Pharmacological Profile of Lurasidone, a Novel Antipsychotic Agent with Potent 5-Hydroxytryptamine 7 (5-HT\textsubscript{7}) and 5-HT\textsubscript{1A} Receptor Activity

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ABSTRACT

Lurasidone [(3aR,4S,7R,7aS)-2-[[1R,2R]-2-[4-(1,2-benzisothiazol-3-yl)piperazine-1-ylmethyl]cyclohexylmethyl]hexahydro-4,7-methano-2H-isooindole-1,3-dione hydrochloride; SM-13496] is an azapirone derivative and a novel antipsychotic candidate. The objective of the current studies was to investigate the in vitro and in vivo pharmacological properties of lurasidone. Receptor binding affinities of lurasidone and several antipsychotic drugs were tested under comparable assay conditions using cloned human receptors or membrane fractions prepared from animal tissue. Lurasidone was found to have potent binding affinity for dopamine D\textsubscript{2}, 5-hydroxytryptamine 2A (5-HT\textsubscript{2A}), 5-HT\textsubscript{7}, 5-HT\textsubscript{1A} and noradrenaline \textalpha\textsubscript{2C} receptors. Affinity for noradrenaline \textalpha\textsubscript{1}, \textalpha\textsubscript{2A} and 5-HT\textsubscript{1C} receptors was weak, whereas affinity for histamine H\textsubscript{1} and muscarinic acetylcholine receptors was negligible. In vitro functional assays demonstrated that lurasidone acts as an antagonist at D\textsubscript{2} and 5-HT\textsubscript{7} receptors and as a partial agonist at the 5-HT\textsubscript{1A} receptor subtype. Lurasidone showed potent effects predictive of antipsychotic activity, such as inhibition of methamphetamine-induced hyperactivity and apomorphine-induced stereotyped behavior in rats, similar to other antipsychotics. Furthermore, lurasidone had only weak extrapyramidal effects in rodent models. In animal models of anxiety disorders and depression, treatment with lurasidone was associated with significant improvement. Lurasidone showed a preferential effect on the frontal cortex (versus striatum) in increasing dopamine turnover. Anti-\textalpha\textsubscript{1}-noradrenergic, anticholinergic, and central nervous system (CNS) depressant actions of lurasidone were also very weak. These results demonstrate that lurasidone possesses antipsychotic activity and antidepressant- or anxiolytic-like effects with potentially reduced liability for extrapyramidal and CNS depressant side effects.

Schizophrenia is a heterogeneous disease with diverse symptomatology including positive symptoms (e.g., hallucinations, delusions, and excitement), negative symptoms (e.g., flattened affect, apathy, and social withdrawal), dysphoric mood symptoms (e.g., anxiety and depression), and cognitive dysfunction (e.g., deficit in working memory, executive function, attentional processing, and memory) (Andreasen et al., 1990; Meltzer, 1999).

First-generation antipsychotics, such as haloperidol, which mainly have dopamine D\textsubscript{2} antagonist action, are effective against positive symptoms, but they are relatively less beneficial in treating negative and associated mood symptoms (Lieberman, 1993). In addition, the D\textsubscript{2} antagonists frequently induce extrapyramidal side effects (EPS; e.g., parkinsonian symptoms). In contrast, second-generation antipsychotics, such as clozapine and olanzapine, which mainly have dopamine D\textsubscript{2} antagonist action, are effective against negative symptoms and cognitive symptoms, but they are associated with a risk of metabolic side effects (e.g., weight gain, diabetes, and dyslipidemia). Second-generation antipsychotics also have a moderate risk of EPS, but they are less effective against positive symptoms (Meltzer, 1999). Lurasidone is a potentially promising antipsychotic agent with a balanced profile of antipsychotic activity and reduced liability for extrapyramidal side effects and metabolic adverse events.
kinstonism, dystonia, akathisia, and tardive dyskinesia) that are thought to reflect blockade of D<sub>2</sub> receptors in the basal ganglia (Casey, 1996). Second-generation antipsychotics, which commonly have combined 5-hydroxytryptamine 2A (5-HT<sub>2A</sub>) and D<sub>2</sub> blocking activity, may offer greater improvement in negative symptoms (Meltzer et al., 2003; Leucht et al., 2009) and have a more favorable tolerability profile with markedly reduced risk of EPS; however, several second-generation antipsychotics (e.g., clozapine, olanzapine) are associated with significant weight gain and metabolic dysfunction (Haddad, 2005). Furthermore, most second-generation antipsychotics possess relatively potent α<sub>1</sub> antagonistic activity, which is associated with postural hypotension and sedation; muscarinic antagonistic activity, which is associated with impairment of the parasympathetic autonomic system and impairment in cognitive function; and H<sub>3</sub> antagonistic activity, which is associated with additional sedative effects and weight gain (Kroese et al., 2003). Existing drugs seem to have only limited efficacy in treating cognitive deficits, which are a core feature of schizophrenia (Harvey et al., 2004). Thus, there is a continued need for new agents with improved efficacy and safety profile for the treatment of schizophrenia, bipolar disorder, and other types of psychosis.

