LEADING ARTICLE

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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.

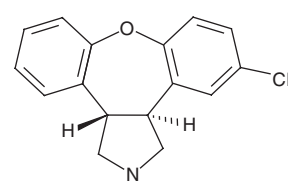


Fig. 1. Structural formula of asenapine ((3a*S*,12b*S*)-5-chloro-2,3,3-a,12b-tetrahydro-2-methyl-1*H*-dibenz[2,3:6,7] oxepino[4,5-c]pyrrole).

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.

The behavioural effects of asenapine in rats, as assessed by *in vivo* microdialysis, have been found to be accompanied by an increase in dopamine release in the three brain regions examined: the medial prefrontal cortex, nucleus accumbens and striatum.[54] Asenapine induced a marked enhancement of dopamine efflux to a greater extent in the shell region of the nucleus accumbens than in the core region, thus sharing a similar profile to atypical drugs.[54] Microdialysis and electrophysiological assessments showed that asenapine potentiated both prefrontal dopaminergic and glutamatergic transmission. These effects may also contribute to improvement of negative symptoms and cognitive deficits.[54,55] Furthermore, the very low concentration of asenapine required to facilitate glutamatergic transmission, even lower than that for clozapine, suggests an important cognitive-enhancing action.[54]

2.1.2 Clinical Studies

A randomized, double-blind, placebo- and risperidone-controlled, fixed-dose, 6-week trial of asenapine was carried out in the US.[56] Patients were randomly assigned to receive sublingual asenapine 5 mg twice daily, placebo or oral risperidone 3 mg twice daily. Results for the primary efficacy outcome measure, the Positive and Negative Syndrome Scale (PANSS) total score,[57] for the intention-to-treat population showed mean changes at endpoint from baseline were −15.9 with asenapine and −5.3 with placebo ($p < 0.005$). The PANSS positive subscale score showed mean changes at endpoint from baseline of −5.5 for asenapine compared with −2.5 for placebo ($p = 0.01$) and −5.1 for risperidone (also significant compared with placebo; $p < 0.05$). PANSS negative subscale score results showed mean changes at endpoint from a baseline of −3.2 for asenapine compared with −0.6 for placebo ($p = 0.01$).

The main efficacy findings from this study were that asenapine 5 mg twice daily was superior to placebo in treating both the positive and negative symptoms of schizophrenia. Risperidone (3 mg twice daily), on the other hand, was superior to placebo in treating positive symptoms, but it was not more effective than placebo in treating negative symptoms. This is not consistent with findings from earlier trials showing risperidone 6 mg/day having greater improvement on the PANSS negative subscale score compared with placebo.[58,59] Although statistical comparisons between asenapine and risperidone were not performed, it is perhaps important to note that discontinuations due to ineffectiveness of treatments were more common with risperidone than asenapine.[56]

The incidence of adverse effects was similar across all three treatment groups, with the most frequent reports for asenapine being insomnia (11%), somnolence (11%), nausea (11%), anxiety (10%) and agitation (9%).[56] Asenapine showed a placebo-equivalent risk of significant weight gain, whereas risperidone was associated with a higher incidence of clinically significant weight gain, consistent with previous reports,[60,61] along with a high incidence of hyperprolactinaemia.[56] Laboratory findings in this study also showed that asenapine was not associated with metabolic disturbances or adverse effects on cardiovascular function such as changes in blood pressure, heart rate or corrected QT interval prolongation.[56]

In summary, the receptor profile and combined data from preclinical and clinical studies predict that asenapine has an ability to improve positive, negative and cognitive symptoms of schizophrenia, while causing limited extrapyramidal, antimuscarinic and metabolic adverse effects. It may therefore prove to be a useful option in patients with predominant or resistant negative symptoms. Further large-scale studies will be needed in order to confirm these findings and to distinguish it from other D_2/5-HT_2 receptor antagonists such as risperidone.

2.2 Bifeprunox

Bifeprunox (figure 2) is an antipsychotic showing partial agonist activity at D_2, D_4 and 5-HT_{1A} receptors, and antagonism at D_3 receptors. Unlike many other antipsychotics, it shows no marked activity at the 5-HT_{2A}, 5-HT_{2C}, noradrenergic, muscarinic or histaminergic receptors.[46,62]

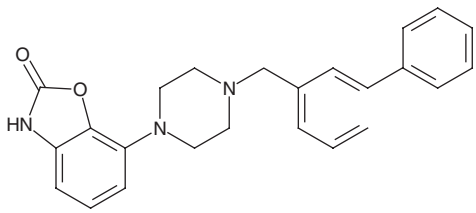


Fig. 2. Structural formula of bifeprunox (7-[4-[(3-phenylphenyl)-methyl]iperazin-1-yl]-3H-benzooxazol-2-one).

2.2.1 Preclinical Studies

In *in vitro* preclinical studies, bifeprunox demonstrated partial dopamine agonist properties. Agonist effects were seen to be induced when endogenous dopamine tone was low, for example in adenylate cyclase activity assays in Chinese hamster ovary cells and in rat striatal slices.[46] In contrast, in the presence of a full D_2 receptor agonist (i.e. when endogenous dopamine was high) bifeprunox acted as a functional antagonist.[46,63] Results suggest a distinct antipsychotic profile, showing functional agonist activity in the prefrontal cortex region and a functional antagonist activity in brain regions such as the nucleus accumbens where dopaminergic neurotransmission is thought to be increased in schizophrenia.[62]

In vivo preclinical studies on rats showed that bifeprunox, unlike conventional antipsychotics, caused suppression of the CAR at near maximal D_2 receptor occupancy. This suppression was dose related and, based on the relationship observed, bifeprunox was predicted to be clinically effective at doses ≥10 mg, producing >90% D_2 receptor occupancy at these doses.[64] Receptor occupancy has also been studied in humans using positron emission tomography (PET). D_2 receptor occupancy was also found to be dose related, with a plateau in occupancy observed at 90% for bifeprunox doses ≥10 mg (figure 3).[63]

2.2.2 Clinical Studies

The following four randomized clinical trials have examined the efficacy and safety of bifeprunox. Casey and co-workers[65] conducted a multicentre, 6-week, randomized, placebo-controlled, risperidone-referenced, dose-finding study including 589 patients with acute exacerbation of schizophrenia. The efficacy, safety and tolerability of three fixed once-daily doses of bifeprunox (5, 10 and 20 mg) were evaluated.

In this study, only bifeprunox 20 mg showed a statistically significant reduction in PANSS total score[57] compared with placebo. In the last-observation-carried-forward (LOCF) analysis, mean changes in PANSS total score were −11.3 and −5.3 points for bifeprunox 20 mg and placebo, respectively (adjusted p = 0.031; treatment effect CI −11.1, −0.4). Bifeprunox 5 and 10 mg produced mean changes of −9.7 and −5.0 points, respectively, but the difference compared with placebo was not statistically significant (adjusted p = 0.128, treatment effect CI −9.2, 0.9 for 5 mg; p = 1.000, treatment effect CI −4.4, 5.5 for 10 mg). A statistically significant −15.7-point change was observed in the risperidone arm (p < 0.0001 vs placebo; 95% CI −14.5, −6.5).[65] Bifeprunox 20 mg also produced statistically significant changes versus placebo in the PANSS-positive (p = 0.037; treatment effect CI −2.9, −0.1) and PANSS-negative (p = 0.026; treatment effect CI −2.6, −0.2) subscales.

