Serotonin 2A receptor antagonists for treatment of schizophrenia

Bjørn H Ebdrup*, Hans Rasmussen*†, Jørn Arnt & Birte Glenthøj†

†Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital Glostrup, Faculty of Health Sciences, Psychiatric Center Glostrup, Glostrup, Denmark

Introduction: All approved antipsychotic drugs share an affinity for the dopamine 2 (D2) receptor; however, these drugs only partially ameliorate the symptoms of schizophrenia. It is, therefore, of paramount importance to identify new treatment strategies for schizophrenia.

Areas covered: Preclinical, clinical and post-mortem studies of the serotonin 5-HT2A system in schizophrenia are reviewed. The implications of a combined D2 and 5-HT2A receptor blockade, which is obtained by several current antipsychotic drugs, are discussed, and the rationale for the development of more selective 5-HT2A receptor antagonists is evaluated. Moreover, the investigational pipeline of major pharmaceutical companies is examined and an Internet search conducted to identify other pharmaceutical companies investigating 5-HT2A receptor antagonists for the treatment of schizophrenia.

Expert opinion: 5-HT2A receptor antagonists appear to assume an intermediate position by being marginally superior to placebo but inferior to conventional antipsychotic drugs. Three previous 5-HT2A receptor antagonists have been discontinued after Phase II or III trials, and available Phase IIa data on the remaining 5-HT2A receptor antagonist will need substantial additional validation to be approved as a new treatment strategy against schizophrenia.

Keywords: 5-HT2A, CYR-101, drug development, eplivanserin, M100907, pimavanserin, schizophrenia, serotonin


1. Introduction

Schizophrenia is a severe and heterogeneous brain disease with a prevalence of ~ 0.5% of the world population [1]. According to the WHO, schizophrenia is among the seven most disabling diseases in the age group between 20 and 45 years thereby surpassing diabetes, cardiovascular disease and HIV-AIDS [2]. The symptoms typically start in young adulthood. They are commonly classified as: positive symptoms (hallucinations, delusions and thought disorder), negative symptoms (affective flattening, poverty of speech and anhedonia) and cognitive deficits (attention, memory and executive functions) [3,4]. The etiology of schizophrenia is complex and appears to be influenced by genetic liability and environmental factors, resulting in disturbances in brain biology and function [5]. In all, 40 – 80% of patients with schizophrenia have reduced capability for learning, working, self-care, interpersonal relationships and maintaining general living skills. The estimated annual costs of schizophrenia comprised $62.7 billion in the US (in 2002) [6] and £6.7 billion in the UK (in 2004 – 05) [7]. The main cost is related to non-healthcare costs such as unemployment and loss of productivity.

Antipsychotic drugs constitute a crucial intervention in the treatment of schizophrenia. In most patients, the drugs reduce but do not eliminate the positive symptoms. The effects of antipsychotic drugs on the disabling cognitive symptoms and negative symptoms are even more limited. Overall, one-fifth to one-third of
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2. Serotonin

2.1 General

In the 1950s, it was discovered that the monoamine neurotransmitter serotonin (5-HT) had similar clinical effects as lysergic acid diethylamide, a drug known to cause psychotic-like symptoms [14]. The naturally occurring drug psilocybin, which can induce profound changes in mood, thought, intuition, sensory perception and the experience of time and space, was characterized as a serotonergic agonist. These observations led to a hyper-serotonin hypothesis of schizophrenia, which was mainly focused on the 5-HT_{2A} receptor subtype [15]. Subsequently, selective 5-HT_{2A} receptor agonists, particularly 2,5-dimethoxy-4-iodoamphetamine and 2,5-dimethoxy-4-methylamphetamine, have been developed, and these drugs have been widely used in preclinical investigations of the relationship between the 5-HT_{2A} receptor system and psychosis [16,17].

It has been proposed that the psychosis associated with 5-HT_{2A} receptor stimulation shares the clinical characteristics of the early stage of schizophrenia rather than the more chronic stages [15]. This could suggest that different receptor systems may be implicated at different stages of the disease.

2.2 Serotonin receptors

Serotonin is synthesized from the essential amino-acid tryptophan and released by nerve cells in the raphe nuclei projecting throughout the brain. 5-HT_{2A} receptors belong to a family of serotonin receptors comprised of 15 different receptors each encoded by distinct genes. The serotonin receptors are divided into seven major classes: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7. Most of these classes can be divided into subtypes, for example, the 5-HT_2 into 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. Except for the 5-HT_3 subtype, all of the 5-HT receptors are members of the G-protein-coupled superfamily [18]. The 5-HT_{2A} receptor is widely distributed throughout the brain with a high density in cortical areas, a lower density in the midbrain and thalamic areas, and a negligible expression in the cerebellum (Figure 1) [19].