Lurasidone [(3αR,4S,7R,7αS)-2-[(1R,2R)-2-[(4-(1,2-benzothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl]hexahydro-4,7-methano-2H-isindole-1,3-dione hydrochloride, SM-13496; Fig. 1] is an azapirone derivative, based on structure–activity relationship studies, and a novel antipsychotic candidate. Previous studies revealed that lurasidone reversed activity relationship studies, and a novel antipsychotic can-

Materials and Methods

Animals. Male Sprague-Dawley (SD) rats (Japan SLC Inc., Shizuoka, Japan or Charles River Laboratories Japan Inc., Yokohama, Japan), male Wistar rats (Charles River Laboratories Japan Inc.), male Lister hooded rats (Japan Lab Animals Co., Ltd., Osaka, Japan), and male ddY mice and male Hartley guinea pigs (Japan SLC Inc.) were used. All animals were housed in a controlled environment (23 ± 2°C, 55 ± 10% humidity) with a 12-h light/dark cycle (lights on at 8:00 AM). They had free access to food and water unless specified.

In Vitro Functional Studies

In Vitro Binding Experiments. Binding assays were carried out by using standard protocols (Hirose et al., 1990; Kato et al., 1990). Assay conditions, membrane fractions, radioligands, and displacers are summarized in Table 1. An IC<sub>50</sub> value of the drug, which inhibits specific binding of the ligand by 50%, was calculated from Hill plot analysis. The K<sub>s</sub> values were calculated by the following equation: K<sub>s</sub> = IC<sub>50</sub>/A + S/K<sub>d</sub>, where S is the radioligand concentration used in the assay and K<sub>d</sub> is the dissociation constant.

In Vitro Functional Studies

[^35]GTP·S Binding Experiments for Dopamine D<sub>2</sub> and 5-HT<sub>1A</sub> Receptors. [^35]GTP·S binding experiments for the human dopamine D<sub>2</sub>, or 5-HT<sub>1A</sub> receptors stably expressed in the membranes of recombinant Chinese hamster ovary (CHO) cells were performed following the methods of Yabuuchi et al. (2004) with slight modifications. Shortly after dopamine (or serotonin) and/or lurasidone were incubated for 20 min at room temperature with the cell membrane preparation containing [^35]GTP·S (0.05 nM for D<sub>2</sub> or 0.2 nM for 5-HT<sub>1A</sub>), the membranes were filtered through glass filters and the radioactivity bound to each filter was measured with a liquid scintillation counter. For nonspecific binding, cold GTP·S (20 μM for D<sub>2</sub> or 10 μM for 5-HT<sub>1A</sub>) was added with[^35]GTP·S. The K<sub>s</sub> value for the inhibition of dopamine-stimulated[^35]GTP·S binding by lurasidone was calculated according to the Cheng-Prusoff equation: K<sub>i</sub> = IC<sub>50</sub> of lurasidone/(1 + agonist/EC<sub>50</sub> of agonist), where agonist is the concentration of dopamine, and EC<sub>50</sub> is the IC<sub>50</sub> of dopamine alone.

The maximum activity of lurasidone in stimulating[^35]GTP·S binding was calculated by using the “Dx calculation (logistic curve fitting)” method in the SAS Application for Preclinical Study version 5.0 (SAS Institute, Cary, NC).

Fig. 1. Chemical structure of lurasidone.
cAMP Accumulation Assay for 5-HT7 Receptor. Cell lines with stable expression of recombinant human 5-HT7 receptors (CHO/h5-HT7) were incubated in a 96-well plate at a density of 1 × 10^4 cells/well for 24 h and then washed with phosphate-buffered saline, and the assay buffer [Hanks' buffer, 20 mM HEPES (pH 7.4), 1 mM ascorbic acid, and 1 mM 3-isobutyl-1-methylxanthine] was added. After preincubation at 37°C for 15 min, the cells were incubated with test drugs and the assay buffer at 37°C for 30 min. Accumulation of the intracellular cAMP was measured with the cAMP HiRange kit (Cisbio Bioassays, Bedford, MA). Ki value was calculated according to the Cheng-Prusoff equation (see above).

