AN UPDATE OF THE PRECLINICAL PROFILE OF LURASIDONE

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Abstract

Lurasidone is a novel antipsychotic drug approved by the US Food and Drug Adminstration (FDA) for the treatment of schizophrenia and bipolar disorder in adults, and by the European Medicines Agency (EMA) for the treatment of schizophrenia.

This article reviews published preclinical studies, and analyses the pharmacological, behavioural and molecular mechanisms of lurasidone and their contribution to its therapeutic activity.

Lurasidone is an antagonist for dopamine D_2, serotonin 5-HT_{2A}, and 5-HT_7 receptors, and a partial agonist for serotonin 5-HT_{1A} receptors, whereas it has negligible affinity for histamine H_1 and muscarinic M_1 receptors.

Studies with animal models predictive of antipsychotic and antidepressant activities demonstrated a high efficacy of lurasidone. Moreover, pro-cognitive effects were observed in several animal models that assessed memory, cognition and executive functions. The clinical meaning of these results in human patients is not well understood, yet.

At a cellular level, lurasidone promoted neuronal plasticity, modulated epigenetic mechanisms controlling gene transcription, and increased the expression of the neurotrophic factor BDNF in cortical and limbic brain regions.

Key words: Lurasidone, schizophrenia, bipolar disorder

Introduction

Second-generation antipsychotics have been widely used for schizophrenia. Drugs, such as olanzapine, ziprasidone, risperidone, clozapine, and quetiapine, share the ability to antagonize D_2 and 5-hydroxytryptamine$_{2A}$ (5-HT_{2A}) receptors. They are effective for treating positive symptoms, such as hallucinations, delusions, and excitement, and may improve negative symptoms (flattened affect, apathy, and social withdrawal) [1,2]. Unfortunately, many second-generation antipsychotics (e.g., clozapine and olanzapine) are associated with a high risk of metabolic dysfunction and weight gain [3]. This drawback of available drugs caused an unmet medical need for new agents for the treatment of schizophrenia, with a good safety profile.

Lurasidone [(3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl]-cyclohexylmethyl}-hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride] is a novel azapirone derivative, an antipsychotic drug approved by the US Food and Drug Adminstration (FDA) for the treatment of schizophrenia and bipolar disorder in adults, and by the European Medicines Agency (EMA) for schizophrenia patients [4,5]. Preclinical studies demonstrated that lurasidone has antipsychotic, anxiolytic and antidepressant effects in rodents; such efficacy

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was associated with a low potential to induce extrapyramidal side effects [6]. Lurasidone proved to be effective in the treatment of acute schizophrenia, acting both on positive and on negative symptoms, and to be well tolerated [7]. Receptor binding affinities, structural features and neuroplastic properties (shown in animal models) may contribute to the pharmacological profile of lurasidone, which could explain the clinical efficacy.

Lurasidone has high affinity as antagonist for dopamine D_2, serotonin 5-HT_{2A}, and 5-HT_7 receptors, and as partial agonist for serotonin 5-HT_{1A} receptors, whereas it has and negligible affinity for histamine H_1 and muscarinic M_1 receptors, which are thought to contribute to side effects such as weight gain, sedation, and deterioration of cognitive function [4].

Studies with animal models predictive of antipsychotic and antidepressant activities demonstrated a potential high efficacy of lurasidone. Moreover, this novel drug had pro-cognitive effects, as shown in several animal models that assessed memory, cognition and executive functions. At a cellular level, lurasidone promoted neuronal plasticity, modulated epigenetic mechanisms controlling gene transcription, and increased the expression of the neurotrophic factor BDNF in cortical and limbic brain regions [4].

This review focuses on the preclinical evidence on lurasidone. Data on the pharmacological profile, receptor binding activity, behavioural and molecular mechanisms are reported highlighting their potential contribution to the therapeutic characteristics of the drug. Information is based on published preclinical studies, and product labels.

Methods

This article is based on published preclinical studies, accessed by querying the literature databases PubMed and EMBASE, for the search term “lurasidone” and reviewing articles with preclinical information. Product labeling provided further information, and the manufaturer’s website was examined.