2.3 Post-mortem studies of 5-HT_{2A} receptors in schizophrenia

Eleven [20-30] of sixteen [31-35] post-mortem studies of brain tissue from schizophrenia patients have reported a decreased 5-HT_{2A} receptor expression in cortical areas. The decreased receptor density appears to be most pronounced in the frontal cortex. Also, the cortical 5-HT_{2A} mRNA expression has been reported to be lower in schizophrenia patients compared to healthy subjects [36]. However, post-mortem studies are potentially confounded by illness chronicity and previous treatment with antipsychotic drugs, both of which may decrease 5-HT_{2A} receptor expression [37].
In vivo studies of 5-HT2A receptors in schizophrenia

Receptor density and receptor blockade by antipsychotic drugs can be investigated in vivo using positron emission tomography (PET), and PET ligands selective for the 5-HT2A receptor have been developed. At present, only five PET studies of the 5-HT2A receptor have been carried out in antipsychotic-naive schizophrenia patients, and generally in a very limited number of patients. Three of these studies detected no significant differences between patients and control subjects (n < 10) [38-40]. Two studies found a decreased frontal 5-HT2A receptor density: In one study of six antipsychotic-naive patients, a decreased binding in the left lateral frontal cortex was found [41]. The second, and so far the largest, PET study of 30 antipsychotic-naive first-episode schizophrenia patients reported an overall decreased 5-HT2A receptor binding in cortex, and this decrease was most pronounced in the frontal cortex [42]. Moreover, the decreased binding was associated with more positive symptoms in male patients [42]. Preliminary data from a subgroup of the same cohort (n = 15) had also suggested increased 5-HT2A receptor binding in the caudate nucleus [43]. This finding, however, was not replicated in the larger cohort [42]. The authors ascribed their failure to replicate the preliminary finding to the relatively low 5-HT2A receptor density in the caudate nucleus and the possibility of a type II error.

A decreased cortical 5-HT2A receptor binding has also been described in subjects at high risk of developing schizophrenia [44]. It has been proposed that the reduced 5-HT2A receptor density could reflect a compensatory downregulation in response to altered endogenous serotonin levels [42]. This notion supports the rationale for the development of specific 5-HT2A receptors antagonists for the treatment of schizophrenia. Alternatively, the reduced 5-HT2A receptor density could indicate a downregulation compensating for hyperactivity in other transmitter systems which interact with the 5-HT2A receptors. Finally, reduced 5-HT2A receptor density could represent a primary pathophysiologic disturbance in schizophrenia.

Overall, in vivo studies provide some support of the post-mortem observations of a decreased frontal 5-HT2A receptor density in schizophrenia; however, further validation studies are warranted.

2.5 Genetic studies of 5-HT2A receptors in schizophrenia

Estimations from twin studies show that schizophrenia is highly heritable [45], and recently it has been shown that the cortical 5-HT2A receptor binding pattern in the human brain is strongly genetically determined [46]. Although not been consistently reported [47], a meta-analysis has indicated an association between the T102C polymorphism in the
5-HT$_{2A}$ receptor gene and the overall risk of developing schizophrenia [48]. Deficits in sensorimotor gating have been associated with the T102C and A-1438G polymorphisms of the 5-HT$_{2A}$ receptor gene [49], a finding which was later replicated in an independent cohort [50]. Furthermore, the T102C polymorphism may characterize a subgroup of schizophrenia patients with poor response to antipsychotic treatment and poor long-term outcome [51]. Finally, the clinical response to clozapine may also be affected by the T102C polymorphism [52].

2.6 5-HT$_{2A}$ receptors and antipsychotic compounds

Twenty years ago, it was shown that clozapine was superior to the ‘typical’ antipsychotic drugs haloperidol and chlorpromazine with regard to treating positive and negative symptoms of otherwise treatment-resistant schizophrenia [53]. Moreover, clozapine only induced minimal EPS. Since then, several ‘atypical’ antipsychotic drugs (more recently referred to as SGAs) have been developed. SGAs are characterized by reduced risk of development of EPS compared to FGAs (e.g., haloperidol) when administered as monotherapy at optimal clinically effective doses [54]. Like clozapine, most SGAs such as risperidone, paliperidone, olanzapine, quetiapine, ser-tindole, asenapine and ziprasidone have a broad receptor profile and/or a relatively loose binding (high dissociation rate constant; $k_{off}$) to the D$_2$ receptors [55]. For example, clozapine has a high affinity for a number of serotonin (5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_{6}$, 5-HT$_{7}$), dopamine (D$_{4}$), muscarinic (M$_{1}$, M$_{2}$, M$_{3}$, M$_{4}$, M$_{5}$), adrenergic ($\alpha_{1}$- and $\alpha_{2}$-subtypes) and other biogenic amine receptors, such as histamine (H$_{1}$) receptors [56]. Another common feature shared by SGAs (with amisulpride as an exception) is a relatively potent blockade of 5-HT$_{2A}$ receptors coupled with a weaker antagonism of D$_{2}$ receptors [57]. However, most SGAs also share a potent $\alpha_{1}$-adrenoceptor antagonism [58], which in combination with the 5-HT$_{2A}$ antagonism may additionally modulate the striatal dopamine release [59].

