Similarly, the human test for executive control, the CANTAB intra- and extra-dimensional (ID-ED) set shifting task, has a rodent analog, the attentional set shifting task (ASST); both the human and rodent tests have homologies in prefrontal circuitry involvement, suggesting good construct validity. Work is ongoing to develop similar translational paradigms to assay other cognitive processes such as perception and social cognition and long term memory (Pratt et al., 2012). Using an optogenetic approach to manipulate local neural activity and functional magnetic resonance imaging to visualize such activity, Ferenczi et al (2016) have recently shown that mPFC stimulation can

modulate dopamine mediated striatal reward circuitry in rats. It is thus possible to induce anhedonia, an example of a translational biomarker..

Given the constantly evolving etiopathological models of psychotic disorders, there is a need to keep updating translationally relevant biomarker measures. For example, neuroinflammatory processes are being increasingly implicated in psychotic disorder; these processes include microglial activation, quantifiable in vivo using (R)-[(11)C]PK11195 and PET. The binding potential of this ligand appears to be increased in gray matter in patients in the early course of SCZ (van Berckel et al., 2008). Another in vivo biomarker for brain neuroinflammation is extracellular water as measured by DTI; Observations for increased extracellular volume in early course SCZ using this approach has been argued as supporting increased brain inflammation in this phase of illness (Pasternak et al., 2012). Measures of oxidative stress are also being investigated in SCZ. Early course SCZ patients have elevations in glutathione, an antioxidant, as measured by ¹H MRS (Wood et al., 2009). Thus, biomarkers may be developed based on novel pathophysiological models. Candidates for such in vivo imaging biomarkers may then be tested in animal models (Kellendonk et al., 2009). Translational discovery needs to be bi-directional, and at least some aspects of human imaging data can potentially be modelled in animals, and then used to test predictions in clinical populations. . Thus, intrinsic brain connectivity,, can be investigated using resting-state fMRI (an advantage is that the animals do not have to perform tasks) across species. Such approaches can potentially help developing translational biomarkers in the future.

Neurophysiological signals can serve as potentially translatable biomarkers for testing disease processes in preclinical models (Phillips and Uhlhaas 2015)**. An example is the gamma oscillations which are generated by the GABAergic neurons reported to be abnormal in SCZ (Lewis et al., 2008; Javitt et al., 2008), and consistent with observations of impaired working memory and altered post-mortem GABA expression in this illness. A future step would be to see whether GABAergic drugs would alleviate gamma alterations and cognitive deficits in genetic and pharmacological animal models (McNally et al., 2011).

5.3. Translationally relevant preclinical models

Recent insights into the genetic and neural bases of SCZ, can potentially serve to address translational gap and facilitate the development of more effective therapeutic targets.. Serendipity should be replaced by hypothesis-driven approaches for drug discovery. Pathophysiological targets in the recent disease models need to be validated by translationally relevant measures to be tested in the appropriate animal models. This will hopefully increase the likelihood of success in SCZ drug discovery and eventually lead to effective treatments.

An emerging technology that could potentially accelerate treatment discovery is the use of human induced pluripotent stem cells (iPSCs) which can be derived directly from the patients' skin or blood cells. It should be possible to generate iPSC derived neurons, and use them as model systems for characterizing disease physiology as well as for assays of new drug therapies. While this technology is still evolving, initial iPSC findings are emerging in SCZ (Brennand et al., 2012).

