LEADING ARTICLE

Drugs 2008; 68 (16): 2269-2292
0012-6667/08/0016-2269/$53.45/0

Upcoming Agents for the Treatment of Schizophrenia

Mechanism of Action, Efficacy and Tolerability

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Abstract

Since the introduction of a group of atypical antipsychotics in the 1990s, there has been a decline in the rate of new antipsychotics being introduced into clinical practice. However, with increasing safety and efficacy concerns over currently available drugs and a dearth of options available for atypical depot formulations, there is a considerable need for the development of new formulations and agents. This review examines the profile of seven antipsychotic drugs currently in the premarketing stage of development and summarizes their mechanism of action, clinical potential and safety.

Asenapine is an antipsychotic with activity for multiple receptors and has potential to improve negative and cognitive symptoms of schizophrenia. Bifeprunox is a partial dopamine D_2 and serotonin 5-HT_{1A} receptor agonist showing a less than convincing efficacy profile, but which may offer safety advantages over available agents by means of a reduced risk of metabolic complications. Iloperidone is a D_2 and 5-HT_{2A} receptor antagonist requiring further studies to establish its effectiveness. It has a high affinity for α_1-adrenoceptors, which can lead to associated haemodynamic adverse effects. Nemonapride is essentially a typical antipsychotic drug, similar in structure to sulpiride, which has been available for some time in Japan. It has efficacy against positive symptoms and has shown some antidepressant and anxiolytic properties, although efficacy data for it are somewhat limited. Norclozapine (N-desmethylclozapine) is a major metabolite of clozapine formed by its demethylation. Its partial agonist activity at D_2 receptors has raised interest in it as an antipsychotic in its own right. In addition, it appears to have muscarinic agonist activity, which is believed to be responsible for the observed positive effects it has on cognition. It was envisaged to be effective as an adjunct to other agents or at high doses in the treatment of refractory schizophrenia, although a recent randomized, controlled study showed that it was no more effective than placebo in patients with schizophrenia experiencing an acute psychotic episode. Olanzapine pamoate depot injection has shown comparable efficacy to oral olanzapine in several studies. However, it has provoked considerable safety concerns by its association with inadvertent intravascular injection events in numerous patients. This accidental intravascular administration of olanzapine pamoate leads to excessive sedation, confusion, dizziness and altered speech. Post-injection observation periods and postmarketing surveillance are planned following the introduction of the depot. Paliperidone palmitate is the

palmitate ester of paliperidone, the major metabolite of risperidone, and is formulated as a long-acting injection for intramuscular use. Its pharmacology is comparable to risperidone, having D_2 and 5-HT_{2A} receptor antagonist activity. Efficacy studies have shown positive results, and because paliperidone has no antagonistic activity at cholinergic receptors, it has low potential for anticholinergic adverse effects, including cognitive dysfunction. However, with higher doses, the frequency of extrapyramidal side effects and orthostatic hypotension have been shown to be greater than with placebo.

Schizophrenia is a severely debilitating psychiatric disorder observed worldwide. It often results in lengthy hospitalizations and is a considerable burden upon medical resources.[1] Prevalence amongst adults tends to vary between studies but is usually reported to be in the range of 0.5–1.5%.[2] Since the introduction of chlorpromazine in the 1950s, the number of antipsychotic drugs available has notably increased. By the 1980s, several conventional or first-generation antipsychotics had been developed and were found to be effective in treating the positive symptoms of schizophrenia, such as delusions and hallucinations. However, the negative symptoms of the illness, (emotional withdrawal, apathy, avolition and cognitive dysfunction) were not effectively managed by these drugs. In addition, these antipsychotics were found to produce a high burden of extrapyramidal side effects (EPS)[3] and adverse effects related to elevation of serum prolactin.[4] Moreover, their tendency to cause tardive dyskinesia[5] in the longer term made their continued use problematic.

