Published in final edited form as:

Trends Pharmacol Sci. 2012 October ; 33(10): 515–521. doi:10.1016/j.tips.2012.06.006.

From antipsychotic to anti-schizophrenia drugs: role of animal models

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Abstract

Current drugs treating schizophrenia are mostly variations on a theme that was started over 50 years ago. Sadly, clinical efficacy has not improved substantially over the years. We argue that both clinical and preclinical researchers have focused too much on psychosis, which is only one of the hallmarks of schizophrenia. This narrow focus has hampered the development of relevant animal models and human experimental medicine paradigms. Other fields in psychiatry, most notably in the realms of addiction and anxiety, did prosper from results obtained in parallel studies using animal models and experimental human studies. Lessons to be learned from those models and recent genetic and cognitive insights in schizophrenia can be utilized to develop better animal and human models and, potentially, novel treatment strategies.

Keywords

Schizophrenia; psychosis; cognition; dopamine; translational psychiatry

Introduction

Although the first drugs used in the treatment of disorders of the central nervous system (CNS) (e.g. potassium bromide, chloral hydrate and lithium) were already discovered in the 19th century, it was not until the discovery of a series of psychotropic drugs in the 1950s that the pharmaceutical industry developed a strong interest in psychiatric disorders. Typical examples of these early psychotropic drugs include the anxiolytics meprobamate and chlordiazepoxide, antipsychotics such as chlorpromazine, and the antidepressant drugs imipramine and iproniazid.

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¹This article summarizes the 2011 Neuroscience & Cognition Utrecht Debate

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Serendipity played a key role in these discoveries, and certainly in the identification of the prototypic psychotropics [1]. For instance, the emergence of chlorpromazine was due to the fortuitous finding that an antihistaminergic phenothiazine structure, promethazine, induced “euphoric quietude”, a “state of indifference” in non-psychiatric patients, whereas surgery patients remained “calm, somewhat somnolent and relaxed” [2]. A chemically closely related structure, chlorpromazine, was subsequently developed and successfully tested clinically by Laborit and coworkers [3]. This success led to a rapid spread of the use of chlorpromazine as the first antipsychotic drug, revolutionizing the clinical treatment of schizophrenia patients.

The next decades were characterized by the further development of these so-called first-generation (or ‘typical’) antipsychotics, all being potent dopamine D2 receptor antagonists [4]. These typical antipsychotics – often called neuroleptics – treat the psychosis (delusions and hallucinations) that is part of schizophrenia. Wards became quiet, patients manageable, and it greatly improved the prognosis of the illness, if only by reducing the deadly catatonia [2]. However, these drugs proved to be less effective in treating symptoms such as anhedonia or lack of motivation [5], core symptoms according to Bleuler, currently called ‘negative’ symptoms. Neuroleptics are equally ineffective in normalizing cognitive dysfunctions [6], described as the core symptom by Kraepelin (Box 1).

Neuroleptics have some severe and burdensome extrapyramidal side effects, such as dystonia and parkinsonism [5]. One of the promising antipsychotics from this early era was clozapine because, in contrast to the typical antipsychotics, this drug does not lead to extrapyramidal side effects. Nevertheless, because 1% of patients develop agranulocytosis when treated with clozapine, the drug was withdrawn from the market; however, it was later reintroduced as a third-line treatment under a strict safety protocol on the basis of its unique efficacy to treat refractory psychosis [7]. Actually, clozapine heralded the development of the second-generation (or ‘atypical’) antipsychotics, which largely lack extrapyramidal side effects and do not increase prolactin levels, as do typical antipsychotic drugs.

The past 20 years have been characterized by an intense search for clozapine-like atypical antipsychotics that lack serious side effects. Several new atypical drugs have been developed (e.g. risperidone, olanzapine, quetiapine, ziprasidone and the partial dopamine receptor agonist aripiprazole) with high expectations that these compounds could treat both negative and cognitive symptoms. Unfortunately, it is now clear that these drugs have little or no added value to the classic typical antipsychotic drugs, at least with regard to the negative [5] and cognitive aspects of schizophrenia [6]. Although newer antipsychotics generally induce considerably fewer extrapyramidal side effects than the first-generation antipsychotics, they have introduced other serious side effects, notably weight gain and metabolic syndrome [5].