5.4. Leveraging advances in genetics

Recent advances in the genetic architecture and disease pathways in SCZ have been exciting, and have raised the hope that they will pave the way toward novel therapeutic discoveries. However, the path from finding genes to developing new drugs is not straightforward, and is limited by the fact that the majority of genes are of small effect, and involve complex gene-gene and gene environmental interactions. Schubert et al (Schubert et al., 2014) have outlined a series of steps which may make this possible (Figure 3). First, the relevant phenotypes (which may be the clinical diagnosis, or the intermediate phenotypes that may get us closer to the genotype) need to be characterized. Second, the genes associated with these phenotypes need to be identified using either candidate gene or GWAS strategies. Custom microarray chips such as PsychChip (Crowley and Kensuke, 2015), have made this cost-effective. These genes need to then be prioritized to include those where the functional significance is known, using gene annotation (attaching known biological function and physiological pathways to the identified gene elements). Several automated tools are available to quickly annotate genes, such as DAVID and KEGG. Third, the directionality of the gene effect on the target physiological process needs to be determined; studies of gene expression and gene knockout animal models help in this process. These steps will then lead to the identification of actionable therapeutic targets. The next task will be to identify a therapeutic agent that matches the physiological target. Finally, the safety of such a compound will need to be determined in animal toxicology, and phase 1 human clinical trials.

Through genomewide association studies (GWAS), we are able to test the entire genome for variation, rather than simply testing hypotheses about candidate genes like in the past. The Psychiatric Genomics Consortium (PGC) was established, by a consortium of researchers around the world jointly analyzing their GWAS datasets. In so doing, roughly 200 genetic associations have been discovered, including more than 100 SNPs associated with SCZ (Nature 2014). One of the major advantages that has come from GWAS and the identification of susceptibility loci is that in some cases, the results have become demonstrative of specific biological pathways, as opposed to just a list of susceptible genes.

Several actionable targets may already be identifiable, though much work remains to be done in characterizing these targets before they are ready for clinical testing. For example, SCZ has been linked to pathways implicated in immune function and glial cell function (Duncan et al., 2014), postsynaptic density structure (Purcell et al., 2014), glutamatergic pathway (Purcell et al., 2014), calcium channel signaling (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), and the fragile x mental retardation protein (Purcell et al., 2014). Several L-type calcium channel genes such as CACNA1c, CACNA1B2 and CACNA1D have been linked to both SCZ and bipolar disorder. Calcium channel blockers are available for treatment of hypertension, and have yet to be systematically tested in SCZ or bipolar disorder. Another example is the several genes linked to glutamatergic neurotransmission (Schubert et al., 2014), such as GRIN2A, GRIA1 and CLCN3, which suggest potential avenues for glutamatergic modulators in these disorders (Stevenson et al 2016)..

Lencz and Malhotra (2015) examined the 341 genes within the 108 loci recently implicated in schizophrenia (Schizophrenia Working Group, 2014) against available databases of registered and approved drugs, and identified 20 “druggable” genes. Prioritized genes of neuropsychiatric interest included those related to dopamine function (DRD2), glutamate (GRIN2A) and calcium or potassium channels (CACNA1C, CACNB2, CACNA1I, and HCN1). While much work remains to be done, such efforts offer us a good start in developing novel therapeutic targets for future drug development.

Additionally, stratification of patient samples based on genetic and phenotypic data (similar to cancer studies) might increase the yield in demonstrating clinically meaningful effect sizes (Rabinowitz et al., 2013). For example, a strong association in a recent GWAS of SCZ was in the dopamine 2 (DRD2) receptor gene, the target of all currently used antipsychotics. However, amongst these variations, some are more target-able than others, especially mutations that reflect gain-of-function. Drugs that modulate these genes may have a good chance at being therapeutic. There are currently Phase II trials for inhibitors gain-of-function mutations in cholesterol metabolism, with the idea that they could be effective for patients unable to tolerate statins (Dadu and Ballantyne, 2014).

Another way in which genetics has been implicated in locating new targets is in imaging-genetic analyses. Unlike studies like GWAS, these studies can illuminate clusters of SNPs that interact, each one contributing toward a quantitative trait related to illness-associated biological pathways. In this way, the functionality of genes and the pathways of gene clusters can be used to achieve a greater understanding of disease mechanism. Studies using functional MRI scan have identified impairments in functional neural connectivity across schizophrenia cohorts, mediated by genes regulating specific neurodevelopmental processes. By identifying these altered pathways and underlying gene mutations, they have formed another platform for novel, targeted drug therapies (Meda et al., 2014).