In an effort to develop novel agents that would treat both the positive and negative symptoms of schizophrenia while affording a low propensity for movement disorders, the pharmaceutical industry developed several antipsychotics in the 1990s, referred to as second-generation antipsychotics, considered to be 'atypical'. While these drugs have probably been of some benefit to patients, full expectations have not been realized. Despite having a somewhat improved (although debatable) efficacy in treating the negative symptoms of schizophrenia as well as a lower propensity to cause movement disorders, these benefits have been accompanied by other effects, including metabolic adverse effects[6] such as weight gain[7,8] and impaired glucose metabolism.[9] Furthermore, similar to conventional antipsychotics, atypical antipsychotics have not proved to be effective in treatment-refractory patients. Until recently, clozapine, discovered shortly after chlorpromazine, remained the only drug to have demonstrated clinical superiority to other agents in treatment-resistant schizophrenia[10] and in suicidality.[11] Attempts to develop new drugs based on its pharmacology in an effort to mimic its superior efficacy have so far largely been unsuccessful. However, a recent paper reported that higher than typically prescribed doses of olanzapine may be as effective as conventional doses of clozapine in treatment-resistant schizophrenia.[12]

In the last decade, antipsychotic drug development has remained somewhat static, at least in terms of new drug introductions. This may be because of poorly defined pathophysiology of the disorder and incomplete understanding of the pharmacology of available drugs,[13] resulting in confusion as to the ideal mode of action required. In addition, failure of some drugs in early clinical trials and the increased costs of drug development may have contributed to the recent dearth of new agents being launched. Since many currently available atypical antipsychotics will soon lose patent protection, there is increased pressure on the pharmaceutical industry to develop novel treatments, and so a renewed interest in drug development for schizophrenia has emerged.[13]

This article reviews the antipsychotic agents that have undergone extensive clinical development for the treatment of schizophrenia and reached the premarketing stage of development, and examines

their pharmacology, clinical potential and tolerability.

1. Pharmacology of Currently Available Antipsychotics

1.1 Conventional (Typical) Antipsychotics

Since the dopamine hypothesis was first proposed in the 1960s, it has remained the central pivot around which antipsychotic agents have been developed.[14] Conventional antipsychotic drugs all show at least some affinity for the dopamine D_2 receptors and there is a strong correlation between clinical efficacy of the drugs and their binding affinities.[15] Positive symptoms of schizophrenia are believed to result from dopaminergic hyperactivity,[16] while negative symptoms have been attributed to reduced functioning in the prefrontal cortex, mainly resulting from underactivity of prefrontal dopaminergic neurons. Therefore, these symptoms are potentially improved by agents that reduce serotonergic function (by serotonin 5-HT_{1A} receptor agonist activity), thus promoting increased dopamine activity in the prefrontal cortex, and by drugs that block presynaptic dopamine receptors.[17] Such an effect may also improve cognitive impairment because of the resulting stimulation of D_1 receptors.[18] These concepts are consistent with the clinical profile of conventional antipsychotics, which are effective in treating positive symptoms, presumably by reducing overactivity in the mesolimbic pathways, but offer little benefit to the negative symptoms or cognitive deficits because of inadequate or adverse effects in the mesocortical pathways (where dopamine activity is already decreased).[19]

The high rates of movement disorders caused by conventional antipsychotics are believed to arise from dopamine antagonism in the nigrostriatal pathways. The subsequent reduced dopamine activity leads to a relative increase in cholinergic activity, and the resulting imbalance accounts for these troublesome adverse effects.[3] Elevation of prolactin caused by these drugs stems from their dopamine antagonist effects on the tuberoinfundibular pathway.[20]

1.2 Atypical Antipsychotics

Because of the problems encountered with conventional antipsychotics, the atypical antipsychotics were developed based to a large extent on the complex pharmacology of clozapine. Clozapine has affinity for a diverse range of receptors including D_1, D_2 and D_4 dopaminergic, α_1 and α_2 adrenergic, H_1 histaminergic, muscarinic and various serotonin receptor subtypes.[21-23] Its supported clinical superiority[10] and near absence of the debilitating EPS has fuelled an intense effort over the last 20 years to develop similar agents.

