



Pharmacological Treatment of Schizophrenia: Current Issues and Future Perspectives

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ABSTRACT

In the past decade, four main topics have shaped research and clinical practice. 1) In randomized controlled trials, researchers have investigated whether treating prodromal symptoms of schizophrenia helps to reduce the conversion risk to full-blown schizophrenia. Results are ambiguous and the discussion on whether or not an intervention at the stage is justified is ongoing. 2) Following the enhanced understanding of the pathophysiology of schizophrenia, also with respect to specific symptom domains, pharmacological targets beyond D₂ receptor antagonism have been explored. Much work and enthusiasm has revolved around nicotinic and glutamatergic compounds, so far with mostly discouraging results. 3) Several new-generation antipsychotics have become available as long-acting formulations. All of them have demonstrated a significant positive impact on relapse rates in placebo controlled studies. Whether these compounds also have advantages over first-generation depots and/or oral antipsychotics is still debated. The development of an inhalable antipsychotic has complemented the treatment options for the management of acutely agitated patients. 4) Lastly, attempts from various perspectives, including genetics and neuroimaging, have investigated whether it is possible to predict treatment response and drug safety. Although some look promising, they have not yet reached a stage in which they can be applied to everyday clinical practice. What has become clear, though, is that early non response predicts late non response, leading to the recommendation to switch antipsychotics much earlier than stated in most treatment guidelines.

Keywords: *schizophrenia, early intervention, long-acting depot formulations, antipsychotic, prodromal symptoms, attenuated psychosis syndrome*

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INTRODUCTION

Schizophrenia is a serious mental disorder characterized by positive, negative, affective, and cognitive symptoms. It is associated with an increased risk of mortality and social or occupational decline that can be difficult to reverse. Most patients with schizophrenia usually need life-long management and care, and pharmacological treatment represents the mainstay of its therapeutic strategy [1].

In the past decade, four main topics have shaped

research and clinical practice in the treatment of schizophrenia. These have dealt with: 1) early intervention in the prediagnostic stage, i.e. the attenuated psychosis syndrome; 2) novel neurobiological treatment targets; 3) the introduction of alternative formulations; 4) attempts to predict treatment response. This article provides a brief review of these topics and discusses current issues and future perspectives in the pharmacological treatment of schizophrenia.

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EARLY INTERVENTION AT THE PRODROMAL STAGE

Over the last two decades, the prodromal stage of schizophrenia and other psychotic disorders has become a major focus of research, which has led to the development of early intervention services [2-4]. Investigators have established clinically-defined prodromal diagnostic criteria to identify “ultra-high risk (UHR)” (also known as the “at-risk mental state” [ARMS], “prodromal stage,” and “clinical high risk [CHR]) individuals [3, 5-7]. The proposed diagnosis of Attenuated Psychosis Syndrome (APS), formerly known as the “psychosis risk syndrome”, was not included in the main text of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), but assigned to a category in the appendix (Section 3) of DSM-5 as a condition for further study [7, 8]. In a meta-analysis of 2,502 UHR individuals, there was a mean transition risk of 18% at 6 months of follow-up, 22% at 1 year, 29% at 2 years, 32% at 3 years, and 36% after 3 years [9].

The main goals of interventions at the prodromal stage are to attenuate prodromal symptoms and to delay or prevent the progression to florid schizophrenia [10]. Other potential advantages of early intervention may be prevention of neurotoxicity and sociotoxicity, and prevention or reduction of suffering of UHR individuals [11]. However, these potential benefits have to be weighed against possible risks of unnecessary treatment, adverse events, stigmatization, discrimination, and cost [4, 11].

In a number of randomized controlled trials (RCTs), researchers have investigated whether treating prodromal symptoms of schizophrenia helps to reduce the conversion risk to full-blown schizophrenia. The evidence-based approaches to interventions at the prodromal stage include antipsychotic drugs (APDs), antidepressants, cognitive behavioral therapy, omega-3 fatty acids, and clinical monitoring [3, 11]. The main outcome variable was prevention of conversion into manifest schizophrenia. Four RCTs in people with prodromal symptoms assessing the efficacy of new-generation antipsychotics (NGAs) suggest that the use of NGAs (amisulpride, olanzapine, and risperidone) in UHR individuals may delay the onset of frank psychosis, ameliorate subthreshold psychotic symptoms, and improve functioning [12-15], although three of the trials failed to demonstrate statistical significance on the main outcome variable. These trials involved a relatively small number of subjects. Furthermore, the use of APDs in subjects who may not convert to psychosis has raised

considerable ethical concerns given the risk of long-term adverse side effects such as weight gain. Also, given the low conversion rate in the placebo group, inappropriate treatment in young people, who may not be at true risk, remains an issue. Accordingly, recent treatment guidelines for subjects at UHR for psychosis recommend the use of APDs only in exceptional conditions and with considerable precautions [16-18]. Notably, interventions with omega-3 fatty acids may also be effective for averting transition to psychosis [19] and this represents an active area of research [20].