Some neuroimaging studies have indicated that the optimal interval for D$_2$ blockade to obtain an antipsychotic effect lies between 65 and 80% [60]. However, this association has not been consistently reported [61], rendering the minimal D$_2$ occupancy required for therapeutic response uncertain. Nevertheless, D$_{2}$ receptor blockade > 80% is associated with an increased risk of developing EPS [62]. It should be noted that aripiprazole in clinically effective doses blocks around 90% of the D$_{2}$ receptors because of its different mechanism of action (partial D$_{2}$ subfamily agonism) [63]. Consequently, aripiprazole by some authors has been designated as a third generation antipsychotic [64].

During optimal dosing of SGAs, the blockade of the 5-HT$_{2A}$ receptors in the cortex generally exceeds the level of D$_{2}$ blockade in the striatum [65]. Therapeutic doses of clozapine, risperidone, olanzapine and ziprasidone induce very high cortical 5-HT$_{2A}$ receptor blockade (> 85%) [62,66-68], whereas the blockade induced by quetiapine and aripiprazole is somewhat lower (54 – 70%) [68-70]. Quetiapine is characterized by a low D$_{2}$ affinity and aripiprazole is a partial D$_{2}$ agonist. Because of the half-lifes of the drugs, some of the variation in the degree of blockade between studies may be attributable to the time between drug administration and image acquisition [71].

Despite the broad receptor profiles of most SGAs it has been proposed by Kapur and Seeman that their effect may be fully explained by a transiently high D$_{2}$ blockade and fast dissociation rate ($k_{off}$) from the D$_{2}$ receptor [12]. Accordingly, the blockade of the 5-HT$_{2A}$ receptor or other receptor systems ‘may neither be necessary nor sufficient’ to achieve an antipsychotic effect [12]. However, for all antipsychotic drugs the $k_{on}$ rate is very rapid with little difference between drugs and, therefore, the affinity (i.e., $k_{off}/k_{on}$) is driven by the $k_{off}$ rate constant.

Conversely, Meltzer et al. have argued that ‘atypicality’ is conferred by a weak striatal D$_{2}$ receptor antagonism in combination with 5-HT$_{2A}$ receptor antagonism which in turn modulates the dopamine system [11]. It is argued that only drugs with low affinity for the D$_{2}$ receptor (such as quetiapine and clozapine) have fast dissociation rates, whereas SGAs such as olanzapine, risperidone, ziprasidone, iloperidone and blonanserin have slower $k_{off}$ properties. Also, ser-tindole, which in clinical doses induces very little risk of EPS, has a slower $k_{off}$ than haloperidol. Similarly, olanzapine has a $k_{off}$ that is only marginally faster than chlorpromazine and much slower than quetiapine and clozapine. Thus, Meltzer et al. conclude that the fast $k_{off}$ hypothesis as a general model for antipsychotic effect is not sufficiently supported [11].

To summarize, D$_{2}$ receptor blockade is essential for the antipsychotic effect of both FGAs and SGAs. Nevertheless, an antipsychotic effect may also be obtained by a relatively low striatal D$_{2}$ receptor blockade in combination with a concurrent frontal 5-HT$_{2A}$ receptor blockade. Because SGAs differ considerably with regard to receptor profile and various properties, including side effects, it has recently been proposed that SGAs should not be viewed as one homogeneous class [72]. Therefore, a discussion of individual drugs rather than putative classes of drugs would be constructive.

2.7 5-HT$_{2A}$ interactions with other neurotransmitter systems

As outlined above, the 5-HT$_{2A}$ receptors interact with other neurotransmitter systems, in particular the dopamine [73,74] and the glutamate systems [35]. Moreover, 5-HT$_{2A}$ receptor stimulation may also affect the firing rate of serotonergic cell bodies in the raphe nuclei through GABA-mediated interneurons [75]. For elaboration on the involvement of the dopaminergic, glutamnergic and GABA-contained systems in schizophrenia, see [76]. Preclinical data have indicated that the majority of prefrontal cortical pyramidal neurons that project to the dorsal raphe nuclei and ventral tegmental area express 5-HT$_{2A}$ receptors [77]. Consequently, blockade of
prefrontal 5-HT$_{2A}$ receptors may modulate pyramidal neurons projecting to the midbrain.

5-HT$_{2A}$ antagonism inhibits the dopaminergic system in the midbrain as well as in the dopaminergic terminals in the forebrain [66]. The formation of hetero-dimerization of the 5-HT$_{3A}$ and the D$_{2}$ receptors, which was recently reported in a preclinical study, may also contribute to the potential antipsychotic effect of 5-HT$_{2A}$ receptor blockade [78].

