Progress in Neurobiology 152 (2017) 3–20

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

New drug developments in psychosis: Challenges, opportunities and strategies

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ARTICLE INFO

Article history:
Received 5 July 2016
Accepted 11 July 2016
Available online 9 August 2016

Keywords:
Psychosis
Schizophrenia
Antipsychotics
Glutamate
Dopamine
Clinical trials
Efficacy
Drug development
Pharmacology

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.

Contents

Abbreviations: SCZ, Schizophrenia; GWAS, Genome-wide association studies; CNVs, Copy number variants.

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http://dx.doi.org/10.1016/j.pneurobio.2016.07.004
0301-0082/

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, 1956). 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