Another issue with validating targets is ensuring that therapeutic levels of a drug can be delivered to the brain and that the drug binds its target and modifies the neural circuit in the desired direction, at that therapeutic level. It has been pointed out that previous clinical trials where targets were invalidated may not have actually been testing this hypothesis. With cost and efficiency as large considerations, it is important to convincingly validate and invalidate targets. Finally, having targetable, novel genes or biomarkers to create new therapeutics may re-convince some of the biotechnology and pharmaceutical industries who have fled from psychiatry into other fields such as cancer or metabolism with more directable molecular targets (Pankevich et al., 2014).

Regardless of the study design or method, the prevailing emphasis has centered on neural connectivity and circuitry in obtaining better understanding of underlying disease mechanism. This complexity, while perhaps serving as a barrier to therapeutics, may also ultimately provide the key for development of more efficacious future treatments. Optogenetics has been used to accelerate the pace of research into mechanism of disease by manipulating individual neural circuit elements underlying disease-related behaviors in rodents. Understanding the neural circuits mediating these behaviors may ultimately inform

the rational development of therapeutic interventions—whether they be oral pills, electrical, magnetic, or optic in nature (Steinberg et al., 2015).

5.5. Minimizing failure in early pre-clinical trials

Treatment development is slow and highly expensive. The industry spends nearly two billion Us\$ to bring a drug into the market; of every 10,000 compounds investigated, about 250 make it to the preclinical testing, and about 5 enter clinical trials, and perhaps one gets approved for clinical use (Paul et al 2010; Director's blog: experimental medicine <http://www.nimh.nih.gov/about/director/2012/experimental-medicine.shtml>). In order to address this, NIMH has proposed new guidelines for clinical trials to improve the “hit rate” of new treatments. This “Experimental medicine” approach: involves quick win- fast fail strategies, whereby early indications of a treatment being likely to fail (i.e. not showing target engagement, such as showing full receptor occupancy coupled with clinical benefits) will lead to a “no go” decision”, while early indication of target engagement will lead to a “go” decision. (Insel and Gogtay 2014).

5.6. Maximizing yield of Clinical trials

Some of the steps that can and should be taken to minimize failure rate in the later phases of clinical trials include: a) include study samples that mirror “real-world” patients, b) test the highest tolerated doses of experimental drugs in clinical trials to reduce the “off-label” high doses that are often used for chronic patients who frequently develop treatment-resistance after multiple episodes, c) allow schizophrenia subjects whose urine screen is positive for marijuana [the most widely used recreational drug in schizophrenia with tobacco] because up to 70 % of eligible subjects are excluded for that reason which prolongs the trials and their costs and deprives the field from knowing the efficacy of new agents in “real-world” patients, d) include endophenotypes in the selection of the sample so that a semblance of homogeneity is achieved to dilute the disruptive effects of heterogeneity in this syndrome, e) require a minimum threshold of intra- and inter-rater reliability on the rating scale [such as the PANSS] so that the huge variability in measurement is narrowed, f) allow testing new drugs for symptoms, not an artificial diagnosis comprised of a cluster of symptoms agreed upon by a committee, g) give more respect to secondary outcomes that are postulated pre-hoc, h) exclude sites with an “outlier” placebo response in two prior studies [which requires data mining and sharing by industry], i) the FDA should grant a significantly longer exclusivity [upto 25 years instead of 17 years] for drugs with a completely new mechanism of action developed via translational research that builds on emerging pathophysiological findings to incentivize companies to re-invest more R&D for schizophrenia, whose disability and financial burden to society are huge. This is particularly important given recent reports that mental disorders are among the most costly conditions, costing over 200 billion in the US (Roerhig 2016).