These mechanisms may explain how an antipsychotic effect may be obtained by the combination of a high 5-HT$_{2A}$ receptor blockade and a lower D$_{2}$ receptor blockade, which constitute a feature of some SGAs [79].

Finally, an accumulating body of evidence points towards the involvement of the glutamatergic system in schizophrenia [80]. Cortical metabotropic glutamate (mGlu2) receptors can form complexes with 5-HT$_{2A}$ receptors, and alterations in these complexes may, among others, be responsible for the deficits in sensory gating observed in psychosis [35]. Previously, a Phase II study of the mGlu2/3 agonist (LY2140023) provided encouraging results regarding a potential antipsychotic effect [81]. However, in a recent Phase II study LY2140023 did not separate from placebo (but neither did the comparison drug, olanzapine) [82]. For a description of the further Phase II trial, see [83]. A study on induced locomotor activity in rats indicated that administration of a 5-HT$_{2A}$ receptor antagonist (M100907) in combination with LY2140023 resulted in a more pronounced effect than treatment with LY2140023 alone [84]. Thus, the mGlu2-5-HT$_{2A}$ receptor complex may also constitute a specific new target for antipsychotic drug development.

2.8 Clinical effect related to 5-HT$_{2A}$ receptor blockade
Results from a recent PET study using quetiapine in initially antipsychotic-naïve first-episode schizophrenia patients suggested that blockade of 5-HT$_{2A}$ receptors was associated with a reduction in positive symptoms [71]. This 5-HT$_{2A}$ related clinical effect appeared to be most pronounced within a therapeutic window of 60 – 70% blockade, corresponding to a dose of around 400 mg quetiapine. The authors speculated that the data could indicate that patients who respond to higher doses of quetiapine (> 70%, ~538 mg) might require a more comprehensive D$_{2}$ receptor blockade. A structural MRI study of the same cohort provided indirect support for this assumption by indicating a relative striatal volume increase in patients treated with high quetiapine doses (≥538 mg) as compared with patients treated with low doses [85]. It is well established that antipsychotic drugs, and especially FGAs with a potent D$_{2}$ receptor blockade, are associated with striatal volume increases [86].

Taken together, these data support that a modest 5-HT$_{2A}$ receptor blockade, either alone or in combination with a low D$_{2}$ receptor blockade, may be beneficial for some patients. Moreover, they suggest that other patients require a more comprehensive D$_{2}$ receptor blockade, although more research is needed to identify such subgroups of schizophrenia patients.

3. Discontinued 5-HT$_{2A}$ receptor antagonists
Available affinity constants for drug included in Sections 3 and 4 are provided in Table 1.

3.1 M100907
M100907 was the first drug with a highly selective 5-HT$_{2A}$ receptor antagonism to enter a clinical trial [87]. In a 6-week Phase II trial, 47 schizophrenia patients were administered 10, 20 or 40 mg M100907. After 6 weeks, the M100907 treated patients had improved with 11.3, 20.8 and 7.8%, respectively, on the brief psychiatric rating scale (BPRS), whereas the placebo group worsened by 22.3% [87]. However, after two Phase III trials with M100907 showing greater efficacy than placebo, but less than haloperidol, the compound was discontinued [87]. A PET study in schizophrenia patients indicated that daily treatment with 20 mg M100907 induced a very high 5-HT$_{2A}$ receptor blockade (> 90%) in the frontal cortex [88].

Although development of M100907 for schizophrenia has been discontinued, the drug is still widely used for quantification and visualization of the 5-HT$_{2A}$ receptors both in rodent autoradiography and in vivo binding studies [89,90].

3.2 Eplivanserin
Eplivanserin (SR-46349) is a selective 5-HT$_{2A}$/2C receptor antagonist developed by Sanofi-Synthélabo (since 2004: Sanofi-Aventis) [91]. Initially, eplivanserin was developed with an indication for schizophrenia; however, later this indication changed to insomnia. Rats treated with eplivanserin have shown increased basal dopamine release in the medial prefrontal cortex, but not in the nucleus accumbens. Moreover, administration of eplivanserin at 3 mg/kg has been shown to potentiate haloperidol-induced dopamine release in the medial prefrontal cortex and nucleus accumbens. Administration of 10 mg/kg may increase dopamine release in the medial prefrontal cortex without affecting dopamine release in the nucleus accumbens [92]. These results indicate that eplivanserin modulates the mesolimbic and mesocortical dopamine release, which are areas also implicated in schizophrenia.