The incidence of patients withdrawing from the study because of adverse effects was similar in the bifeprunox and placebo groups. No statistically significant difference was observed at endpoint on any movement disorder scales between bifeprunox and placebo. Treatment with bifeprunox at all doses was associated with statistically significant weight decreases, reduction in non-fasting total cholesterol and triglycerides, as well as decreases in prolactin levels compared with placebo.[65]

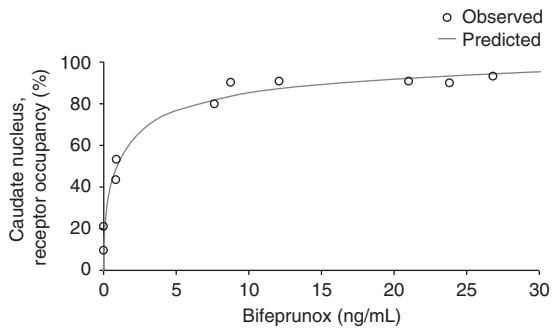


Fig. 3. Bifeprunox plasma concentration at 2 hours after administration and dopamine D_2 receptor occupancy in caudate nucleus.[63]

A very similar study was conducted by Rapaport and colleagues,[66] which evaluated the efficacy and safety of bifeprunox at once-daily doses of 30 and 40 mg compared with placebo and with a reference risperidone arm. In the LOCF analysis, bifeprunox 30 mg produced a statistically significant difference from placebo in the change in PANSS total score.[57] Mean changes were −13.5 and −7.7, respectively (p = 0.020; 95% CI −10.3, −1.4). Bifeprunox 40 mg, on the other hand, produced a mean −10.3-point change, but the difference from placebo was not statistically significant (adjusted p = 0.156; 95% CI −7.7, 1.2).

In terms of safety assessments, the most frequent adverse events seen in bifeprunox 30 and 40 mg groups compared with placebo and risperidone were gastrointestinal in nature. For bifeprunox 30 mg, they included constipation (13%), dyspepsia (11%), nausea (18%), vomiting (12%) and dizziness (8%). Similar results were seen with the higher dose.[66] Decreases in weight were greater with bifeprunox compared with placebo. Non-fasting cholesterol, glucose and triglyceride levels were also lower with bifeprunox 30 and 40 mg. Bifeprunox was also associated with a lower incidence of EPS than the active reference drug, risperidone.[66]

Barbato and colleagues[67] used the same study design but examined once-daily doses of bifeprunox 20 and 30 mg versus placebo, this time with olanzapine 15 mg/day as the reference drug. In this study, no statistically significant change in PANSS total score[57] was observed with bifeprunox 20 or 30 mg compared with placebo, whereas the reference agent olanzapine did show significant improvement on measures of efficacy over placebo.

In contrast with these efficacy findings, bifeprunox showed some safety advantages over olanzapine. At the 6-week study endpoint, the groups treated with bifeprunox 20 mg, bifeprunox 30 mg and placebo showed mean weight decreases of 1.05, 0.5 and 0.59 kg, respectively, whereas olanzapine was associated with a weight increase of 0.26 kg (p < 0.0001 vs placebo).[67] Movement-related adverse effects occurred with equal frequency across groups and ECG results were also comparable. Both doses of bifeprunox produced statistically significant decreases in prolactin levels (p = 0.0001), whereas placebo and olanzapine were associated with non-significant increases from baseline.[67]

In order to assess long-term efficacy and safety of bifeprunox, a 6-month, randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study was conducted.[68] Patients received bifeprunox 20 or 30 mg/day or placebo. The primary endpoint was the time from randomization to deterioration, defined as a Clinical Global Impression (CGI)-Improvement[69] score ≥5 or PANSS[57] item P7 (hostility) and/or G8 (uncooperativeness) score ≥5 for 2 consecutive days or ≥20% increase in PANSS total score from baseline. Other efficacy and safety assessments were similar to the studies mentioned previously. In this study, treatment with bifeprunox 20 and 30 mg resulted in statistically significant (p = 0.008 and p = 0.006, respectively) longer time to deterioration compared with placebo (LOCF).[68] The proportion of patients who deteriorated was 40.5% in the bifeprunox 20 mg group, 38.4% in the 30 mg group and 59.0% in the placebo group. In the placebo group, the risk of deterioration was found to be approximately 1.5-fold higher than the bifeprunox 20 and 30 mg groups (hazard ratio 0.656 and 0.653, respectively).

Long-term safety data showed that treatment-emergent adverse events were 72.3%, 83.1% and 57.8% in bifeprunox 20 mg, 30 mg and placebo groups, respectively. Movement-related disorders occurred in 10%, 15% and 4% in the bifeprunox 20 mg, 30 mg and placebo groups, respectively, although there were no clinically relevant changes in the Barnes Akathisia Rating Scale (BARS),[70] Simpson-Angus Scale (SAS)[71] and Abnormal Involuntary Movement Scale (AIMS)[72] total scores at endpoint in all three treatment groups. Bifeprunox 30 mg reached statistical significance in reduction in adjusted mean weight (p = 0.027) and triglycerides (p = 0.006) versus placebo, but the other dose and safety parameters did not reach statistical significance. There was no difference between the groups in incidence of abnormal ECG findings.[68]

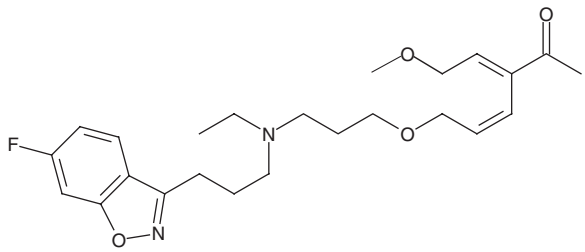


Fig. 4. Structural formula of iloperidone (1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone).

A pooled analysis from existing studies was performed in order to evaluate the metabolic effects of bifeprunox compared with placebo and the active reference agents used. Findings from this analysis reflected those shown in the studies discussed in this section. Bifeprunox treatment was associated with a reduction in weight, total cholesterol and triglyceride levels and minimal changes in plasma glucose levels.[73]

2.3 Iloperidone

Iloperidone (figure 4) is an atypical antipsychotic initially chosen for development because of its high affinity for 5-HT_2 receptors and moderate affinity for D_2 receptors in rats. It acts as a broad spectrum dopamine, serotonin and noradrenaline receptor antagonist.[47]

Pharmacological studies have shown that iloperidone binds with a high affinity to α_1-adrenoceptors, 5-HT_{2A} receptors and D_3 receptors, but a lower affinity to D_{2A} and D_4 receptors, α_{2A}- and α_{2C}-adrenoceptors, and 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C} and 5-H_{T6} receptors.