5.7. Repurposing drugs

“Repurposing”, which refers to the discovery of new uses drug treatments that are currently or no longer used, cost much less to develop than new drugs (Boguski et al., 2009). Thalidomide, originally used for morning sickness and dropped from use because of major birth defects, has recently been found to have benefits in treating certain complications of

leprosy. Duloxetine and antidepressant, has now a new indication in stress incontinence, and bupropion is now marketed for its beneficial effects on reducing nicotine craving. Mining post-marketing safety monitoring data could potentially yield useful insights; another way is to capitalize on online communities, crowdsourcing and social media where communities of medication consumers may share individual genetic data or report potential beneficial side effects of existing drugs (Boguski et al., 2009).

5.8. Using existing treatments more effectively to optimize individual outcomes

Recognizing that development of new more effective treatments is a hope for the future, it is imperative that practitioners utilize existing treatments in the best-possible way to optimize outcomes for each of their schizophrenia patients. While several clinical practice guidelines outlining best practices have been published, essential principles can be summarized as informed practice, targeted and measurement-based care, and individualized collaborative treatment (Tandon et al., 2006).

5. CONCLUSIONS

The pharmacological treatment of SCZ is in need of a paradigm shift. Following the introduction of antipsychotics into clinical practice over half a century ago, progress has been modest. Current treatments are fairly effective in treating some aspects of the illness, but not others. Presently, we lack proven preventive strategies or effective treatments for the prodromal phase when substantial damage occurs. Persons with SCZ demonstrate extremely varied responses to the different therapeutic interventions and our lack of reliable methods to predict such variations necessitates a trial-and-error treatment strategy. Treatments continue to be associated with significant adverse effects. In large measure, this state of affairs is the result of an inadequate understanding of the pathophysiological substrate underlying this complex syndrome. While much effort has gone into modifying and changing existing antidopaminergic medications; the added benefits of such incremental research have been modest.

Spectacular recent advances in genetics and molecular neurobiology, however, generate enthusiasm about the potential of applying these strategies to substantially upgrade the drug treatment of SCZ. Genomic advances now enable a more precise dissection of the heterogeneity of SCZ and the development of therapeutic agents directed at defined “disease-specific” targets. Such advances will allow the schizophrenia syndrome to be deconstructed into etiologically distinct subgroups. There is likely to be more dividend from systematic investigation of non-dopaminergic mechanisms that may underlie schizophrenia pathophysiology.. Future research needs to invest in clinically meaningful and translationally relevant animal models and in vivo screening methods for novel therapeutic targets, optimal clinical trial design and trial designs, As we wait for these methodologies to deliver on their promise in the near future, however, it is important to more optimally utilize existing agents by practicing evidence-based and measurement-based medicine.,

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Abbreviations

SCZ	Schizophrenia
GWAS	Genome-wide association studies
CNVs	Copy number variants

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Figure 1.
Pathophysiological models of SCZ (adapted from: Keshavan et al 2011).

Figure 2.

Proposed treatment targets in schizophrenia. GABA, gamma aminobutyric acid; NMDA: N-methyl D-aspartate; MGLu: metabotropic glutamate; COMT: catechol o-methyl transferase; CB1: cannabinoid 1 receptor; PDE: phosphodiesterase; GlyT: glycine transporter. SHT: 5 hydroxy tryptamine.

Figure 3.
Steps to identify putative therapeutic targets for schizophrenia.