The clinical effects of eplivanserin have been investigated in one placebo-controlled study along with three other investigational drugs for schizophrenia. Schizophrenia patients ($n = 481$) were randomly assigned the investigational drugs, placebo or haloperidol (10 mg/day) for 6 weeks. When compared to placebo, treatment with haloperidol improved all primary psychopathological parameters investigated: positive and negative syndrome scale (PANSS) total score; BPRS total score; BPRS psychosis cluster score and clinical global impression severity of illness score. In contrast, on the primary end points, treatment with eplivanserin at 5 mg resulted in significant reductions only on the total PANSS and BPRS scores. Eplivanserin treatment resulted in
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Table 1. Shows the affinity constants for the compounds included in the present review. A low affinity constant indicates higher receptor affinity.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Receptor</th>
<th>Tissue</th>
<th>$K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M100907</td>
<td>5-HT$_{2A}$</td>
<td>NIH-3T3 Cells</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>5-HT$_{2C}$</td>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>1A</td>
<td>Rat striatum</td>
<td>2250</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Rat brain</td>
<td>87*</td>
</tr>
<tr>
<td></td>
<td>2A</td>
<td>Rat cortex</td>
<td>130*</td>
</tr>
<tr>
<td>Eplivanserin</td>
<td>5-HT$_{2A}$</td>
<td>NIH-3T3 Cells</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>5-HT$_{2C}$</td>
<td></td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Rat striatum</td>
<td>$&gt; 10,000^d$</td>
</tr>
<tr>
<td></td>
<td>1A</td>
<td>Rat cortex</td>
<td>3400*</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>5-HT$_{2A}$</td>
<td>NIH-3T3 Cells</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>5-HT$_{2C}$</td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>1A</td>
<td>Rat striatum</td>
<td>$&gt; 1000$</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Rat brain</td>
<td>NDA</td>
</tr>
<tr>
<td></td>
<td>2A</td>
<td>Rat cortex</td>
<td>$&gt; 1000$</td>
</tr>
<tr>
<td>CYR-101$^f$</td>
<td>5-HT$_{2A}$</td>
<td>Rat cerebral cortex</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>5-HT$_{2C}$</td>
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<td>NDA</td>
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<td>1A</td>
<td>Guinea-pig brain</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Rat brain</td>
<td>14</td>
</tr>
</tbody>
</table>

The table is adapted from [97] and $K_i$ values are calculated from $pK_i$ values.

$^a$Adapted from [110].

$^b$Adapted from [111].

Unpublished data provided by the company (Cyrenaic Pharmaceuticals, Inc.).

$K_i$: Affinity constant; NDA: No data available.

negligible EPS and weight gain [54] although 5-HT$_{2C}$ receptor antagonism has previously been associated with weight gain [93]. The absence of weight gain with eplivanserin may be explained by the high ratio of 5-HT$_{2A}$/5-HT$_{2C}$ receptor antagonism (Table 1).

As a consequence of a Complete Response Letter regarding the benefit: risk ratio of eplivanserin issued by the FDA (September 2009), Sanofi-Aventis recently withdrew the US and EU applications for approval of eplivanserin against chronic insomnia [94].

4. Current 5-HT$_{2A}$ receptor targeting agents in the pipeline

4.1 Pimavanserin

Pimavanserin tartrate (ACP-103) is a 5-HT$_{2A}$ receptor antagonist which has been studied in clinical trials for the treatment of psychosis in Parkinson’s and Alzheimer’s diseases and as adjunctive therapy in the treatment of schizophrenia. Recently, a specific review and drug evaluation on pimavanserin were published [95]. Initially, pimavanserin was promoted by Biovail, but after Acadia Pharmaceuticals, Inc. re-gained all rights to further development, pimavanserin was discontinued in development for Alzheimer’s disease and schizophrenia. Still, Acadia continues to conduct the ongoing Phase III trials on psychosis in Parkinson’s disease [96].

4.1.1 Preclinical studies

In combination with haloperidol, pimavanserin has been shown to reduce amphetamine-induced hyperactivity in rats. Furthermore, administration of pimavanserin in combination with either haloperidol or risperidone appears to suppress the hyperactivity induced by the N-methyl-d-aspartate receptor antagonist MK-801. Finally, pimavanserin may also attenuate the prolactinemia and catalepsy induced by haloperidol or risperidone [97].

4.1.2 Human in vivo studies

In a double-blind, placebo-controlled study, conducted by the company (Acadia Pharmaceuticals), 18 healthy volunteers were administered a single dose of 7.5 mg haloperidol. Eleven of the subjects developed akathisia. Moreover, a threefold increase in prolactin levels was observed. Administration of a single dose of 100 mg pimavanserin appeared to reduce akathisia in the majority of the subjects and the prolactin secretion was reduced by 33%. According to the company, the pharmacokinetic parameters of the compounds were unaffected by co-administration, and no adverse effects were observed [98].