Like the typical antipsychotics, most second-generation drugs still share some dopamine D2 receptor antagonism (in combination with blockade of various serotonin – particularly 5-HT₂ – receptors) [8]. Most compounds developed thus far, and most of those in the clinical pipeline, are to some extent based on comparable dopaminergic and serotonergic receptor affinities, although recently other drugs targeting cholinergic and glutamatergic transmission have appeared (e.g. [9]). Importantly, all available drugs are mainly (or only) active in reducing psychotic symptoms; no breakthroughs have occurred in finding real ‘anti-schizophrenia’ drugs (i.e. medicines that also reduce the symptoms that form the core of the illness, such as the negative and cognitive symptoms). In that sense, one could state that the clinical pipeline for new drugs for schizophrenia is virtually empty, although a variety of targets such as glutamate and GABA are currently being tested in clinical and preclinical settings. Moreover, the more recent emphasis on developmental abnormalities as a

pathogenic mechanism in schizophrenia may eventually prove to be fruitful in the development of new drugs.

Fundamentally, the barrier in the discovery of novel treatments for schizophrenia lies in our lack of understanding of the underlying biological processes and the differences between the brains of healthy subjects and those of schizophrenia patients. However, the introduction of powerful genetic and neuroimaging tools have changed our insights, highlighting which classes of genes confer vulnerability to schizophrenia and how exactly brain development is attenuated (see next section). Unfortunately, to date most animal models or tests used to find new antipsychotics are still based on narrow biological hypotheses regarding the disease (see for comprehensive review [10]); new animal models based e.g. on developmental or genetic manipulations have been introduced, but these still need to establish their predictive value because they have not yet generated clinically approved therapeutics. New insights into biological mechanisms in the human brain along with the development of relevant animal models are urgently needed to make a next step in pharmaceutical treatment. Clearly, this is easier said than done. Yet, lessons can be learned from good practices in other fields of psychiatry, where a better understanding of neurobiological causes has helped to come to entirely new treatments. Several of these examples will be highlighted in this article. We will end by proposing how such successful examples in combination with current insights from human research can lead to more relevant research on the neurobiology of schizophrenia, and break through the present deadlock.

Moving from antipsychotic to anti-schizophrenia treatments

As indicated in the previous section, currently licensed antipsychotics are dopamine receptor blockers and mainly decrease psychosis. Although recent studies using selective knockouts (e.g. targeting specifically glutamate synapses; see review [11]) start to differentiate models from the old “amphetamine antagonism” models, it is important to realize that most of the currently licensed antipsychotics were validated using animal models that have essentially not changed over the last six decades [12]. Consequently, the prognosis of schizophrenia has not changed fundamentally since the introduction of chlorpromazine [13]. Indeed, the descriptions by Kraepelin and Bleuler suggest that they considered psychosis no more than a non-specific phenomenon of the illness; psychosis is also not specific for schizophrenia but also seen in other psychiatric disorders. This perspective would suggest, in turn, that the dopamine system, though important in the pathogenesis of psychosis, may not be that relevant for schizophrenia. In the multitude of genetic studies, currently encompassing over tens of thousands of schizophrenia patients, genes identified as conferring increased risk for schizophrenia almost without exception do not code for the dopamine system, but rather are related to synaptic and glia function, neuronal growth, and the development and stabilization of cortical microcircuitry [14].

These genetic findings dovetail with clinical and epidemiological data suggesting that schizophrenia is in part a neurodevelopmental disorder. We now know, as suggested by Kraepelin over a century ago, that the onset of schizophrenia is heralded by cognitive and negative symptoms [15]. Consistent with the descriptions by Kraepelin, we have found that the cognitive symptoms precede the onset of frank psychosis by an average of nine years [16]. Moreover, children at risk for schizophrenia show developmental delays, especially in the social domain [17]. Evidence from post-mortem neuropathological studies furthermore suggests that schizophrenia is at least partially due to abnormal neurodevelopment [18]. For instance, histological studies have shown aberrantly located or clustered neurons, especially in layers of the entorhinal cortex and in the neocortical white matter; such abnormalities are indicative of an early neurodevelopmental anomaly affecting neuronal migration, survival, and connectivity [18] (Figure 1). Consistent with these post-mortem studies, recent *in-vivo*

neuroimaging studies show small, but detectable, decrements in brain volume at psychosis onset and these abnormalities progress as the illness develops [19]. This progressive loss of brain volume is related to global outcome of the illness [20]. In short: All of the recent genetic and neuroimaging studies confirm what psychiatrists who had no other tools than their own observational powers already knew; that is, schizophrenia is not primarily, if at all, a psychotic disorder: it is a cognitive illness with various degrees of cognitive decline.