Pharmacology

Pharmacokinetics

Lurasidone is rapidly absorbed after oral administration, reaching the peak plasma concentration in 1-3 hours [5]. The adsorption is highly increased when the drug is administered with food; the area under the curve and C_{max} are increased 2- and 3-fold respectively in fed versus fasting subjects. Area under the curve and C_{max} increase linearly with the dose between 20 and 160 mg. Steady state is reached in 7 days [5]. Protein binding is extensive (99.8%), with a high affinity for albumin and α-1-glycoprotein. Lurasidone is a substrate for CYP3A4 [8], and has two active metabolites ID-14283 and ID-14326, representing approximately 25% and 3% of the exposure to the parent compound. Hepatic metabolism of lurasidone contributes to its low bioavailabilty, that may explain the effect of food on lurasidone adsorption [9]. Renal and hepatic impairment can increase the exposure to lurasidone [5]. The mean elimination half life of lurasidone is 18 hours, but may be longer after the steady state has been reached [8]. This half life falls in the range that is considered safe for administration once a day with reasonable efficacy and tolerability [9].

Pharmacodynamics

Receptor binding affinities were determined in experiments with cloned human receptors or animal tissue membrane fractions. High affinity was shown for 5-HT_7 (K_i = 0.5 nM), D_2 (K_i = 1.6 nM), 5-HT_{2A} (K_i = 2.0 nM), 5-HT_{1A} (K_i = 6.8 nM), and adrenergic α_{2C} (K_i = 10.8 nM) receptors. Lurasidone had moderate affinity for α_1 (K_i = 48 nM) and α_{2A} (K_i = 41 nM) receptors, weak affinity for D_1 (K_i = 262 nM) and 5-HT_{2C} (K_i = 415 nM), and very low affinity for histamine H_1, muscarinic, nicotinic, glutamate and sigma receptors, and dopamine and serotonin transporters (see Table 1)[6].

Lurasidone is an antagonist of D_2 and 5-HT_7 receptors and a partial agonist of 5-HT_{1A} receptors [6]. In vitro studies showed that it antagonizes [^{35}S]GTPγS binding stimulated by dopamine in D_2 membrane preparations and antagonizes 5-HT-stimulated cAMP accumulation in CHO/h5-HT_7 cells. Binding of [^{35}S]GTPγS to human 5-HT_{1A} membrane preparations was partially stimulated [6]. In vivo studies with microdialysis found that lurasidone dose-dependently and preferentially increased ratio of dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC)/dopamine in frontal cortex vs striatum of adult rats [6].

Receptor occupancy was studied in vivo to evaluate the contribution of receptor subtypes to the antipsychotic activity of lurasidone and to provide evidence for the low liability to induce extrapyramidal side effects. Dopamine and serotonin are considered pivotal neurotransmitters in schizophrenia and their receptors represent an important target for the action of antipsychotic drugs. Antagonism of D_2 receptors in the mesolimbic system is important for the treatment of positive symptoms in schizophrenia, while block-

Table I. Receptor binding affinity of lurasidone as compared to three major second-generation antipsychotic drugs: risperidone, olanzapine, and clozapine [6].
Lurasidone demonstrated greater receptor binding affinity (lower Ki values) for 5-HT_7 receptors than other atypical antipsychotics tested, as well as high D_2 and 5-HT_{2A} binding. Lurasidone also exhibited relatively high receptor binding affinities for 5-HT_{1A}, and α_{2C} receptors, but negligible binding at H_1 and M_1 receptors.

Receptor Subtype	Ki (nM)			
	Lurasidone	Risperidone	Olanzapine	Clozapine
Serotonergic 5-HT_7	0.5	2.7	–	42.2
Dopaminergic D_2	1.7	2.9	14.4	108
Serotonergic 5-HT_{2A}	2.0	0.2	5.8	9.2
Serotonergic 5-HT_{1A}	6.8	262	> 1000	123
Adrenergic α_{2C}	11	11	–	16
Adrenergic α_{2A}	41	13.7	–	147
Adrenergic α_1	48	1.4	22	17.5
Histamine H_1	> 1000	3.5	3.8	2.0
Muscarinic M_1	> 1000	> 1000	7.6	4.9