In another study conducted by the company, 34 patients with a clinical diagnosis of schizophrenia or schizoaffective disorder who had haloperidol-induced akathisia were randomized to treatment with either 60 mg of pimavanserin (once daily) for 5 days or placebo. According to the company, treatment with pimavanserin reduced akathisia on day 5 but no significant effect of pimavanserin on the main outcome measure (global clinical assessment of akathisia) was observed. Also, no significant improvement in positive or negative symptoms was found. The company explained the modest results by a large placebo response and the short treatment period. Treatment with pimavanserin did not induce EPS nor did it increase prolactin levels [99].

In a Phase II multi-center study, 423 schizophrenia patients were assigned to one of the following five study arms: risperidone 2 mg plus pimavanserin 20 mg; risperidone 2 mg plus placebo; risperidone 6 mg plus placebo; haloperidol 2 mg plus pimavanserin 20 mg and haloperidol 2 mg plus placebo [100]. At day 42, risperidone 2 mg plus pimavanserin resulted in a significant improvement on PANSS total score (PANSS total mean change = -27.4%). According to the company, this effect was similar to that of risperidone 6 mg (PANSS total mean change = -23.2; 26.4%) and was significantly more pronounced than the effect of treatment with risperidone 2 mg with placebo (PANSS total mean change = -16.6; 19.0%). Treatment with haloperidol plus pimavanserin and haloperidol with placebo resulted in comparable and significant clinical improvements (PANSS total mean change = -21.6; 25.6% and PANSS total mean change = -25.1; 29.2%).

The company reported that pimavanserin treatment both with risperidone 2 mg and haloperidol 2 mg resulted in a significantly faster onset of action, with 50% more patients...
in the co-therapy arm responding after 2 weeks of treatment compared with the two patient groups receiving risperidone with placebo (2 and 6 mg, respectively) (‘response’ defined as > 20% improvement on the total PANSS score). However, it is not described whether the definition of ‘response’ and the time of measurement were defined _a priori_. Hence, the indications of a faster treatment response with pimavanserin as an adjunctive treatment agent may be a result of _post hoc_ analyses. According to the company, treatment with pimavanserin plus haloperidol was associated with less weight gain than with haloperidol with placebo. No serious adverse events were observed in the study.

In a recent study of 15 patients with Parkinson’s disease, administration of pimavanserin in monotherapy (mean dose: 44.8 mg) also reduced hallucinations and delusions. This supports the hypothesis that blockade of 5-HT\(_{2A}\) receptors might be a means of diminishing positive symptoms [101]. Nevertheless, the main outcome measure (the scale for the assessment of positive symptoms) was only reduced at a trend-level after pimavanserin treatment.

4.1.3 Discussion of pimavanserin

Taken together, the results regarding the beneficial effects of adding pimavanserin to a conventional antipsychotic drug are inconclusive and only partially support the contention that 5-HT\(_{2A}\) receptor antagonism could be a potential means of obtaining antipsychotic effect with a lower degree of D\(_2\) blockade. Furthermore, the clinically compelling results of adjunctive treatment were based on the combination of pimavanserin and risperidone 2 mg, and it has been shown that risperidone already in relatively low doses (3 and 3.6 mg/day, respectively) induced a substantial frontal 5-HT\(_{2A}\) blockade (around 85%) [62,102]. Therefore, from a pharmacokinetic perspective, administration of 20 mg of pimavanserin in combination with risperidone 2 mg is unlikely to increase frontal 5-HT\(_{2A}\) receptor blockade more than marginally. Therefore, pimavanserin is unlikely to yield a substantial clinical effect when used as an adjunctive compound, particularly in combination with risperidone or other antipsychotic drugs with a pronounced 5-HT\(_{2A}\) antagonistic activity.

An interesting aspect of treatment with pimavanserin in combination with haloperidol is the finding of reduced risk of development of side effects and even an amelioration of side effects that were already present in patients. These findings may partly be explained by a 5-HT\(_{2A}\) receptor-mediated modulation of the striatal D\(_2\) blockade.

A PET study in four healthy volunteers indicated that administration of doses 10 or 20 mg of pimavanserin induced a cortical 5-HT\(_{2A}\) receptor blockade of 65 – 74% and administration of > 20 mg pimavanserin did not yield additional cortical receptor blockade [103]. While 5-HT\(_{2A}\) receptor availability appears to be affected in schizophrenia [42], some of the clinical studies on pimavanserin reviewed above may have used unnecessarily high doses (e.g., 60 and 100 mg) to obtain a receptor blockade.

Interestingly, the data suggest a possible antipsychotic effect of pimavanserin monotherapy on psychotic symptoms in Parkinson’s disease. Because the pathophysiology of schizophrenia and Parkinson’s disease differ substantially [104], the question of a potent antipsychotic effect of monotherapy with pimavanserin in treatment of schizophrenia remains unanswered.