The focus on treating psychosis that has dominated pharmacological research in schizophrenia over the last sixty years was therefore not based on any theoretical concept of the illness, but on the practical feasibility to develop such drugs. Since it has become clear that schizophrenia cannot be reduced to its psychotic symptoms and is not (only) a result of abnormal dopamine functioning, but rather a progressive neurodevelopmental cognitive disorder, the time has come to take the earliest descriptions of the illness seriously and focus on the cognitive core of the disorder. There is an urgent need to better utilize some of the newer animal models that take these insights from human studies into account, so that new drugs can be developed with better predictive validity with regard to the cognitive dysfunction associated with schizophrenia.

Best practices in other realms

To develop animal models that have better power for predicting clinical efficacy, it may be useful to examine cases in other fields of psychiatry where predictive models have been implemented successfully [21]. However, even within the field of schizophrenia research as previously envisioned, animal models predictive of antipsychotic efficacy are well-established. For example, in rats, the ability of a compound to block the disruptive effects of a dopamine agonist on prepulse inhibition of startle (a measure of sensorimotor gating that is deficient in patients with schizophrenia) has been used for years as a highly reliable predictor of antipsychotic efficacy [22]. A benefit of this model is that homologous behaviors are assessed in both the animal and the clinical condition. Nevertheless, it suffers greatly from what has been termed “receptor tautology” insofar as the abnormal behavior is elicited by a dopamine D₂ receptor agonist and is, tautologically, sensitive to any antagonist at the same receptor. As argued above, such dopamine agonist-induced animal models are ineffective in identifying treatments for the important cognitive deficits and negative symptoms that are not mostly responsive to dopamine D₂ antagonists.

Other examples of successful animal models provide further encouragement that such limitations can be overcome. In the field of drug abuse, for example, preclinical animal model research in combination with parallel human studies led to a new treatment for nicotine dependence. Using parallel experimental designs, rodents, infrahuman primates, and humans all self-administer nicotine [23,24], which is believed to support the tobacco smoking habit. Mice lacking a particular subset of nicotinic acetylcholine receptors (nAChR) – the beta₂ subunit – were found to not self-administer nicotine, although they still self-administered cocaine [25]. Restoring beta₂-nAChRs in the brain reward circuit restored nicotine self-administration in the mutant mice [26]. Rodent studies then demonstrated that varenicline – a partial agonist at beta₂ nAChRs – decreased nicotine self-administration [27]. Based on these animal model experiments, human experimental medicine studies using parallel research designs in clinical trials confirmed that varenicline helps people to quit smoking [28]. Thus, as predicted by the preclinical research, varenicline is now used clinically as one of the best treatments available for smoking cessation.

Similarly, in the field of panic disorders and phobias, animal model research has engendered clinical research that is showing promise for a novel treatment strategy, combining pharmacotherapy with cognitive behavioral therapy (CBT). Fear-related disorders are often

treated with antidepressants, but these drugs are clearly not optimal, need many months of treatment (with all the side-effects for free), and are hardly better than placebo. Because chronic administrations of traditional anti-anxiety or antidepressant drugs have not proven satisfactory, CBT remains the most effective therapy for panic, post-traumatic stress disorder, and other fear-related disorders, but it is expensive. Basic studies in animals demonstrated that extinction learning – i.e. the basis of CBT – involves distinct neuronal populations and targets that differ from those supporting the original fear learning [29](Box 2). Further animal studies using a fear-potentiated startle paradigm then demonstrated that this extinction learning could be accelerated by treatment with the glutamatergic partial agonist d-cycloserine [30,31]. Subsequent experimental medicine studies confirmed similar effects in patients, using parallel methods based on the animal literature [32,33]. As a result, a novel therapeutic intervention has been developed [34].

Some lessons may be learned from these and related examples of successful animal models having predictive validity for clinical efficacy. One feature that is common to many validated animal models is that the outcome being measured in the animals exhibits some degree of homology or at least close analogy to parallel measures used in efficacy trials early in clinical development. Many of these cross-species translational measures qualify as endophenotypes that have been associated with the psychiatric disorder in question. Thus, the chances for developing a predictive animal model appear to increase to the degree that the measures used can be validated in human experimental medicine studies [21]. The outcomes of these early human studies are then translated into appropriately designed clinical trials involving larger populations of patients. When animal model findings are used to move directly to large-scale clinical trials involving only rating scales of clinical status, the success rate is quite low (Figure 2). Overall, successful examples were based on insights regarding the mechanism underlying disturbed function, in the rodent and human brain.