Levels of Dopamine and Metabolites. SD rats were sacrificed by decapitation 2 h after oral administration of test drugs, and brain tissues were dissected on ice. The levels of dopamine and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), in brain tissues were determined with a high-performance liquid chromatography with electrochemical detection system as described previously (Tatsuno et al., 1989).

Behavioral Tests That Predict Antipsychotic Efficacy

Most in vivo experiments were performed according to the methods of Hirose et al. (1990).

Effects on MAP-Induced Hyperactivity in Rats. SD rats were individually isolated in clear plastic cages and injected with MAP (1 mg/kg i.p.) 1 h after the administration of drugs or vehicle. In the test of persistence of the effect, lurasidone was administered 1, 2, 4, and 8 h before the MAP injection. Locomotor activity was measured for 80 min from 10 min after MAP injection. Four or five groups of 6 to 13 rats were used to calculate the ED_{50} value that inhibits MAP-induced hyperactivity by 50% of the animals tested.

Effects on APO-Induced Stereotyped Behavior in Rats. SD rats were individually placed in stainless-steel mesh cages and given APO (1.25 mg/kg i.v.) 1 h after the administration of study drugs. Inhibition of APO-induced stereotypy was judged to be positive unless stereotyped licking or biting was observed for 30 min after APO injection. Three or four groups of 6 to 12 rats were used to calculate the ED_{50} value that inhibits the APO-induced stereotyped behavior in 50% of the animals tested.

Effects on APO-Induced Climbing Behavior in Mice. Mice were placed in cylindrical cages made of stainless-steel rods. APO (1 mg/kg s.c.) was administered at 1 h after the administration of drugs or vehicle. The climbing behavior was observed for 20 min from 10 min after APO administration and was scored by a four-point ranked scale as follows: 0, absent; 1, slight; 2, moderate; and 3, pronounced. Four or five groups of five mice were used to calculate the ED_{50} value that reduces the score of APO-induced climbing behavior by 50%.

Effects on Conditioned Avoidance Response in Rats. SD rats were trained (6.5 min × 13 trials) once daily in a two-compartment shuttle box (Medical Agent, Kyoto, Japan) to learn conditioned avoidance response (CAR). In each trial, rats were given a 5-s warning sound and light stimulus (conditioned stimulus) followed by a 5-s electroshock (unconditioned stimulus (US)) via a metal grid of the cage floor. CAR refers to the movement of rats to the other compartment during the conditioned stimulus–US interval (5 s) to avoid the electroshock. Escape response refers to the movement of rats to the other compartment during the US. The number of CARs was measured in 10 trials excluding the first three trials from each day’s training (13 trials), and only animals that showed a CAR in at least 9 of 10 trials were subjected to drug testing. In the experiment, CAR was measured on 2 consecutive days, and the values on the first day were used as the control. On the second day, animals were administered drugs at 1 h before the assessment of CAR. Inhibition of the conditioned avoidance or escape response was expressed as a percentage of the control response. Three to five groups of 7 to 16 rats were used to calculate the ED_{50} value that reduces the number of CARs by 50%. Animals were tested repeatedly with a washout period of 1 week.

Effect on TRY-Induced Forepaw Clonic Seizure. SD rats were placed individually in clear plastic cages. TRY (40 mg/kg i.v.) was given at 1 h after the administration of drugs. If no clonic seizure developed during the 5 min immediately after administration of TRY, inhibition of TRY-induced seizure was judged as positive. Three groups of six rats were used to calculate the ED_{50} value that inhibits TRY-induced seizure in 50% of animals.

Effect on p-CAMP-Induced Hyperthermia in Rats. SD rats were given drug or vehicle and p-CAMP (4 mg/kg s.c.) simultaneously, and the increase in rectal temperature between before and 1 h after p-CAMP administration was measured (model BAT-12; Sensortek, Costa Mesa, CA). Four or five groups of 10 rats were used to calculate the ED_{50} value that inhibits p-CAMP-induced hyperthermia by 50%.