In the development of atypical antipsychotics, researchers have tried to mimic the pharmacological action of clozapine while trying to avoid its own serious adverse effects, such as agranulocytosis.[24] Like conventional antipsychotics, atypical antipsychotics are also antagonists at D_2 receptors. However, they do show an additional range of binding activity at various other receptor sites. In particular, their antagonist activity at serotonin receptors was thought to account for the differences between the two classes of agents. Atypical drugs show a higher affinity for 5-HT_{2A} receptors compared with D_2 receptors, and this ratio of affinities has been hypothesized to account for their enhanced efficacy and fewer EPS.[25,26] Antagonism at 5-HT_{2A} receptors leading to an increase of dopamine activity in the prefrontal cortex has also been suggested to account for the beneficial effects that atypical antipsychotics have against negative symptoms.[26] However, amisulpride has no affinity for 5-HT_{2A} receptors[27] but clearly has atypical antipsychotic properties,[28] suggesting that this 5-HT_{2A}/D_2 receptor hypothesis may not hold true for all drugs or that other receptor systems also play an important role in the atypicality of antipsychotics.

It has also been suggested that atypical antipsychotic activity may be explained by differences in the occupancy and dissociation of antipsychotics from D_2 receptors.[29-31] Agents showing a relatively low D_2 receptor affinity, such as clozapine,[32,33] quetiapine[34] and olanzapine,[35] and fast dissociation from the receptor, have atypical properties. This loose D_2 receptor binding may also account for the

Table I. New antipsychotic drugs

Drug	Mechanism of action	Manufacturer	Development status	Expected launch date
Asenapine	Multiple receptors	Organon	Phase III	2009
Bifeprunox	Partial D_2 and 5-HT_{1A} receptor agonist	Lundbeck/Solvay	Phase III	2010/2011
Iloperidone	D_2 and 5-HT_{2A} receptor antagonist	Titan Pharmaceuticals	Phase III	Not known
Norclozapine	Partial D_2 and muscarinic receptor agonist	ACADIA Pharmaceuticals	Phase II	Not known
Nemonapride	D_2, D_3 and D_4 receptor antagonist	Astellas	Launched in Japan	No plans for launch in US, UK or Europe
Olanzapine pamoate	D_2 and 5-HT_{2A} receptor antagonist	Eli Lilly	Phase III	Late 2008
Paliperidone palmitate	D_2 and 5-HT_{2A} receptor antagonist	Janssen-Cilag	Phase III	2009

observed limbic selectivity observed for some drugs such as clozapine.[36]

1.3 Dopamine Partial Agonists

More recently, a new class of antipsychotics has been introduced, the dopamine partial agonists, of which aripiprazole is the only one currently available in clinical practice. Aripiprazole is a potent partial agonist at D_2 and 5-HT_{1A} receptors and acts as an antagonist at 5-HT_{2A} receptors.[37,38] While both typical and atypical antipsychotics act as full antagonists at dopamine receptors, schizophrenia as outlined is thought to arise from a combination of over- and under-activity in different dopamine pathways. Thus, blocking dopamine activity in all parts of the system may account for the problems encountered with drug therapy already discussed. Therefore, in theory, the capacity for an agent to alter dopamine neurotransmission differently in separate areas of the dopaminergic system may have both therapeutic and safety advantages.

Partial agonists are thought to exert their effects by acting effectively as dopamine antagonists in the mesolimbic pathway. However, in the mesocortical pathway, where reduced dopamine activity is thought to produce negative symptoms and cognitive impairment, they effectively act as dopamine agonists. Furthermore, because dopamine partial agonists do not produce complete dopamine activity blockade in the nigrostriatal and tuberoinfundibular pathways, their propensity to cause EPS and elevated prolactin levels may be reduced.[19]

2. New Antipsychotics

We are now approaching an exciting and challenging time for the development of new treatments for schizophrenia. With continual, if somewhat slow, improvements in our understanding of the pathophysiology of the disease and complex pharmacology of the drugs, novel approaches for drug discovery are being studied. The following agents (table I) are presently in their developmental stages and are due to be introduced for clinical practice in the near future.

2.1 Asenapine

Asenapine (figure 1) is a novel psychotropic agent being developed for the treatment of schizophrenia and bipolar disorder. Its chemical structure and pharmacological action are distinct from currently available drugs.