Although the individual studies were less convincing, a recent meta-analysis of 10 RCTs of early interventions reported that the risk of developing psychosis was reduced by 54% after one year with a Number Needed to Treat (NNT) of 9, and by 37% with a NNT of 12 between 2 and 4 years [20]. Currently, several large-scale clinical trials, including psychological interventions, are underway and further data are expected to clarify the utility and safety of various interventions during the prodromal stage.

In summary, results of an early intervention are ambiguous and the discussion on whether or not an intervention at the stage is justified is ongoing [11].

NEW DRUGS WITH FAMILIAR MECHANISMS

Since the introduction of chlorpromazine in 1952, the dopamine D₂ receptor represents the one consistent target around which APDs development has been organized, resulting in the development of various first-generation antipsychotics (FGAs) and NGAs with largely similar efficacy [21]. However, current APDs generally lack the efficacy for negative symptoms and cognitive impairment associated with schizophrenia, which have a strong impact on functional outcome [22]. Furthermore, a substantial number of patients are refractory to available APDs and while the newer APDs produce fewer extrapyramidal side effects (EPS), safety and tolerability concerns about weight gain and metabolic side effects have emerged. Consequently, there remains a great unmet need for more effective and better-tolerated APDs.

Relatively potent antagonism of serotonin 5-HT_{2A} receptors combined with relatively weaker D₂ antagonism is the essential pharmacological characteristic shared by many NGAs [21, 22]. This profile has become a favored model for developing new APDs with familiar mechanisms, including asenapine, blonanserin, brexpiprazole, cariprazine, iloperidone,

lurasidone, and perospirone. Of these, we will briefly describe brexpiprazole, cariprazine and lurasidone, as they are the most recently introduced.

Lurasidone is a benzoisothiazol derivative with very high affinity for D₂, 5-HT_{2A}, and 5-HT₇ receptors [23, 24]. It is also a partial agonist at 5-HT_{1A} receptors and has moderate affinity for α_{2C} receptors. It has virtually no affinity for histaminergic H₁ and muscarinic M₁ receptors, and minimal affinity for adrenergic α_1 , α_{2A} , D₁, D₃, and 5-HT_{2C} receptors [24].

In a 6-week RCT of 488 inpatients, lurasidone, at fixed dosages of 80 and 160 mg/day, was effective and well tolerated for patients experiencing an acute exacerbation of chronic schizophrenia [25]. In a subsequent RCT of 292 outpatients, lurasidone (40-160 mg/day) was non-inferior to quetiapine XR (QXR) (200-800 mg/day) in time-to-relapse, with a numerically lower probability of relapse at 12 months in the lurasidone group compared with the QXR group (23.7% vs. 33.6%, $p = 0.28$) [26]. In both studies, the influence of lurasidone on weight and metabolic parameters was minimal.

Brexpiprazole acts as a partial agonist at D₂/D₃ and 5-HT_{1A} receptors [27]. Compared with aripiprazole, brexpiprazole has lower intrinsic activity at D₂ receptors. Brexpiprazole has also potent antagonist effects on 5-HT_{2A}, α_{1B} , and α_{2C} receptors and shows moderate affinity for H₁ receptors. Although both brexpiprazole and aripiprazole have high affinities for D₂ and 5-HT_{1A} receptors, brexpiprazole has a slightly higher affinity for 5-HT_{1A} than D₂ receptors, and aripiprazole displays the reverse affinities [27].

The results of 6-week phase III RCT of 674 patients with an acute episode of schizophrenia demonstrated that treatment with brexpiprazole (4 mg/day) showed superior improvement in psychopathological symptoms compared with placebo [28]. Brexpiprazole was well tolerated and, the most common treatment-emergent adverse events were headache, insomnia, and agitation. Akathisia was less frequently observed in the brexpiprazole groups (4.2-6.5%) than in the placebo group (7.1%).

Cariprazine shows partial agonism at D₂/D₃ receptors, with preferential binding to D₃ receptors, and partial agonism at 5-HT_{1A} receptors [29, 30]. Compared with aripiprazole, cariprazine showed lower affinity for D₂ and higher affinity for D₃ receptors [30]. The dopamine D₃ receptor is thought to play roles in the regulation of cognitive and emotional functions [31]. Cariprazine acts as antagonist with moderate affinity at 5-HT_{2A} and H₁ receptors, but it has no affinity for muscarinic receptors [30].