ade of D_2 receptors in other brain structures may cause side effects [10].
One important aspect in the pharmacodynamic profile of lurasidone is represented by its affinity, as antagonist, at serotonin 5-HT_7 receptors, which has drawn great interest for central nervous system disorders also considering that different antipsychotic and antidepressant drugs have affinity for this receptor subtype [11]. 5-HT_7 antagonism has been associated with antidepressant properties and pro-cognitive effects in several animal models, suggesting that it can be relevant to ameliorate mood and cognitive impairments in individuals suffering from psychiatric disorders [4,6]. Using [^{3}H]SB-269970 autoradiography, it was demonstrated that 5-HT_7 receptors are expressed in rat limbic brain structures. Lurasidone showed concentration-dependent inhibition of the radioligand binding in various regions of the rat brain [11].
Considering that dose-dependent changes in receptor occupancy may differentially impact gene transcription, acute and chronic treatments with different doses of lurasidone (1, 3 and 10 mg/kg) were used to investigate its ability to modulate the expression of the activity-regulated genes Arc, Zif268 and Npas4, which are markers of neuronal activation and are also associated with neuroadaptive mechanisms. Dose-dependent and anatomically-selective differences after acute and chronic lurasidone treatment were observed. Acute treatment with different doses of lurasidone appears to exert modulatory activity in different brain regions based on selected neurotransmitter receptors. In fact, low doses of the drug were effective in the hippocampus, while high doses were active in the striatum, reflecting the high predominance of D_2 receptor expression in this brain region. On the contrary, chronic treatment with lurasidone revealed a different pattern of gene modulation, suggesting that repeated drug exposure may lead to neuroadaptive changes affecting specific brain regions in a dose-dependent manner [12].

Activity in behavioural models of disease

Behavioural studies found that lurasidone is effective in several animal models of psychiatric disease [4].

Antipsychotic activity

Lurasidone at doses 1-10 mg/kg dose-dependently inhibited conditioned avoidance response in rats behaviour when administered 1 hour before the test, with a median ED_{50} of 6.3 mg/kg [6 13].
Administration of lurasidone before the injection of methamphetamine dose-dependently inhibited the locomotor hyperactivity in adult rats for > 8 hours, providing evidence of D_2 receptor blockade [6].

Activity on cognitive impairment

Lurasidone in a dose range between 1 and 30 mg/kg did not affect learning and memory functions in rodents, as assessed by the passive avoidance test. In addition, it reversed the impairment of the response induced by MK-801, suggesting that lurasidone can restore the memory consolidation process disrupted by MK-801. This mechanism may be clinically useful for the treatment of cognitive deficits of schizophrenia [14]. In addition it was suggested that the 5-HT_7 receptor antagonistic activity of lurasidone has a role in this process of ameliorating MK-801-induced cogni-

tive deficits in the rat passive avoidance test [15].
Lurasidone at doses between 1 and 3 mg/kg significantly decreased the escape latency, swimming distance, and frequency of diving behaviours in rats treated with MK-801 at a dose of 0.15 mg/kg [16].
Eventually, it reversed the impairment of novel object recognition (considered a measure of working memory) induced by phencyclidine. This effect was dependent on lurasidone activity as partial agonist at 5-HT_{1A} receptors and as an antagonist at 5-HT_7 receptors [17 18].

Activity on models of depression
Lurasidone reduced the immobility of mice in the forced swim test at doses between 0.3 and 1.0 mg/kg, showing an antidepressant effect. Lower doses of lurasidone alone were not effective but combined with a low dose of citalopram reduced immobility [19]. It was also observed that this effect was not present in mice lacking functional 5-HT_7 receptor, suggesting that the interaction with this serotonergic receptor subtype may mediate the antidepressant activity of lurasidone [19].