4.2 CYR-101

CYR-101 (previously called MT-210) is a novel investigational drug for the treatment of schizophrenia [96]. The following section is based on available online data and personal communication with the company. CYR-101 should not be considered a selective 5-HT\(_{2A}\) antagonist (Table 1); however, no affinity (> 1000 nM) for other serotonergic, dopaminergic, muscarinic or cholinergic receptor subtypes has been found. CYR-101 produces two major metabolites with a binding profile similar to that of the parent compound, while one of the metabolites has some affinity for the histamine H\(_1\) receptor (guinea-pig brain: 43.6 nM).

Clinical results from a double-blind, randomized, placebo-controlled, multi-center Phase IIa study conducted in Europe were recently announced [105] (30 November 2010). One hundred patients (mean age 42 years) with a Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of schizophrenia participated in the study. The primary purpose of the study was to evaluate safety and acquire preliminary information about the efficacy of the drug in the target patient population and as such the study was not powered to achieve definite answers in terms of efficacy. The inclusion criteria were the following: an acute relapse necessitating hospitalization and a need for change in medication. The total PANSS score had to be above 60. Before inclusion, the patients underwent a 10 days washout phase of previous antipsychotic treatment (both FGAs and SGAs). During the 3 months’ treatment period, benzodiazepines were allowed to reduce acute agitation and anxiety. Patients who required continuous benzodiazepine treatment were excluded. CYR-101 was administered orally twice a day with a titration period of 4 days followed by fixed daily doses of 64 mg. Additional analyses of sleep were performed using polysomnographic recordings (objective exploration of sleep) and subjective exploration of sleep with the Pittsburgh Sleep Quality Index (PSQI). On examination days, CYR-101 was administered 2 h before cognitive testing and sleep exploration, respectively.

At inclusion, the mean PANSS total score was 75. Three months’ treatment with CYR-101 compared to placebo resulted in a nonsignificant reduction in PANSS total and subscores (positive and general scores) with the reduction in negative symptoms reaching trend-level significance (p = 0.06). The decrease of the negative score was ~ 7 points and the difference between CYR-101 and placebo was ~ 4 points.

CYR-101 treatment also resulted in nonsignificant cognitive improvements on the items verbal fluency, verbal...
memory and motor speed as measured by the brief assessment of cognition in schizophrenia. No effects on attention and speed, working memory and executive functions were reported.

Analyses of sleep patterns after 2 weeks of treatment with CYR, as compared to placebo, showed normalization of the slow wave sleep distribution (SWS) over the night (recovery of the exponential decline of SWS over the night) and shortening of the sleep onset latency. After 3 months, the CYR-101 treated patients reported improvement of sleep on the PSQI, and the improvements of objective sleep patterns observed at week 2 were partly sustained. In general, CYR-101 was well tolerated with no evidence of side effects, including weight gain, prolactin increase and EPS.

4.2.1 Discussion of CYR-101
The available data on the antipsychotic and pro-cognitive effect of CYR-101 do not rule out an effect on these parameters, but the magnitude of the potential improvements appears modest at best. The observed effect on sleep may be beneficial to some psychotic patients, and this change in sleep patterns could contribute to the reported (but nonsignificant) improvements in cognition and trend-level effects on negative symptoms. Overall, the present Phase IIa data need further validation from Phase IIb-III studies in order to provide a more detailed evaluation of CYR-101 as a potentially novel antipsychotic drug.

5. Expert opinion
In this review, we focus on investigational 5-HT_{2A} antagonists as potential new agents to treat schizophrenia. We find that there is substantial and converging evidence supporting an involvement of the 5-HT_{2A} receptor system in the pathophysiology of schizophrenia. Although all approved FGAs and SGAs have been shown to reduce positive symptoms, a large proportion of schizophrenia patients are not treated satisfactorily [8]. The treatment effects of the current antipsychotic drugs on negative symptoms are equivocal and the effect on cognitive symptoms dubious [106]. Therefore, the theoretical rationale for investigating 5-HT_{2A} receptor antagonists in the treatment of schizophrenia is sound.

Of the four 5-HT_{2A} receptor antagonists reviewed here, only CYR-101 is currently in the investigational pipeline for schizophrenia. M100907 and eplivanserin were included because the data on these drugs contribute to the evaluation of possible clinical effects of 5-HT_{2A} antagonism. Pimavanserin is still in development, but the indication has been changed from schizophrenia to psychosis in Parkinson’s disease.

Overall, there is some evidence supporting that an antipsychotic effect can be obtained solely by 5-HT_{2A} receptor antagonism. However, the clinical effect of monotherapy with M100907, eplivanserin, pimavanserin and CYR-101 appears to be of modest magnitude. Although to date no head-to-head studies with CYR-101 and conventional antipsychotic drugs are available, it is the overall impression that the 5-HT_{2A} receptor antagonists generally assume an intermediate position by being marginally superior to placebo but inferior to the conventional antipsychotic drug. Nevertheless, an attractive feature of 5-HT_{2A} receptor antagonism is the absence of severe side effects. The existence of a subgroup of schizophrenia patients with a more pronounced disturbance in the serotonergic system is plausible, and could partly explain why some patients respond insufficiently to D_{2} receptor blockade [42,71,85]. Currently, it is not possible to reliably identify such subgroups of patients, and specific drug development of 5-HT_{2A} antagonists tailored to these putative subgroups, therefore, seems premature.