How to proceed in schizophrenia?

Although these examples of successful animal models share the use of cross-species translational measures to assess outcome, few utilize manipulations that have clear etiological validity. Because we do not have psychiatrically disordered rodents [10], investigators must select both a manipulation and a measure in order to define an animal model [35]. For example, antipsychotic drugs are traditionally assessed using a dopamine agonist, such as amphetamine, as the manipulation and a schizophrenia-related behavior, such as reduced sensorimotor gating, as the measure. Using gating measures in combination with other disruptive agents, such as hallucinogens, does not provide a model that predicts antipsychotics. Thus, both the manipulation and the measure must be appropriate.

Missing in most of the animal model work done in the field of schizophrenia is the utilization of developmental perturbations that might capture aspects of the etiological factors that impact the early course of the disorder, as emphasized above. Recent studies, however, are increasingly using developmental manipulations in conjunction with measures relevant to the core cognitive deficits that negatively impact functional outcome in patients. A range of relevant perturbations applied perinatally or during early development in rodents, such as viral or pharmacological challenges, maternal deprivation, or social isolation, have proven to yield schizophrenia-like behavioral and cognitive abnormalities that emerge most prominently around the time of puberty [36]. Not only might such developmentally specific models provide platforms for the discovery of novel pro-cognitive compounds for use in schizophrenia, they may also set the stage for the identification of disease-modifying agents that could be useful during the prodrome, before the illness has reached its full expression.

These advancements in animal models need to go hand in hand with advances in the clinical field. As outlined in Box 1, cognitive deficits comprise the core disturbance in schizophrenia. Yet, so far we remain without a single established treatment for these problems. To begin to rectify this concern, the NIMH-funded MATRICS Program (Measurement and Treatment Research to Improve Cognition in Schizophrenia) developed a broad consensus regarding the nature of the cognitive impairments in schizophrenia and how they might best be assessed and treated. MATRICS identified seven domains of cognitive deficits in schizophrenia, and the USA Food and Drug Administration then expressed willingness to license compounds to treat any or all of these cognitive domains in patients already maintained on antipsychotic medications. The subsequent NIMH-funded TURNS Program (Treatment Units for Research on Neurocognition in Schizophrenia) tried to develop and validate clinical trial approaches for use in assessing the efficacy of compounds intended to treat cognitive deficits in schizophrenia patients already maintained on stable antipsychotic medications, but so far has met with little success.

After MATRICS, several potential pro-cognitive compounds were tested in Phase 2 trials with schizophrenia patients. Selections of the initial compounds were based on weak preclinical evidence derived primarily from studies having more relevance to Alzheimer's disease than schizophrenia, and none were examined in experimental medicine paradigms based on the preclinical findings. Some encouraging results with alpha-7 nicotinic agonists having positive effects on cognition in schizophrenia have been presented recently at meetings [37]. Similarly, explorations of glycine uptake inhibitors have shown promise for treating negative symptoms, although the animal models used to move these compounds forward were not designed to assess negative symptoms [38]. To date, the eagerness to identify a first-in-class anti-schizophrenia treatment may have precluded a rational systematic approach to drug discovery and development in this difficult area.

To modernize our approach to developing pro-cognitive treatments, the CNTRICS (Cognitive Neuroscience measures of Treatment Response of Impaired Cognition in Schizophrenia) program conducted a series of workshops on how to better utilize neuroscience- and brain-based translational approaches to the understanding and modification of cognition. The goal of these meetings was to further improve the clinical assessment of potential pro-cognitive agents in schizophrenia, using experimental medicine paradigms that can be linked empirically to parallel studies in animals. It must be emphasized that the identification of efficacious pro-cognitive treatments will be difficult, as highlighted by the meager results from the small-scale attempts to demonstrate clinical efficacy to date. One promising recent approach to address this degree of difficulty comes from public-private partnerships such as the European Union's "Novel Methods leading to New Medications in Depression and Schizophrenia" (NEWMEDS) initiative, in which multiple pharmaceutical companies are partnering together with academics to pool knowledge and resources in validating improved psychiatric animal models. Although not yet solving the problem, these programs have at least laid the foundation for identifying anti-schizophrenia treatments that might ameliorate the core deficits seen in this group of disorders [39].