As seen with other new antipsychotics, the high affinity of iloperidone for 5-HT_{2A} and α_1-adrenergic receptors but more moderate affinity for D_2 receptors is thought to portend antipsychotic efficacy with a reduced propensity to cause EPS. The moderate D_2 receptor affinity balanced by affinity for 5-HT_{2C} and α_2-adrenergic receptors suggests a potential effect on negative symptoms and cognition. In addition, blockade of α_{2C}-adrenoceptors might provide anxiolytic activity.[74,75] Low binding affinity for histamine H_1 receptors suggests a limited propensity to cause sedation and weight gain,[60] and minimal activity at cholinergic receptors indicates that anticholinergic adverse effects may be avoided. Moreover, as a result of the low affinity for α_{2A} adrenoceptors, iloperidone is not expected to induce convulsions.[47,76,77]

2.3.1 Preclinical Studies

In animal behavioural models, iloperidone exhibited potent, long-lasting 'antipsychotic' activity against the positive symptoms of schizophrenia as seen in the climbing mouse assay and CAR in rats. However, it was 300-fold less potent in causing catalepsy and in inhibiting apomorphine-induced stereotyped behaviour in rats. These two measures evaluate activity in the nigrostriatal dopamine pathway and postsynaptic dopamine receptors in the striatum, thereby predicting EPS potential. These results suggest that at effective doses of iloperidone, it is unlikely to cause EPS.[78]

Iloperidone also showed activity against negative symptoms in a number of animal models, such as the rat social interaction paradigm. Other agents with higher affinity for 5-HT_2 than D_2 receptors, such as clozapine and risperidone, also increase social interaction behaviour in the unfamiliar rat paradigm, suggesting efficacy against negative symptoms. In addition, iloperidone also disinhibited behaviour in the elevated plus maze assay, exhibiting an anxiolytic profile. Similar results are seen with clozapine, whereas risperidone and haloperidol do not disinhibit behaviour in this assay.[78]

Iloperidol is an antagonist with high binding affinity for α_1-adrenoceptors. Dose-dependent hypotensive effects have been observed in studies on rats and dogs, indicating that a dose titration regimen

would be necessary to reduce orthostatic hypotension in human subjects.[78]

2.3.2 Clinical Studies

Phase I studies examined three doses of iloperidone in healthy volunteers. While single doses of 1 mg did not show adverse effects, higher doses produced mild transient adverse effects such as dizziness, lightheadedness, drowsiness, nasal congestion, headache, nausea and dry mouth. Dose-related orthostatic hypotension was also seen, as expected from the animal studies. A 5 mg dose produced effects on both heart rate and systolic blood pressure. Concurrent ingestion of food was found to slow absorption of iloperidone and improve its tolerability.[78]

A 6-week, randomized, double-blind, placebo-controlled, multicentre, phase II study has also been conducted. Fixed doses of iloperidone 4 or 8 mg/day were administered, and efficacy and safety were assessed weekly using the PANSS total score, CGI and Brief Psychiatric Rating Scale (BPRS). Both iloperidone treatment groups showed improvements from baseline PANSS total score;[57] however, the greatest improvement was seen in the iloperidone 8 mg/day group, with a mean endpoint improvement of 18 points ($p = 0.077$). The removal of a single investigator because of 'treatment-by-investigator interaction' resulted in a mean endpoint improvement of 21 points for iloperidone 8 mg/day compared with placebo ($p = 0.014$), rendering the result statistically significant. On further investigation, it was found that patients of this investigator had 75% fewer prior hospital admissions than the others in the study. Although improvements in PANSS negative subscales were seen in all groups, iloperidone 8 mg showed an endpoint improvement of 5 points, which was also statistically significant compared with placebo ($p = 0.025$). Results for the other efficacy scores were not statistically significant.[78]

With regard to the safety and tolerability of iloperidone, there were no safety concerns highlighted in this study.[78] No meaningful changes in prolactin levels or clinical signs of hyperprolactinaemia were observed, and endpoint scores of EPS assessed by the SAS[71] were low in all treatment groups, with no statistically significant differences. Rhinitis, impotence, abnormal ejaculation and polyuria, as well as certain cardiovascular events (tachycardia, palpitations, postural hypotension) were observed more frequently with iloperidone than placebo. Many of these adverse events are attributed to the high affinity for α_1-adrenoceptors.[78]

A pooled analysis of three 6-week, prospective, randomized, multicentre, double-blind, placebo- and comparator-controlled trials, including 1943 patients with acute schizophrenia was undertaken in order to assess the safety profile of iloperidone. Patients were exposed to three dose ranges of iloperidone, either haloperidol, risperidone or placebo, and comparisons of rates of serious adverse events were made. Discontinuation rates due to adverse events were 4.8% in the iloperidone group, 7.6% in the haloperidol group, 6.2% in the risperidone group and 4.8% in the placebo group. Overall, patients receiving iloperidone showed better performance on the Extrapyramidal Rating Scale and the BARS than patients receiving risperidone or haloperidol. Iloperidone groups showed a mild increase in bodyweight (range 1.5–2.1 kg), which was similar to the risperidone groups (1.5 kg), whereas haloperidol and placebo groups showed a mean reduction in bodyweight (−0.1 and −0.3 kg, respectively). Corrected QT interval increased significantly across all iloperidone groups (2.9–9.1 msec) and the haloperidol group (5.0 msec); however, no significant changes were seen in the risperidone or placebo groups. Iloperidone was associated with mild elevation of serum glucose, slight decrease in triglycerides and no change in total colesterol from baseline measures. Iloperidone was associated with a reduction in prolactin levels, whereas there was a significant increase in prolactin with haloperidol and risperidone.[79]

2.4 Nemonapride

Nemonapride (figure 5) is a benzamide derivative antipsychotic agent structurally similar to sulpiride that was developed in Japan and launched in 1997. It was also undergoing phase II clinical trials

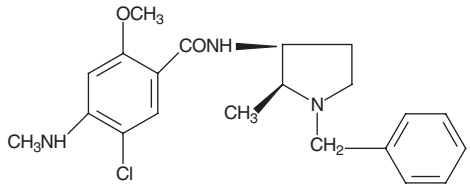


Fig. 5. Structural formula of nemonapride (N-[(2RS, 3RS)-1-benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide).

in France but development was discontinued there in 2001.