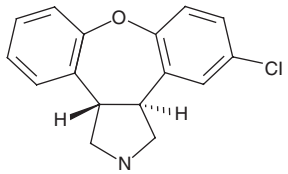

Fig. 1. Structural formula of asenapine ((3a*S*,12b*S*)-5-chloro-2,3,3-a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7] oxepino[4,5-c]pyrrole).

Asenapine has higher affinity for a variety of serotonergic (5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7), noradrenergic (α_{2A}, α_{2B}, α_{2C}) and dopaminergic (D_3, D_4) receptors than D_2 receptors, but minimal affinity for muscarinic receptors (see table II for comparison of binding affinities).[39]

One of the mechanisms for alleviating negative symptoms is believed to be the blockade of 5-HT_{2A} and 5-HT_{2C} receptors. Asenapine binds to these receptors 19-fold and 38-fold, respectively, higher than D_2 receptors, suggesting a potential for improving negative symptoms.[39] Asenapine is thought to maintain adequate but not excessive blockade of D_2 receptors, and so it may allow control of positive symptoms without the resulting EPS and elevation of prolactin. Similarly, activity at α-adrenergic receptors has been suggested to improve negative and cognitive symptoms via α_2-receptor antagonism and positive symptoms via α_1-adrenoceptor antagonism.[52] Asenapine appears to have relatively high affinity for adrenergic receptors, which may offer potential therapeutic advantages, although there is no such evidence as yet. In contrast, it has been shown to have very low affinity for muscarinic and other CNS receptors. The D_2 receptor affinity of asenapine is approximately 6000-fold greater than the affinity for M_1 receptors, thus minimizing the risk of antimuscarinic adverse effects that are seen with many other agents.[39]

2.1.1 Preclinical Studies

Results from preclinical studies using animal models have been consistent with the receptor profiles described in the previous section. Using the conditioned avoidance response (CAR) test in rats, the dose-response relationship for the antipsychotic-like effect of asenapine was determined. For apparently adequate antipsychotic effect (i.e. 80% suppression of CAR[53]), the dose needed was 0.1–0.2 mg/kg (dose that produces a 50% effective response = 0.12 mg/kg).[54] When tested in the catalepsy test, asenapine 0.1 and 0.2 mg/kg did not reach a score of 2 (where catalepsy is considered to begin[53]) at any time interval examined. These findings suggest that asenapine may exhibit a potent antipsychotic effect without inducing EPS.[53,54]

Table II. Antipsychotic receptor-binding profiles[39-50] (adapted from Chou,[51] with permission)

Receptor	Ki (nmol/L)												
	ARI	OLA	RIS	PAL	QUE	ZIP	CLO	HAL	ASE	BIF	ILO	NEM	
D_1		31	430		455	525	85	210	1.4		216		
D_2	0.34	11	4	4.8	160	5	125	0.7	1.3	3.2	21.4	0.16	
D_3	0.8	49	10	6.9	340	7	473	2	0.42	0.6	7.1	0.26	
D_4	44	27	9	30	1600	32	9–12	3	1.1	1.6	25	0.31	
5-HT_{1A}	1.7	>1000	210	590	2450	3	770	1100	2.7	10.0	93.1	1.8	
5-HT_{2A}	3.4	4	0.5	1.0	220	0.4	12	45	0.07	>>	5.6	9.4	
5-HT_{2C}	15	11	25		615	1	8	>10 000	0.034	>>	42.8		
α_1-Adrenergic	57	19	0.7		7	11	7	6	1.2	>>	0.4		
H_1	61	7	20	32	11	50	6	440	1.0	>>			
M_1	>>	2	>10 000		120	>1000	1.9	>1500	>>	>>	4898		

5-HT = serotonergic; **ARI** = aripiprazole; **ASE** = asenapine; **BIF** = bifeprunox; **CLO** = clozapine; **D** = dopaminergic; **H** = histamine; **HAL** = haloperidol; **ILO** = iloperidone; K_i = dissociation constant; **M** = muscarinic; **NEM** = nemonapride; **OLA** = olanzapine; **PAL** = paliperidone; **QUE** = quetiapine; **RIS** = risperidone; **ZIP** = ziprasidone; >> indicates very high Ki, therefore no appreciable affinity for receptor.

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