In phase II (cariprazine 1.5, 3.0, or 4.5 mg/day) [32] and two phase III (cariprazine 3 to 6 or 6 to 9 mg/day [33]; cariprazine 3 or 6 mg/day [34]) RCTs in patients with acute exacerbation of schizophrenia, cariprazine was effective and generally well tolerated at all doses tested (1.5-9 mg/day). A 26-week phase IIIb RCT of 461 patients with schizophrenia with persistent and predominant negative symptoms showed that cariprazine (target dose 4.5 mg/day) was more effective for negative symptoms compared to risperidone (target dose 4.0 mg/day) [35]. Moreover, cariprazine demonstrated a significant advantage over risperidone on the Personal and Social Performance Scale score. In a longer-term placebo-controlled relapse prevention trial, cariprazine was superior to placebo with respect to relapse prevention [36]. The most common adverse events within the recommended dose range (cariprazine 1.5-3 mg/day and 4.5-6 mg/day vs placebo) in schizophrenia trials were EPS (15%, 19% vs 8%) and akathisia (9%, 13% vs 4%) [37].

NEW DRUGS WITH INNOVATIVE MECHANISMS

Extensive research has identified new molecular mechanisms and novel pharmacological targets beyond D₂ antagonism [22, 38]. Moreover, there has been a growing body of research on approaches for improving specific symptom domains such as cognitive impairments and negative symptoms in schizophrenia, either as monotherapies or as adjunctive treatments added to available APDs [39-41].

1) Other agents influencing dopaminergic neurotransmission

A number of dopaminergic agents have been developed, including D₁ antagonists (e.g., SCH39166 and NNC 01-0687), D₁/D₂ agonists (e.g., dihydrexidine, lisdexamphetamine, and DAR01000A), D₃ antagonists (e.g., ABT-925), and D₄ antagonists (e.g., finanserin, sonopiprazole, and L-745,870) [22]. However, the results of clinical trials of these compounds were mostly discouraging.

2) Glutamatergic agents

N-methyl-D-aspartate receptor (NMDA-R) hypofunction has been hypothesized to contribute to the pathophysiology of schizophrenia [42-44]. Moreover, NMDA-R hypofunction may result in compensatory hyperactivity of glutamatergic neurotransmission at non-NMDA receptors [45]. Compounds that enhance

NMDA-R activity, including glycine site modulators (e.g., glycine, D-serine, D-cycloserine, and D-alanine) and glycine reuptake inhibitors (e.g., sarcosine and bitopertin), have been considered for their therapeutic potential for schizophrenia [22, 42-44]. Other glutamatergic compounds include metabotropic glutamate receptor agonists (e.g., LY2140023), metabotropic glutamate receptor modulators (e.g., ADX47273), and ampakines (e.g., CX516 and farampator) [22]. So far, however, most of the clinical trials of these compounds have yielded negative results.

3) Cholinergic agents

A number of cholinergic agents have been tested, mostly for the treatment of cognitive deficits in schizophrenia. They include α_7 nicotinic acetylcholine receptor (nAChR) agonists (e.g., 3-2,4-dimethoxybenzylidene anabaseine [DMXB-A], encenicline [46], tropisetron, RG 3487, TC-5619 [47], and ABT-126), $\alpha_4 \beta_2$ nAChR agonists (e.g., varenicline and AZD 3480), muscarinic receptor agonists (e.g., xanomeline), and acetylcholinesterase inhibitors [22].

In a recent 12-week phase II double-blind RCT, adjunctive encenicline demonstrated significant improvement in global cognitive function as measured by the CogState overall cognitive index (encenicline 0.27 mg vs placebo, $p = 0.034$), clinical function as measured by the Schizophrenia Cognition Rating Scale (SCoRS) (encenicline 0.9 mg vs placebo, $p = 0.011$), and negative symptoms (encenicline 0.9 mg vs placebo, $p = 0.028$) when compared to placebo in 307 chronic schizophrenia patients treated with a NGA [46]. However, the effect of the 0.9 mg dose of encenicline as measured by MATRICS Consensus Cognitive Battery (MCCB) was not significantly better compared to that of placebo ($p = 0.069$). Encenicline was generally well tolerated.

4) Miscellaneous targets

Other targets and strategies with various mechanisms for drug development have been explored for the treatment of schizophrenia [38]. They include antioxidants (e.g., erythropoietin, ginkgo, N-acetylcysteine, and carnosine), antiinflammatory agents/antibiotics (e.g., minocycline, celecoxib, and aspirin), neurosteroids/hormones (e.g., estrogen, testosterone, pregnenolone, and dehydroepiandrosterone), omega-3 fatty acids (e.g., docosahexaenoic acid and eicosapentaenoic acid), oxytocin, phosphodiesterase 10A inhibitors (e.g., MP-10), secretin, pravastatin, monoamine oxidase-B inhibitors (e.g., selegiline and rasagiline), and sodium nitroprusside.

Some of them provided promising evidence, suggesting potentially viable future treatments for schizophrenia. However, given the limited data from rigorous phase II trials, further studies are warranted with larger sample sizes, broader dose ranges, and longer durations of treatment. Moreover, evaluation of longer term safety and tolerability is necessary.