Nemonapride is a potent and selective antagonist at D_2,[80,81] D_3 and D_4[82] receptors, but it has very weak affinity for others such as D_1, 5-HT_2, noradrenaline (norepinephrine) and cholinergic receptors.[48,81] It also has a strong agonist affinity for 5-HT_{1A} receptors both *in vitro* and *in vivo*.[83]

2.4.1 Preclinical Studies

The effect of reserpine treatment on the striatal uptake of radiolabelled nemonapride was investigated in mice and rats. The study showed that the binding of nemonapride to D_2 receptors was not affected by endogenous dopamine-depletion produced by treatment with reserpine, thus suggesting a high affinity for the receptors.[84]

When studied in rats, nemonapride was found to be more potent than haloperidol and chlorpromazine in inhibiting CARs and apomorphine- or methamfetamine-induced stereotypy, but it also possessed cataleptogenic activity.[85]

The electrophysiological and cataleptogenic properties of nemonapride were studied in the cat and compared with haloperidol, chlorpromazine and sulpiride.[80] The study demonstrated that, although nemonapride had electrophysiological properties similar to the typical drugs, its effect on the dopaminergic system in the caudate nucleus appeared to be less potent than that of haloperidol and chlorpromazine. Nemonapride also proved to be less cataleptogenic than haloperidol and chlorpromazine. Subcutaneous nemonapride dosages of up to 5 mg/kg produced no cataleptic behaviour in the cat, but at higher doses tremor was observed in some cats. Haloperidol and chlorpromazine caused catalepsy at subcutaneous dosages of 0.5 and 5 mg/kg, respectively. In addition, nemonapride showed a slight central depressant activity, as seen by the EEG arousal response to electrical stimulation.[80]

2.4.2 Clinical Studies

The efficacy of nemonapride was evaluated in an 8-week, double-blind, comparative study using haloperidol as the reference drug.[86] A total of 167 patients with schizophrenia were administered nemonapride 3 mg/tablet (n = 81) or haloperidol 2 mg/tablet (n = 86) consisting of a daily dose of three tablets for the first week, and thereafter the dose could be adjusted to up to 12 tablets a day. Following analysis of results, nemonapride was found to be not significantly superior to haloperidol in final global improvement rating. In terms of categorical outcomes, nemonapride was found to be significantly superior to haloperidol in patients with more than 'moderate improvement' but not significantly superior in efficacy rate in those with more than 'slight improvement'.

The efficacy rate of nemonapride was superior to haloperidol in patients whose duration of illness was >5 years, while haloperidol was superior to nemonapride in patients whose duration of illness was <1 year. No significance difference was found between the two drugs in overall safety ratings. Following these results, the authors suggested that nemonapride may have superior efficacy to haloperidol in patients with more chronic schizophrenia.[86]

A study examining patient characteristics and risk factors for acute dystonia with nemonapride was conducted in 39 patients with schizophrenia.[87] The occurrence of acute dystonic reactions was prospectively monitored and the relationship between these adverse events and patient characteristics, as well as plasma drug concentrations and prolactin levels, was investigated. Dosages of nemonapride 9–27 mg/day were used. The study found that 51.3% of patients had dystonic reactions, most of which occurred within 3 days of treatment. This relatively high incidence, comparable with fluphenazine 33.8% and haloperidol 60%,[88,89] is believed to be due to the high affinity of the drug for the haloperidol-sensitive σ receptors in the cortex and cerebel-

lum,[90,91] which is reported to be involved in the occurrence of acute dystonia.[92] Findings revealed that male gender and younger age were risk factors for dystonia. Data also showed that plasma drug concentration was not closely related to the development of acute dystonia, but that prolactin response did reflect vulnerability to the adverse event, at least in male patients.[87]

The relationships between the therapeutic spectrum of nemonapride and the plasma drug concentration and prolactin levels were investigated in a fixed-dose study (18 mg/day for 3 weeks) in 31 patients with acute exacerbation of schizophrenia.[93] Of the 31 patients, 25 (80.6%) were responders showing an improvement of at least 50% in symptom reduction after 3 weeks. Patient characteristics did not affect the response to treatment. The mean values for the percentage improvement in total BPRS[94] and five subscale scores were 71.5% for total, 73.2% for positive, 86.0% for excitement, 53.9% for negative, 84.2% for cognitive and 67.5% for anxiety/depression. The responder group had a higher percentage of improvement in positive and anxiety/depression symptoms compared with the nonresponder group (84.6 ± 17.0% vs 25.9% ± 15.7% [$p < 0.001$] and 76.9 ± 18.8% vs 28.5 ± 39.9% [$p < 0.005$], respectively), whereas no significant differences were seen for other subscale symptoms between the two groups.

A multiple regression analysis confirmed significant correlations between the percentage improvement in total BPRS symptoms and in positive or anxiety/depression symptoms (standardized partial regression coefficient 0.695 [$p < 0.001$] and 0.338 [$p < 0.005$], respectively). The efficacy of nemonapride against positive symptoms was considered to be due to its potent antagonistic effects for D_2 receptors. Its anxiolytic and antidepressant properties were believed to be associated with its 5-HT_{1A} receptor agonist properties. The effect of plasma concentration of nemonapride plus its active metabolite desmethylnemonapride on therapeutic effects showed an inverted U-shaped relationship similar to that seen with haloperidol,[95] perphenazine[96] and fluphenazine,[97] suggesting a comparable dose-response relationship.

Contrary to expectations, the prolactin response and therapeutic effects of nemonapride showed no correlation. This suggests little value in using prolactin response as a predictive value for therapeutic effects of treatment. Prolactin response is greatly affected by other nondrug factors, mainly gender and hormonal differences. Females have higher concentrations of estrogen, which has been documented to stimulate prolactin response.[93,98]

A similar fixed-dose (18 mg/day) study investigating the associations between adverse effects of nemonapride and plasma drug concentration and prolactin levels in 33 patients with acute exacerbation of schizophrenia was conducted.[98] The most frequently observed adverse effects were akathisia (69.7%), dystonia (48.5%), hypokinesia (45.5%), tremor (39.4%) and increased salivation (36.4%). Positive correlations were observed between prolactin response and EPS scores after week 1 (Spearman rank correlation $rs = 0.651$; $p < 0.01$), week 2 ($rs = 0.567$; $p < 0.05$) and week 3 ($rs = 0.670$; $p < 0.01$) in male patients, although no significant correlations were found in female or total patients. Prolactin response may therefore reflect vulnerability for developing EPS in male but not in female patients. No significant correlations were found between plasma drug concentration and adverse effect scores, suggesting that plasma drug concentration does not appear to be a useful predictor of adverse effects. These findings imply that pharmacodynamic rather than pharmacokinetic factors are more predictive of the development of drug-induced adverse effects in male patients with schizophrenia.[98]

2.5 Norclozapine

As previously mentioned, clozapine remains the gold standard in terms of efficacy in schizophrenia. Clozapine undergoes extensive hepatic metabolism, forming two major metabolites: norclozapine (N-desmethylclozapine; NDMC) and clozapine N-oxide (figure 6).[99]

Norclozapine is formed by the demethylation of clozapine by cytochrome P450 (CYP) 1A2 and