Neuroplastic properties. Second generation antipsychotics are widely used for the treatment of disorders characterized by impaired emotional control. Clinical improvement relies on the complex and heterogeneous receptor profile of these drugs but it is also highly dependent upon neuroadaptive and neuroplastic changes that take place following prolonged drug exposure. Along this line of reasoning, we have demonstrated that chronic administration of lurasidone in rats increased the expression of brain-derived neurotrophic factor (BDNF) in hippocampus and prefrontal cortex under basal conditions, and it is also able to modulate neurotrophin responsiveness to stress, which represents a major precipitating element in psychiatric disorders [20]. The modulation of mechanisms correlated with neuronal plasticity may contribute to the amelioration of cognition that is deteriorated in schizophrenic patients.
More recently, the ability of chronic administration of lurasidone to improve emotional control was further investigated in serotonin transporter (SERT) knockout rats, an animal model of mood disturbance. Genetic deletion of SERT in rodents leads to fear extinction, anxiety and depression. This model also exhibits alterations of neuronal plasticity, with a reduced expression of BDNF in the hippocampus and prefrontal cortex [21]. Behavioural experiments showed that lurasidone increased fear extinction in SERT knockout rats, but not in wild type control animals [21]. As BDNF in the prefrontal cortex is known to have a relevant role in fear extinction, we also investigated whether the expression of the neurotrophin could be modulated by lurasidone administration to SERT knockout rats. It was found that lurasidone modulated the levels of specific transcripts in the prefrontal cortex, leading to a normalization of neurotrophin defects associated with SERT deletion [21].
Lurasidone was also investigated in a model of prenatal stress, a condition relevant for mood disturbance. Indeed, on the basis of epidemiological and experimental evidence, it is known that environmental challenges during pregnancy may increase the risk for psychopatology in adulthood [22]. Accordingly, it was also found that exposure to early adversities and stress produced a significant reduction of neuronal plasticity. As an example, we have shown that exposure to prenatal stress leads to a significant reduction of BDNF expression in prefrontal cortex [23 24], which may contribute to the behavioral phenotype of rats born from females stressed during late gestation, including decreased ability to cope with stress, anxious behaviour and depressive-like disturbance. Treatment with lurasidone during adolescence was able to prevent the reduction of BDNF expression in adult rats that had been exposed to prenatal stress [22].
Recently, it was investigated if combination of lurasidone with a mood stabilizer could determine increased changes in neuronal plasticity, in the hypothesis that combinatory strategies rely not only on receptor and synaptic mechanisms but also on long-term downstream targets, that seem to be relevant for functional recovery [25]. Co-administration of lurasidone and valproate produced, when compared to the single drugs, a larger increase in the expression of specific neurotrophin transcripts in the ventral hippocampus. Lurasidone alone up-regulated the mRNA levels of both total and long 3' UTR BDNF (total: +43%, $p < 0.001$ *vs* vehicle; long 3' UTR: +46%, $p < 0.001$ *vs* vehicle); valproate increased only the long 3' UTR BDNF mRNA levels (+26 %, $p < 0.05$ *vs* vehicle). The combination of the two drugs produced a more robust increase of the long 3' UTR BDNF transcript when compared to the single drugs (+74%, $p < 0.001$ *vs* vehicle; +18 %, $p < 0.05$ *vs* lurasidone; +38%, $p < 0.001$ *vs* valproate-treated animals) [25].
Interestingly the modulatory activity of lurasidone-valproate combination is specific for the ventral hippocampus that is primarily involved in the modulation of emotional response and affective states, through its connections with the cortex and the amygdala.

Discussion and Conclusions

Lurasidone was approved by the FDA for the treatment of schizophrenia and bipolar disorder and by EMA for schizophrenia patients, after its activity and safety was established in clinical studies. It has a benign metabolic profile and a low incidence of serious adverse events. Lurasidone has the highest affinity for serotonin 5-HT_7 receptors that may play an important role for cognition and mood, followed by dopamine D_2 receptor and serotonin 5-HT_{2A} and 5-HT_{1A}, with negligible affinity for muscarinic M_1 or histamine H_1 receptors [6]. This receptor binding profile is predictive of activity on psychotic symptoms, with a low potential for extrapyramidal and metabolic side effects. Behavioural tests showed that lurasidone was effective in different animal models of disease, predictive of antipsychotic, and possibly pro-cognitive and antidepressant efficacy. On this basis, lurasidone should present good efficacy for the treatment of patients. If lurasidone displays the capacity to improve cognitive deficits, which represent a major unresolved issue for psychiatric patients [4], is a question that needs to be answered through clinical trials, properly designed to assess cognitive function in this patient population.

Molecular and cellular studies demonstrated that lurasidone is very effective in increasing the expression of the neurotrophin BDNF in the prefrontal cortex of rats after long-term administration. The ability of lurasidone to enhance neuroplasticity that is impaired in schizophrenia and mood disorders may represent an add-on value for long-term efficacy in clinical use [4].

In conclusion, the available preclinical data support the efficacy of lurasidone on psychotic symptoms, with both short-term and long-term effects, with a potential for amelioration of depressive component and of functional capacities that are deteriorated in patients with schizophrenia, bipolar disease and depression.

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Take home messages for psychiatric care

- Lurasidone is a novel second generation antipsychotic (SGA) approved by the US Food and Drug Adminstration (FDA) for the treatment of adult patients with schizophrenia or bipolar depression and by the European Medicines Agency (EMA) for patients with schizophrenia
- Available preclinical data provide a characterization of the pharmacological profile suggesting a high potential for clinical efficacy associated with good tolerability. While, similar to other SGAs, lurasidone is an antagonist at D_2 and 5-HT_{2A} receptors, it is also a potent antagonist at 5-HT_7 receptors, a feature that may hold implications for its activity on cognitive deficits that are present in psychiatric patients
- The potential clinical implications of the 5-HT_7 receptor antagonism need to be further studied in this patient population

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