Table 1

A. “Typical” or First-generation antipsychotics
I. Phenothiazines (22)
Acetophenazine, Butaperazine, Chlorpromazine, Chlorproethazine, Cyamemazine, Dixyrazine, Fluphenazine, Levomepromazine, Mesoridazine, Perazine, Perphenazine, Piperacetazine, Pipoptiazine, Prochlorperazine, Promazine, Propericiazine, Sulfuridazine, Thiopropazate, Thioproperazine, Trifluoperazine, Triflupromazine, Thioridazine.
II. Butyrophenones (11)
Benperidol, Blonanserin, Bromperidol, Droperidol, Fluanisone, Haloperidol, Melperone, Moperone, Pipamperone, Timiperone, Trifluperidol.
III. Thioxanthenes (5)
Chlorprothixene, Clopenthixol, Flupenthixol, Thiothixene, Zuclopenthixol
IV. Dihydroindolones (2)
Molindone, Oxypertine
V. Dibenzoxazepines (2)
Clotiapine, Loxapine,
VI. Diphenylbutylpiperidines (3)
Fluspirilene, Penfluridol Pimozide,
VII. Benzamides (4)
Nemonapride, Sulpiride, Sultopride, Tiapride
VIII. Iminodibenzyl (2)
Clozapramine, Mosapramine
B. “Atypical” or Second-generation antipsychotics
I. Benzo (diaz- or thiaze-) Pines (5)
Asenapine, Clozapine, Olanzapine, Quetiapine, Zotepine
II Indolones and diones Ones (6)
Iloperidone, Lurasidone, Paliperidone, Perospirone, Risperidone, Sertindole, Ziprasidone,
III. Benzamides (1)
Amisulpride
IV. Benzamides (2) (Dopamine D-2 Partial Agonists)
Aripiprazole, Brexpiprazole, Cariprazine

Table 2

History of psychiatric drug development by comparison with the ideal approach seen elsewhere in medicine. Roadblocks and strategies for accelerating drug discovery are identified.

Historical approach	Desirable approach	Roadblocks	Next steps
<div><div>Clinical observation</div><div>↓</div><div>Empirical Open trials/ Case reports</div><div>↓</div><div>RCTs</div><div>↓</div><div>Identify mechanism Of action</div><div>↓</div><div>Search for new drugs with similar effect</div></div>	<div><div>Discover etiopathology</div><div>↓</div><div>Identify treatment target</div><div>↓</div><div>Synthesize/ repurpose novel treatments</div><div>↓</div><div>Animal screening</div><div>↓</div><div>Clinical trials</div></div>	<div><div>Symptom-based nosology used as “gold-standard for validation of etiopathological Biomarkers</div><div>Heterogeneity of causes, course, and outcome; Pleiotropy</div><div>Lack of valid animal Models</div><div>Design issues; regulatory issues</div></div>	<div><div>Trans-diagnostic deconstruction of genomic, proteomic and transcriptomic data, R-DoC Approach</div><div>Repurposing existing treatments</div><div>Rapid screening of Target molecules</div><div>in vitro phenotypes for screening</div><div>National network of clinical trialists</div></div>

Table 3

Novel drugs under development for schizophrenia.