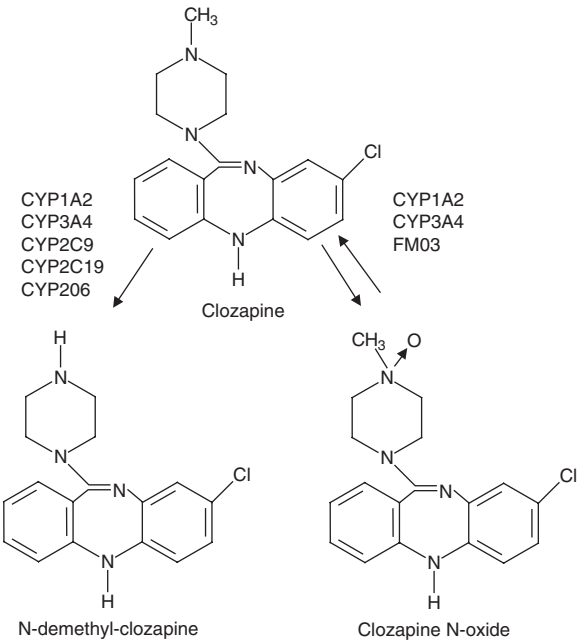


Fig. 6. Metabolic pathways of clozapine. **CYP** = cytochrome P450; **FMO** = flavin-containing mono-oxygenase.

CYP3A4 isoenzymes.[100] Reports indicate that norclozapine has a comparable affinity for D_2 receptors, a lower affinity for D_1 receptors, and a higher affinity for 5-HT_{2A}, 5-HT_{2C} and muscarinic M_1–M_5 receptors than the parent compound clozapine.[101-103] Norclozapine differs from clozapine at muscarinic receptors as it is a more potent partial agonist at M_1 receptors and appears to have increased agonist activity at M_4 and M_5 receptors.[104]

Norclozapine has recently been highlighted as a possible antipsychotic following the discovery of its partial agonist activity at D_2 receptors,[103] similar to aripiprazole.[105] In addition, results from studies implying that a high norclozapine **:** clozapine ratio may be a better predictor of improvement in cognitive functioning and quality of life than plasma levels of either compound alone has also raised considerable interest,[104] although these positive results had not been observed in previous studies.[106,107]

2.5.1 Preclinical Studies

Adult male rats were used to compare the activity profile of norclozapine with that of clozapine, haloperidol and aripiprazole.[108] Subcutaneous norclozapine (10–60 mg/kg) showed a high and dose-dependant 5-HT_2 receptor occupancy (64–79%) but its occupancy for D_2 receptors was relatively low (<15% at 60 mg/kg) 1 hour after administration. In contrast with the other antipsychotics, which significantly inhibited amfetamine-induced hyperlocomotion and CAR in rats, norclozapine was not very effective in reducing them. This low D_2 receptor occupancy was consistent with the lack of catalepsy or prolactin level elevation in rats given norclozapine.

Following these observations, the authors envisaged norclozapine to be effective only at very high doses or as an adjunctive therapy to other antipsychotics, especially in treatment-resistant patients. Moreover, since the muscarinic agonist properties of norclozapine are claimed to be responsible for its efficacy and positive effects on cognition, and clozapine is considered to be a muscarinic antagonist, it is therefore postulated that the overall effects will depend on the ratio of norclozapine to clozapine. However, as previously mentioned in section 2.5, there is conflicting evidence for this theory.[108]

2.5.2 Clinical Studies

Despite high expectations for norclozapine, results from a recent 6-week, multicentre, double-blind, placebo-controlled, phase II study designed to evaluate the safety and efficacy of norclozapine in 247 patients with schizophrenia experiencing an acute psychotic episode were disappointing. Neither dose of norclozapine used (100 or 200 mg twice daily) demonstrated improved efficacy compared with placebo, in either the primary endpoint as measured by the mean change from baseline in the PANSS total score, or secondary endpoints as measured by PANSS subscales and the CGI scale. The most common adverse events in the treatment arms compared with placebo were reported to be hypersalivation, tachycardia and dyspepsia, all of which were noted to be dose related. No significant clinical decreases in neutrophil counts were observed in the study groups. It is anticipated that further studies will not be conducted until these results are thoroughly analysed.[109]

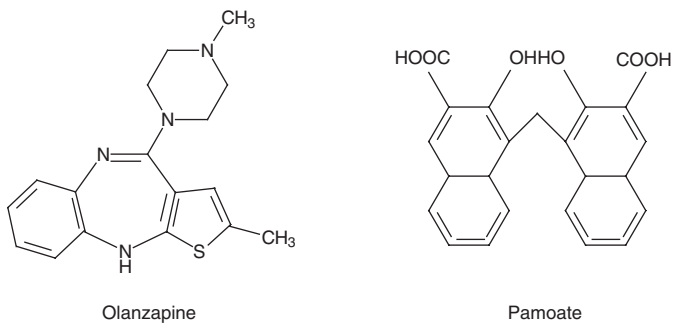
2.6 Olanzapine Pamoate

Olanzapine, a second-generation antipsychotic agent, has been widely used since its introduction in 1996. It is a potent antagonist at 5-HT_{2A}, 5-HT_{2C}, D_1, D_2, D_3 and D_4 receptors, and also has affinity for muscarinic receptors. The efficacy and safety of olanzapine have been extensively studied over many years. Several studies have found oral olanzapine to have clinically meaningful efficacy.[110] The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study[111] compared the effectiveness of five antipsychotic drugs and found that olanzapine had the lowest discontinuation rates for any reason compared with the other antipsychotics studied over the 18-month treatment period. In a meta-analysis including 16 studies, patients treated with olanzapine were found to have a lower all-cause discontinuation rate than those treated with other antipsychotics in the studies.[112]

The safety profile of oral olanzapine has also been closely investigated and has revealed potential risks for causing the 'metabolic syndrome', consisting of hyperglycaemia, hyperlipidaemia, hyperprolactinaemia, elevations in transaminases and weight gain, as well as sedation, a common adverse effect observed during olanzapine therapy.[113]

To date, only one atypical antipsychotic agent has become available in a long-acting injection form. Risperidone long-acting injection was introduced for clinical practice in 2002. Olanzapine pamoate (figure 7) depot is currently undergoing the drug development process, and has recently been examined for its efficacy and safety in various studies. Olanzapine pamoate doses are designed to provide olanzapine steady-state exposure equivalent to daily doses of olanzapine 10–20 mg, as shown in table III.[113]

Oral olanzapine has shown a dose-dependent striatal D_2 receptor occupancy of 60–80% at usual clinical doses.[114] In an effort to determine whether the long-acting olanzapine pamoate depot provided sustained D_2 receptor occupancy for 4 weeks following the injection, an open-label PET study was conducted in patients with schizophrenia and



Olanzapine Pamoate

Fig. 7. Structural formulae of olanzapine and pamoate.