NEW FORMULATIONS OF ANTIPSYCHOTICS

Several antipsychotics have become available as new formulations including an inhalable agent and long-acting intramuscular (i.m.) depot formulations.

1) Inhalable Loxapine

Acutely agitated patients with schizophrenia or bipolar disorder have a substantial risk of self-injury or suicide, and other unpredictable dangerous behaviors to themselves, others, or property [48]. The development of an inhalable antipsychotic has complemented the treatment options for the management of such patients. Inhaled loxapine can be delivered by inhalation using the Staccato system which is a breath-actuated delivery system that delivers loxapine with intravenous-like pharmacokinetics [49]. For example, following inhalation of loxapine, the median T_{max} was 2 minutes.

Phase II [50] and Phase III [51] studies in patients with schizophrenia or schizoaffective disorder demonstrated that inhaled loxapine (5 mg and 10 mg doses) was well tolerated and had dose-dependent anti-agitation effects without evidence of excessive sedation. The superior anti-agitation effects of inhaled loxapine compared with placebo were evident at 10 minutes after administration, and this early onset of action appears to be the most rapid anti-agitation effect ever reported in placebo-controlled trials [51].

2) I.M. Depot Antipsychotics

Long-acting injectable (LAI) formulations allow for stable plasma concentrations of the active drug to remain at a therapeutic dose range for an extended period of time. Thus, they are considered particularly advantageous for patients with – often covert – adherence problems, and for those with a history of severe relapse upon medication discontinuation. They also simplify compliance monitoring, as non-compliance is quickly recognized, if patients do not show up for scheduled injections [52]. Several NGAs, including risperidone LAI, paliperidone palmitate, olanzapine pamoate, and LAI

aripiprazole, have become available as long-acting formulations. All of them have demonstrated a significant positive impact on relapse rates and symptoms in placebo controlled studies [52, 53]. Whether these compounds also have advantages over FGA depots and/or oral antipsychotics is still debated.

When using classical measures of psychopathology as endpoints, previous head-to-head studies of NGA LAIs showed non-inferiority between different LAIs [54, 55]. However, in a recent phase IIIb, 28-week, open-label, head-to-head RCT, treatment with aripiprazole once-monthly 400 mg (AOM 400) demonstrated superior improvements to paliperidone palmitate once-monthly (PP) on health-related quality of life measured with Quality-of-Life Scale and Clinical Global Impression-Severity scale in 295 patients with chronic schizophrenia [56]. Moreover, AOM 400 showed a more favorable tolerability profile compared with PP. This is the first study to show superiority of one NGA LAI over another.

A recently approved 3-month i.m. formulation of paliperidone offers longer injection intervals than currently available LAI formulations. A double-blind RCT showed superiority of 3-month paliperidone palmitate over placebo for delaying time to relapse of symptoms (hazard ratio = 3.81) [57]. The 3 month formulation was also compared to monthly paliperidone palmitate in a non-inferiority study demonstrating a comparably low relapse risk in both groups [58]. Adverse event profiles of the two formulations were similar especially also with respect to injection side complications.

PREDICTION OF TREATMENT RESPONSE AND SAFETY

As the etiology of schizophrenia is complex and not well understood, continued efforts to identify the underlying pathophysiology behind the development of the illness are required to develop better and more targeted treatments [38]. Attempts from various perspectives, including genetics and neuroimaging, have investigated whether it is possible to predict treatment response and drug safety [59, 60]. Although some look promising, they have not yet reached a stage in which they can be applied to everyday clinical practice. What has become clear, though, is that early non response predicts late non response, leading to the recommendation to switch antipsychotics much earlier than stated in most treatment guidelines [61, 62].

CONCLUSIONS

A number of novel non-D₂ mechanisms of action of antipsychotics have been explored over the past 40 years, but no drugs selective for single molecular targets (i.e., ‘magic bullets’) have as yet been proven effective [22]. However, to date, partial dopamine D₂/D₃ agonists look promising for negative symptoms of schizophrenia and preliminary evidence points to pro-cognitive efficacy of α_7 -nicotinic agonists. Moreover, additional formulations allow alternative therapeutic options. Finally, identification of the molecular mechanisms that influence individual responsiveness to treatment are actively sought to establish effective personalized care.

CONFLICTS OF INTEREST

Dr. Fleischhacker has received research grants from Janssen Cilag, Otsuka, and Lundbeck. He has received speaking fees from Janssen, Roche, Lundbeck, Otsuka, Takeda and advisory board honoraria from Otsuka, Janssen, Amgen, Lundbeck, Roche, Takeda, Teva, and Targacept. Dr. Miyamoto has received speaking fees from Dainippon Sumitomo and Otsuka.

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