MOLECULAR TARGET	PSYCHOPATHOLOGICAL TARGET and MECHANISM OF ACTION	COMPOUND and STATUS
DOPAMINE		
<u>D-1 + D-2 Antagonism</u>	Some advantage in animal models	Zicronapine- Phase III
<u>D-1 agonism</u>	Cognitive deficits by modulating prefrontal dopamine function	Dihydraxidine, others. Mixed results despite strong neurobiological rationale
<u>D-2/3 partial agonism</u>	Positive symptoms and disorganization as also negative and cognitive symptoms by “stabilizing” dopamine function Similar to currently available aripiprazole	Bifeprunox- Development stopped in phase III RP 5063- Phase II
<u>Catechol-O-methyltransferase (COMT) inhibitors</u>	Cognition as Add-on to antipsychotic by increasing dopamine in prefrontal cortex where COMT breaks down dopamine	Entacapone and tolcapone that are currently used in Parkinson's disease in conjunction with L-Dopa Tolcapone can better cross the blood-brain barrier but is associated with greater hepatotoxicity. Experimental
<u>Dopamine signaling pathways</u> (A variety of targets)	Cognition Positive symptoms	Exploratory Various
SEROTONIN		
<u>5HT_{2A} antagonists</u>	Psychosis with reduced EPS liability	ITI-007, Phase II
<u>5HT_{2A} Inverse agonist</u>	Augment speed or degree of antipsychotic effect and reduce EPS Build on 5HT _{2A} antagonism	Add-on to antipsychotic treatment Pimavanserin (add-on to antipsychotic)- Phase II
<u>D-2 antagonist</u> + <u>5HT_{1A} agonist</u>	Psychosis with additional benefits on cognition and negative symptoms Modulation of PFC dopamine	Variety of Agents in different stages of development Property of some ‘Second-generation antipsychotics’.
<u>5HT₆ antagonists</u>	Cognitive and negative symptoms Add-on, modulation of dopamine tone	Several agents mostly in Phase II of development
GLUTAMATE		
<u>Glycinergic agents</u>	Positive symptoms, negative symptoms, cognitive symptoms Enhance NMDA activity	Serine, Cycloserine, etc. (Add-on to antipsychotic) Weak and inconsistent effects
<u>Glycine transporter 1 (GlyT1) inhibitors</u>	Positive symptoms, negative symptoms, cognitive symptoms Enhance NMDA activity via allosteric glycine site	Bitopertin- Development stopped after extensive phase III Others at various stages of development
<u>Metabotropic glutamate 2/3 agonists</u>	Positive, cognitive, and negative symptoms. Both Monotherapy + Add-on Modulate glutamate release	Pomuglumetad methionil: Development stopped after phase III Development of others stopped for now
<u>Metabotropic glutamate 1/5 agonists and positive allosteric modulators</u>	Positive symptoms, Cognitive deficits Monotherapy + Add-on Antipsychotic activity in animal models	Several agents in early development. Mixed results thus far
<u>Metabotropic glutamate 5 antagonists and negative allosteric modulators</u>	Cognitive deficits Add-on to antipsychotic Benefit in animal model	Several agents in early development. Mixed results thus far
<u>AMPA receptor agonists and positive modulators</u>	Cognitive deficits, Negative symptoms Add-on	PF-04958242. In Phase I
CHOLINERGIC		

MOLECULAR TARGET	PSYCHOPATHOLOGICAL TARGET and MECHANISM OF ACTION	COMPOUND and STATUS
<u>Muscarinic M-1 agonists and partial agonists</u>	Psychosis, Cognitive deficits Monotherapy	Xanomeline- Development stopped because of toxicity despite evidence of efficacy Other agents in early stages of development
<u>Nicotinic agonists</u> <u>Mainly alpha-7 nicotinic agonists or partial agonists</u> <u>but some alpha4-beta2 agonists</u>	Cognitive deficits Add-on therapy Nicotinic mechanisms in pathophysiology	Several agents in different stages of development. Encenicline has not shown efficacy in in two Phase III trials
GABA		
<u>GABA alpha-2 agonists and partial agonists</u>	Cognitive deficits, Positive symptoms Add-on and monotherapy Synchronize pyramidal cell function and increase gamma power in PFC	Several agents in early development Mixed results thus far despite strong neurobiological rationale
<u>GABA alpha-5 inverse agonists</u>	?? neurogenesis Increase LTP and muscarinic activity	Several agents in early development
ASSORTED		
<u>Phosphodi-esterase PDE4 & 10A inhibitors</u>	Positive symptoms, Cognitive deficits Monotherapy and mostly Add-on	Several agents mostly in Phase II of development Current interest in PDE-10 inhibitors Mixed results thus far
<u>Histamine H-3 antagonists and some inverse agonists</u>	Cognitive deficits Add-on therapy to antipsychotic.	Several agents mostly in Phase II of development Irdabisant is the agent furthest along in phase II
<u>Neurokinin-3 antagonists</u>	Positive symptoms, Cognitive deficits Add-on and monotherapy	No current development because of negative results with osanetant and talnetant
<u>Cannabinoid receptor antagonists</u>	Positive symptoms, Cognitive deficits Monotherapy and add-on Cannabis precipitates psychotic symptoms	Mixed results with rimonabant Currently in development hiatus despite much interest
<u>Methyltransferase and Histone deacetylase inhibitors</u>	Positive symptoms Add-on to antipsychotic Epigenetic strategies	Several agents in early stages of development