Table III. Approximate equivalent doses of olanzapine oral and olanzapine pamoate depot[113]

Dosage of oral olanzapine (mg/day)	Approximate equivalent dosage of olanzapine pamoate depot (mg 2-weekly)	Approximate equivalent dose of olanzapine pamoate depot (mg 4-weekly)
10	150	300
15	210	405
20	300	

schizoaffective disorder.[115] Patients continued to receive their prescribed oral olanzapine (5–20 mg/day) for a 1-week 'lead-in' period whereby baseline procedures were completed. These baseline parameters included plasma olanzapine concentrations and an [^{11}C]raclopride PET scan proximal to trough plasma concentrations. An intramuscular injection of olanzapine pamoate 300 mg was then administered to patients every 4 weeks for the 6 months duration of the study period, comprising a total of six injection cycles. Mean striatal D_2 receptor occupancy, as measured by [^{11}C]raclopride PET, was 69% on oral olanzapine (baseline). During the first injection cycle, the receptor occupancy fell to approximately 70% of baseline measures, but after the second injection cycle a gradual increase was seen in mean D_2 receptor occupancy, reflecting the accumulation of the depot. By the fifth injection cycle, the D_2 receptor occupancy returned to 84% of baseline occupancy level on oral olanzapine, thus a mean of 60% was reached in the last two injection cycles. D_2 receptor occupancy and plasma olanzapine concentrations were significantly correlated ($r = 0.76$; $p \leq 0.001$) over the study period.

This resulting mean D_2 receptor occupancy of approximately ≥60% is consistent with antipsychotic efficacy, and is also seen with oral olanzapine treatment. However, it is suggested that supplementation with oral olanzapine may be required to maintain adequate therapeutic response during the first few injection cycles.[115]

2.6.1 Clinical Studies

Efficacy

The acute efficacy of olanzapine pamoate was assessed in a randomized, multicentre, parallel, 8-week study.[113] Baseline-to-endpoint mean change in PANSS[57] was examined in acutely ill patients with schizophrenia randomly assigned to olanzapine pamoate 300 mg/2 weeks, 405 mg/4 weeks, 210 mg/2 weeks or placebo. All three depot doses were found to be statistically significantly superior to placebo (all $p < 0.001$) with respect to mean change from baseline to endpoint in PANSS total score (−26.32, −22.57 and −22.49, respectively compared with −8.51 for placebo). Statistically significant superiority was also seen when measured against the PANSS positive, negative and general psychopathology subscale scores.[113] These significant improvements were maintained throughout the study. These results were compared with previous efficacy studies for oral olanzapine[116,117] and were shown to be of a similar magnitude.[113]

A 24-week, double-blind, parallel study, designed to assess the efficacy of olanzapine pamoate as maintenance treatment for outpatients with schizophrenia, investigated whether clinically stable patients receiving other antipsychotics would remain stable when switched to olanzapine pamoate.[113] Patients were first switched to oral olanzapine and had to remain stable on it for at least 4 weeks before being randomized to receive olanzapine pamoate 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, 45 mg/4 weeks or oral olanzapine (10, 15 or 20 mg/day). The first three doses of olanzapine pamoate correspond to oral olanzapine 10, 15 and 20 mg. The low dose of 45 mg/4 weeks was included to serve as a comparator in order to demonstrate the superiority of the three therapeutic doses over a low dose with regard to time to exacerbation of symptoms.

In this analysis, results showed that the three therapeutic doses of olanzapine pamoate were statistically superior to the 45 mg/4 weeks dose with respect to time to exacerbation of symptoms ($p < 0.001$, $p < 0.001$ and $p = 0.006$, respectively). These observations were confirmed by the PANSS total scores, which showed that the three therapeutic doses of olanzapine pamoate were effective in maintaining a response throughout the study duration, whereas the 45 mg/4 weeks group showed a statistically significant worsening of total PANSS scores

over the 24 weeks ($p < 0.001$). In addition, a non-inferiority analysis was undertaken that was designed to demonstrate the non-inferiority of the pooled 2-week depot doses (150 mg/2 weeks and 300 mg/2 weeks) to oral olanzapine in terms of exacerbation rate after 24 weeks of maintenance treatment. Results indicated that the pooled 2-week depot dosage regimens were found to be non-inferior to the oral olanzapine group in terms of non-exacerbation rate. The cumulative non-exacerbation rate for the pooled 2-week regimen was 90% and for the oral olanzapine group it was 93%. These results were considered to meet the non-inferiority criteria as previously determined.

Because these studies were of similar design to previous oral olanzapine studies,[118] the authors suggested that these results could be compared in terms of maintenance of effects and estimated relapse rates, and a high degree of consistency was found amongst the studies.[113]

A long-term, open-label study that was designed to assess the long-term efficacy and safety of olanzapine pamoate with doses ranging of 45–405 mg at intervals of 2–4 weeks in patients with schizophrenia or schizoaffective disorder was carried out over a period of up to 4 years.[113] A total of 880 patients were included, and results showed that there was a statistically significant decrease in PANSS total score ($p = 0.013$) from 56.28 to 54.90, indicating that patients remained stable with minimal symptoms. CGI-Severity scores were also analysed and remained in the range 2.91–2.78 throughout the study, indicating minimal to mild severity of illness. All-cause discontinuation, a widely accepted measure of treatment effectiveness, was also investigated and found that at 18 months, 34% of patients had discontinued treatment.[113] Relatively speaking, this rate is low when compared with results from the CATIE study, which showed that 64% of patients discontinued treatment with oral olanzapine for any reason at 18 months, yet this was the lowest rate of discontinuation compared with other antipsychotics investigated in the study.[111] It is also much lower than that seen with risperidone long-acting injection.[119,120]

Safety

An integrated database including 1915 patients having received at least one injection (with the longest exposure for a single patient being 2.6 years) is available.[113] Discontinuation as a result of adverse effects was <6% in all databases, and three deaths (0.2%) have occurred but were deduced by the investigators to be unrelated to the study drug.

There have been no statistically significant differences in adverse events between oral olanzapine and the depot formulation, with the exception of a new potential safety risk that emerged in clinical trials known as inadvertent intravascular (IAIV) injection event. This came to light when an unanticipated degree of sedation was observed in a small number of patients following an injection. Although sedation is a common adverse effect in olanzapine-treated patients, the extent of sedation resulted in further investigation. This adverse event has occurred in 24 patients, an incidence of 1.2% of patients treated with olanzapine pamoate or 0.07% of injections given. The IAIV injection-related adverse event consists of sedation, confusion, dizziness, altered speech/dysarthria and somnolence. These effects usually occur within 1 hour of injection but the median time ranged from 20 minutes to 3 hours post-injection. To date, all patients have recovered fully from this adverse event, usually within 3–72 hours, without permanent sequelae, the majority of whom have continued to receive the depot injections (67%). Further investigation and evidence from the events indicates the mechanism of IAIV injection, a known risk with all intramuscular injections. Blood samples of plasma olanzapine concentrations were taken during the events and were found to be substantially elevated (figure 8).