Concluding remarks

Overall, there is an urgent need for improved translational tools to facilitate preclinical drug discovery and associated clinical proof of concept studies relevant to developing new treatments for cognition in schizophrenia. Although recognized by the MATRICS program [40], the identification and validation of efficacious treatments that can serve as positive control compounds in the development of new preclinical and clinical test paradigms remains of paramount importance. Given the differential neurobiological substrates of the

diverse domains of cognition impacted in schizophrenia, it is likely that positive control compounds will be needed for each of these domains; it is unlikely that all forms of cognitive dysfunction will be ameliorated by any single medication.

Although the challenges are substantial, the potential benefits to patients and society are great because of the immense burden of the life-long impairments associated with schizophrenia. The recently revived recognition of the core cognitive deficits and the willingness of regulatory agencies to license specific treatments for these deficits above and beyond the treatment of psychoses have incentivized new research to address this unmet medical need. Rational solutions will have to come from a combined effort, clinical and preclinical, and need to be based firmly on an improved understanding of the cognitive core symptoms of schizophrenia.

Acknowledgments

M.A. Geyer was supported by National Institute of Mental Health grants MH042228 and MH052885 and by the Veterans Administration VISN 22 Mental Illness Research, Education, and Clinical Center. The authors thank Dr. Athina Markou for contributing to this work.

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Schizophrenia: dementia praecox

Schizophrenia was first delineated as a separate illness by Emil Kraepelin, at the time chair of the Department of Psychiatry in Heidelberg, in 1893 [40]. He had named the illness 'dementia praecox' and had chosen this descriptive name for a good reason: He considered the illness a form of dementia, similar to the one described by his chief of service and colleague, Alois Alzheimer, but commencing at a much earlier age, i.e. around adolescence or early adulthood. Hence, he used the prefix 'praecox' (early onset), to contrast it with the Alzheimer dementia with onset in senescence.

It is hard to overstate the implication of his choice of terminology to describe the illness, since it reflects the core of Kraepelin's concept. He considered the illness we now know as schizophrenia as a disorder characterized by cognitive decline, just as the dementia that he named after his colleague: Alzheimer's disease. Indeed, in his first description of the illness Kraepelin's focus is entirely on the generally slow, but sometimes rapid, decline in cognitive functioning [40]. The other symptoms, which the current definition of the illness in the psychiatric nomenclature according to DSM-IV considers most important, i.e. psychosis, receive much less attention in his description. Similarly, Bleuler, the Swiss psychiatrist who coined the term schizophrenia in the early part of the 20th century, did not regard the presence of psychotic symptoms important, emphasizing withdrawal ('autism') and ambivalence instead [41].

Extinction learning

Extinction of fearful memories is not a matter of erasing earlier stored information, as was originally thought. This view already emanated from experiments by Mark Bouton and colleagues, who showed that extinction paradigms are very sensitive to the context in which they take place [43]. Fearful memories can reappear when the organism is exposed to a context that differs from that in which memories were extinguished, but even spontaneously or when the individual is re-exposed to cues. Decisive evidence was supplied by Mike Davis and collaborators who showed that successful extinction requires activation of glutamatergic NMDA receptors [44], in a synaptic strengthening process very much like that involved in the acquisition of fear memories [45], but involving different populations of neurons and synapses. Projections from the rodent infralimbic cortex to intercalated neurons in the amygdala appeared to be essential for extinction of fear memories [46]. The circuits involved in acquisition and extinction of fearful situations show a great degree of homology between rodents and humans [47]. No doubt, this homology has contributed to the successful transfer of D-cycloserine (which acts as a partial agonist on NMDA receptors) from fear models in rodents to an add-on therapy during CBT in human conditions such as phobias.

Figure 1.

Maps of changes in cortical thickness in millimeters and F values, comparing patients with schizophrenia and healthy control individuals. Patients with schizophrenia show cortical thinning/excessive thinning (in blue) or thickening/excessive thickening (in red) compared with healthy controls. Maps with F values show where patients ($n=154$) have significantly thinner or thicker cortices relative to controls ($n=156$) at inclusion or where change in cortical thickness during the 5-year interval is significantly more pronounced in patients ($n=96$) relative to controls ($n=113$). Reproduced with permission from [20].

Figure 2. Schematic overview of the discovery cycle and target validation in schizophrenia, with emphasis on procognitive drugs. In this article, we highlighted the urgent need for improvement in the encircled parts of the discovery cycle.