Notably, the moderate antipsychotic effect obtained with pimavanserin in monotherapy was investigated in patients with Parkinson’s disease and not in schizophrenia patients [101]. In Parkinson’s disease, direct striatal dopamine blockade induced by antipsychotic drugs, especially by FGAs, is particularly unwanted. Because the antipsychotic effect of frontal 5-HT_{2A} antagonism may be obtained without a direct blockade of the striatal D_{2} receptors [13,77-78], the rationale for the ongoing exploration of the antipsychotic potential pimavanserin in Parkinson’s disease seems to be justified.

As a consequence of only a modest antipsychotic effect, the indication of eplivanserin was changed to cover insomnia. The recent Phase II data on CYR-101 also indicated a positive effect on sleep patterns. There is growing evidence that the 5-HT_{2A} receptor system is implicated in primary and secondary sleep disturbances [107]. A Phase IIa study of patients with primary chronic insomnia treated with ADP125, which is a selective 5-HT_{2A} receptor antagonist (initiated by Arena Pharmaceuticals, June 2006), indicated effects on objective parameters of sleep maintenance and sleep consolidation [108]. However, after unsatisfactory Phase IIb trials APD125 was discontinued [109] (December 2008). Likewise, eplivanserin with the indication of chronic insomnia was recently discontinued [94].

The rationale for selective 5-HT_{2A} receptor antagonism as a target in primary and secondary sleep disorders is compelling. However, at present the evidence for a potent antipsychotic effect of 5-HT_{2A} receptor antagonism is limited.

One important argument driving the investigation of specific 5-HT_{2A} receptor antagonists is the urgent need for drugs which can specifically ameliorate negative and cognitive symptoms in schizophrenia. The recent data on CYR-101 might suggest an improvement in certain cognitive domains and negative symptoms, but it should be noted that the observed improvements on these parameters were nonsignificant and emerged from analyses of a wide range of variables; hence, a risk of a type II error is present. Furthermore, part of the observed effect may be ascribed to a secondary effect on improved sleep. A more thorough evaluation cannot be made until the full data set is published. Nevertheless, the empirical evidence for a direct linkage between the 5-HT_{2A}

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receptor system and negative and cognitive symptoms, respectively, is sparse [42,107]. Therefore, at present a specific improvement of CYR-101 on cognition and negative symptoms in schizophrenia is not substantiated.

An interesting aspect of 5-HT2A receptor antagonism is the potential as adjunct treatment to conventional FGAs or SGAs. In clinical studies, the combinations of haloperidol and 5-HT2A receptor antagonists (eplivanserin and pimavanserin) have been tested. Also, the combination of pimavanserin and risperidone has been tested. However, based on the current data, the effects on psychopathology obtained by combination therapy is debatable. In fact, rather than improving psychopathology, the combination of haloperidol and pimavanserin indicated an amelioration of side effects.

Because risperidone is a potent 5-HT2A receptor antagonist, the pharmacodynamic rationale of this combination can be questioned. We speculate that this fact may have influenced the decision of discontinuation of pimavanserin for schizophrenia. An advantage of adjunctive therapy with a 5-HT2A receptor antagonist to a D2 antagonist is the theoretical possibility of titration of the 5-HT2A receptor blockade without having to proportionally block the striatal D2 receptors to obtain an optimal treatment effect in the individual patient. However, further research is needed to quantify an optimal therapeutic window for frontal 5-HT2A receptor blockade.

In conclusion, there is substantial evidence supporting a role of 5-HT2A receptors in the pathophysiology of schizophrenia. Previous attempts to develop a selective 5-HT2A receptor antagonist to treat schizophrenia have been discontinued or the indication has been modified to other disorders. Currently, only one selective 5-HT2A receptor antagonist is in the investigational pipeline. The present Phase IIa data will need substantial additional validation for CYR-101 to be approved as a novel antipsychotic drug.

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Affiliation
Bjørn H Ebdrup*1 MD PhD,
Hans Rasmussen**1 PhD,
Jørn Arnt1 PhD DSci &
Birte Glenthøj†1 MD DMSc
1Author for correspondence
*Authors contributed equally
1Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital Glostrup, Faculty of Health Sciences, Psychiatric Center Glostrup, Nordre Ringvej 29, DK-2600 Glostrup, Denmark
E-mail: hans@cnsr.dk
2Sunred Pharma Consulting, Svend Gønges Vej 11A, DK-2680 Solrød Strand, Denmark