Solubility experiments have revealed that when olanzapine pamoate depot is injected into the muscle as intended, the dissolution of the salt is very gradual and results in a slow release of drug into the bloodstream. However, if the salt comes into contact with a considerable amount of blood or plasma, as occurs if the needle punctures a vessel or enters a rich capillary bed during administration, the salt dissolves and therefore dissociates more quickly. This dissolution can occur over a period of minutes

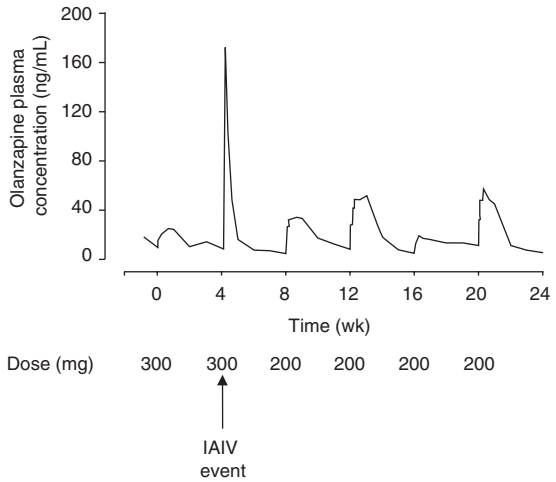


Fig. 8. Olanzapine plasma concentration-time profile after six different depot injections in a patient who experienced an inadvertent intravascular (IAIV) event after the second injection.[113]

to hours in the bloodstream, whereas when it takes place in muscle tissue as intended, it requires a period of days to weeks. Other factors are thought to affect the dissolution rate of the pamoate salt such as the amount of olanzapine pamoate suspension being administered into the blood stream, the volume and rate of blood flow, and the degree of vascular injury.[113]

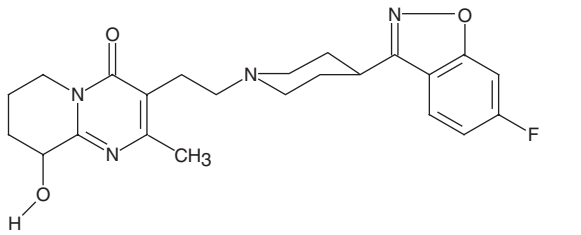
Eli Lilly has a risk management plan regarding this adverse event consisting of accurate product labelling highlighting the risks, training for healthcare providers, continued monitoring, and postmarketing observational study to evaluate risk factors and estimate the incidence rate. In addition, they will be recommending a post-injection observation period of at least 1 hour and a 3-hour post-injection precautionary period during which patients will be advised not to drive or operate heavy machinery, to be vigilant for signs and symptoms of potential IAIV injection events and be able to obtain assistance if required.[113]

2.7 Paliperidone Palmitate

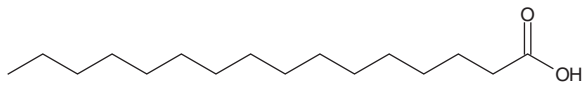
Paliperidone (figure 9), also known as 9-hydroxy-risperidone, is the major plasma metabolite of risperidone. Its pharmacology is therefore believed to be comparable to that of risperidone. It acts as an antagonist at D_2 and 5-HT_{2A} receptors,[121,122] similarly to other atypical antipsychotics. It also has binding activity at 5-HT_{1A}, 5-HT_{2C} and 5-HT_{1D} receptors,[45,122] α_1- and α_2-adrenergic receptors and H_1 receptors. This activity profile[45] would suggest potential for causing adverse effects such as orthostatic hypotension, weight gain and sedation. Paliperidone has no antagonistic activity at cholinergic receptors and therefore has low potential to cause anticholinergic adverse effects, including cognitive dysfunction.[45,123]

2.7.1 Preclinical Studies

In rat studies, the distribution of paliperidone to the different brain regions was found to be more limited than that of risperidone. The conclusion



Paliperidone



Palmitate ester

Fig. 9. Structural formulae of paliperidone and palmitate ester.

drawn was that, although paliperidone contributes to the activity of risperidone *in vivo*, it does so to a lesser extent than plasma concentrations would predict. Mean residence times in the frontal cortex and striatum were found to be 4–6 hours for risperidone compared with about 12 hours for paliperidone.[121,123]

2.7.2 Pharmacokinetics

Paliperidone is primarily excreted renally.[123,124] Its pharmacokinetic profile was studied in hepatic impairment, and unbound plasma paliperidone concentrations were found to be similar to those observed in healthy volunteers.[124] Because a substantial proportion of patients taking risperidone may have a nondetectable plasma risperidone concentration but a measurable amount of paliperidone, it is important to measure plasma paliperidone concentrations in these patients.[125] The coadministration of risperidone with carbamazepine or sodium valproate was investigated for pharmacokinetic interactions in one study. This showed that valproate did not affect plasma concentrations of risperidone or paliperidone, but carbamazepine led to a statistically significant decrease in plasma paliperidone concentrations of approximately 70%. The induction of CYP3A4 metabolism by carbamazepine was thought to be responsible for this reduction in plasma concentration.[123,126]

Paliperidone palmitate is the palmitate ester of paliperidone. It is manufactured in an aqueous nanosuspension into a long-acting formulation for intramuscular injection, to be administered every 4 weeks. Once it is injected and reaches the systemic circulation, the paliperidone palmitate ester is instantly and entirely converted into paliperidone.[127]

2.7.3 Clinical Studies

A 9-week, randomized, double-blind, placebo-controlled study in patients with schizophrenia examined the efficacy and safety of two fixed doses of paliperidone palmitate injection. Patients were randomized to receive placebo, or paliperidone palmitate 50 or 100 mg injection, on days 1, 8 and 36. A significant improvement in mean PANSS total ($p \leq 0.001$), positive ($p \leq 0.001$) and negative ($p \leq 0.010$) scores was seen with both paliperidone palmitate treatment doses at endpoint compared with placebo (table IV).[127]

From day 8 onwards, a significant improvement in mean PANSS total score ($p \leq 0.011$)[57] was seen with both doses of paliperidone palmitate compared with placebo (measured at every post-baseline timepoint), thus estimating an approximate onset of action. The percentage of patients achieving a clinical response (considered as ≥30% change in PANSS total score at endpoint) was significantly greater with paliperidone palmitate 50 and 100 mg than with placebo (33.3% [$p = 0.007$], 36.8% [$p = 0.002$] and 13.6%, respectively). In addition, CGI-Severity scores[69] showed a significant improvement in severity of illness from baseline to endpoint for both doses of paliperidone palmitate (50 mg [$p = 0.004$] and 100 mg [$p < 0.001$]) compared with placebo.[127]

A total of 51% of the 247 patients randomized into the study completed it, of which 32%, 59% and 61% were in the placebo, paliperidone palmitate 50 and 100 mg groups, respectively. The most common reason for treatment discontinuation across the groups was lack of efficacy (placebo = 43%, paliperidone palmitate 50 mg = 29%, 100 mg = 17%). The incidence of adverse effects was 64%, 65% and 60% in placebo, paliperidone palmitate 50 and 100 mg groups, respectively. Treatment discontinuation due to adverse effects occurred more frequently with placebo (10%) than with the other two groups (paliperidone palmitate 50 mg = 3%, 100 mg = 2%) [table V].[127]

No deaths were reported during this study. In the paliperidone palmitate 50 mg group, a higher frequency of adverse effects was reported relating to insomnia and schizophrenia (≥5% difference) compared with placebo, and in the 100 mg group the frequency for EPS was higher compared with placebo (≥5% difference). None of the adverse effects relating to EPS were severe or resulted in discontinuation of treatment. The median change from baseline to endpoint in BARS,[70] SAS global[71] and AIMS[72] total scores was zero for all treatment groups. Orthostatic hypotension was reported more frequently in the paliperidone palmitate groups compared with placebo (6–11% vs 4%, respective-

Table IV. Change from baseline to endpoint in Positive and Negative Syndrome Scale (PANSS) total, and positive and negative factor scores[127]a

	Placebo (n = 66)	Paliperidone palmitate 50 mg (n = 63)	Paliperidone palmitate 100 mg (n = 68)
PANSS total score			
Baseline[b]	87.8 ± 13.9	88.0 ± 12.4	85.2 ± 11.1
Change from baseline[b]	6.2 ± 18.3	−5.2 ± 21.5	−7.8 ± 19.4
Difference in LS means[c]		−11.2 ± 3.4	−14.1 ± 3.3
p-Value vs placebo[d]		0.001	<0.001
Positive factor scores			
Baseline[b]		24.3 ± 5.0	23.9 ± 5.1
Change from baseline[b]	24.1 ± 5.6	−2.0 ± 6.8	−2.9 ± 6.9
Difference in LS means[c]	1.7 ± 5.3	−3.7 ± 1.1	−4.7 ± 1.1
p-Value vs placebo[d]		0.001	<0.001
Negative factor scores			
Baseline[b]	23.6 ± 4.7	23.3 ± 4.9	22.3 ± 4.4
Change from baseline[b]	0.3 ± 5.0	−1.9 ± 5.1	−2.6 ± 4.5
Difference in LS means[c]		−2.2 ± 0.8	−3.4 ± 0.8
p-Value vs placebo[d]		0.010	<0.001

a Intent-to-treat analysis set.

b Mean ± standard deviation; last observation carried forward.

c LS mean difference ± standard error vs placebo.

d p-Value vs placebo without any adjustment for multiplicity.

LS = least-square.

ly). In addition, the mean changes in bodyweight (in kg) at endpoint were −0.3 ± 3.0 (SD), 0.7 ± 2.7 and 1.4 ± 3.5 with placebo, paliperidone palmitate 50 and 100 mg, respectively.

3. Conclusions

The clinical utility of the new antipsychotics reviewed in this article is best judged by reference to current needs in the treatment of schizophrenia. While available antipsychotics are usually effective against positive symptoms, they do little to improve the functional disability widely seen in patients with schizophrenia – for example, only around one in ten patients is engaged in paid employment.[128] It is likely, but not firmly established, that improvements in negative and cognitive symptoms would give rise to functional improvement. Thus, drugs providing clinically significant improvements in those symptom domains are much needed. In addition to this, there is a clear need for an alternative to clozapine in treatment-resistant schizophrenia. This alternative should ideally be well tolerated, with minimal or at least remediate toxicity. Lastly, there is a need for antipsychotic drugs that are either metabolically neutral or beneficial and that are atypical (i.e. have a low rate of movement disorder). This need is already met by aripiprazole, but alternatives would be clearly helpful.

Asenapine is undoubtedly effective in treating positive symptoms and has a significant advantage over placebo in the treatment of negative symptoms. Nonetheless, the size of this latter effect is small and perhaps clinically insignificant (around 3 points on the PANSS negative subscale). It appears to be well tolerated and metabolically neutral, but there is, as yet, no evidence that it has any worthwhile effect on functional disability.

Bifeprunox may have beneficial effects on some metabolic parameters and is well tolerated. Set against these properties are doubts over the efficacy of bifeprunox: there are numerous equivocal findings in placebo-controlled trials. Some of these findings are perhaps explained or mitigated by the use of fixed doses in most trials (fixed doses deny clinicians the facility to titrate dose against effect). Also, bifeprunox has clear longer-term efficacy.

Table V. Incidence of treatment-emergent adverse events occurring in ≥5% of patients in any treatment group[127]

Adverse events	Placebo [n = 84] (%)	Paliperidone palmitate 50 mg [n = 79] (%)	Paliperidone palmitate 100 mg [n = 84] (%)	Total paliperidone palmitate [n = 163] (%)
Total patients with adverse events	54 (64)	51 (65)	50 (60)	101 (62)
Psychiatric disorders				
Insomnia	14 (17)	17 (22)	12 (14)	29 (18)
Schizophrenia	2 (2)	6 (8)	4 (5)	10 (6)
Psychotic disorder	8 (10)	4 (5)	1 (1)	5 (3)
Agitation	10 (12)	4 (5)	4 (5)	8 (5)
CNS/peripheral disorders				
Headache	12 (14)	5 (6)	6 (7)	11 (7)
EPS	0	0	5 (6)	5 (3)
Gastrointestinal disorders				
Constipation	1 (1)	1 (1)	4 (5)	5 (3)
Diarrhoea	4 (5)	0	2 (2)	2 (1)
Vomiting	4 (5)	1 (1)	0	1 (1)

EPS = extrapyramidal side effects.

Taken together, these results suggest bifeprunox may prove a suitable alternative to aripiprazole.

Iloperidone appears to be effective, but its use is complicated by weight gain and haemostatic changes. Nemonapride is essentially a conventional antipsychotic. Neither of these two new antipsychotics has a clear place in therapy.

Norclozapine has the potential to become an alternative to clozapine, but data from a recent clinical study, which found it was no better than placebo, have stalled further studies until full analysis of these results is undertaken. Further clinical efficacy and safety data are clearly required.

Current depot antipsychotics are problematic. Conventional depots are associated with high rates of movement disorder and prolactin-related adverse effects. The only atypical depot available, risperidone, requires special cold storage conditions and may be ineffective at some licensed dosages. Both olanzapine pamoate and paliperidone palmitate are clinically effective, albeit largely against positive symptoms. Olanzapine pamoate is associated with weight gain and metabolic disturbances, while paliperidone palmitate seems to be free of important or severe adverse effects. Both formulations have considerable potential, being very probably less likely to be associated with tardive dyskinesia and other movement disorders than typical depots. The use of olanzapine pamoate is complicated by the incidence of IAIV events and its clinical utility is likely to be compromised by safety measures necessary in practice.

Overall, not one of the emerging drugs for schizophrenia has been shown to satisfy any current clinical need. Some represent incremental improvements to currently available therapies. Real and substantial improvements are perhaps likely to come about only through new, as yet untried, mechanisms of action.

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