Behavioral Tests For Anxiolytic- and Antidepressant-Like Efficacy

Vogel’s Conflict Test. This experiment was performed according to the method of Shimizu et al. (1987). SD rats were deprived of water for 24 h before the first training session. The animals showing 300 to 400 licks or more in the 3-min training session were selected and subjected to water deprivation for another 24 h. The second session (predrug session) consisting of a 3-min period automatically started after completion of the first 20 licks and the first mild electric shock (0.35 mA, 0.5 s) was delivered. After every 20 licks, subsequent licking delivered the mild electric shock. Only animals showing fewer than 260 licks during the rug session were selected and subjected to the test session. Lurasidone was administered 1 h before the test session, and the number of shocks delivered were measured during the 3-min test session. In addition, the effect of lurasidone on spontaneous drinking behavior (number of licks) was examined in a separate experiment.

Social Interaction Test. The experiments were performed according to the methods of Sakamoto et al. (1998). For 2 days before the test session Lister hooded rats were individually housed and

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**Table 1**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Preparation</th>
<th>[H] Ligand</th>
<th>Incubation Temperature and Time</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine D2</td>
<td>Rat striatum</td>
<td>[H]piperone (0.5)</td>
<td>37°C, 10 min</td>
<td>Hirose et al., 1990</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>Rat hippocampus</td>
<td>[H]8-OH-DPAT (0.15)</td>
<td>25°C, 30 min</td>
<td>Kato et al., 1990</td>
</tr>
<tr>
<td>5-HT2A</td>
<td>Rat cortex</td>
<td>[H]ketanserin (1)</td>
<td>37°C, 30 min</td>
<td>Hirose et al., 1990</td>
</tr>
<tr>
<td>5-HT7</td>
<td>Human recombinant</td>
<td>[H]5-CT (1)</td>
<td>r.t., 2 h</td>
<td>To et al., 1995</td>
</tr>
<tr>
<td>Noradrenaline a</td>
<td>Rat cortex</td>
<td>[H]prazosin (0.5)</td>
<td>25°C, 30 min</td>
<td>Kato et al., 1990</td>
</tr>
<tr>
<td>Noradrenaline aCA</td>
<td>Human recombinant</td>
<td>[H]MK-912 (0.7)</td>
<td>27°C, 60 min</td>
<td>Uhlén et al., 1998</td>
</tr>
<tr>
<td>Noradrenaline aC</td>
<td>Human recombinant</td>
<td>[H]MK-912 (0.2)</td>
<td>27°C, 60 min</td>
<td>Uhlén et al., 1998</td>
</tr>
<tr>
<td>Histamine H1</td>
<td>Guinea pig whole brain</td>
<td>[H]pyrilamine (0.4)</td>
<td>25°C, 40 min</td>
<td>Chang et al., 1979</td>
</tr>
<tr>
<td>Muscarinic</td>
<td>Rat cortex</td>
<td>[H]QNB (0.15)</td>
<td>100°C, 60 min</td>
<td>Yamamura et al., 1974</td>
</tr>
</tbody>
</table>

r.t., room temperature; 5-CT, 5-carboxamidotryptamine; MK-912, (2S,12bS)-1,3-dimethylspiro[1,3,4,5,6,7,12-hexahydroid-H]-6H-pyrimido[2,3-a]quinolizine-2,4'-pyrimidin]-2'-one; QNB, quinuclidinyl benzilate.
fully accustomed to handling. On the day of the test session, two rats, previously unexposed to each other, were simultaneously treated with lurasidone. One hour after the administration, each pair was placed in a gray polyvinyl chloride observation chamber (50 × 50 × 35 cm) with 16.6 × 16.6-cm areas marked on the floor, and the social interactions of rats were recorded on a video tape recorder for 10 min. During the experiment, the illumination intensity of the floor of the chamber was maintained at approximately 1200 lux by using a white light, and the temperature inside the chamber was maintained at a constant level by using a fan. Measurement of social behavior recorded on tape was performed manually on a later day. As the indicators of the spontaneous locomotor activity, the number of times the animals crossed over the lines marked on the floor (line crossing) and the number of rearing behaviors were also counted. In this model, we observed that the standard anxiolytic diazepam (5 mg/kg p.o.) significantly increased social interaction time (Sakamoto et al., 1998).

Olfactory Bullectomy Model. Wistar rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.) and placed in a stereotaxic instrument (Narishige, Tokyo, Japan). The olfactory bulbs were removed with a blunt needle and a vacuum pump, according to the methods reported by Kelly et al. (1997). Sham-operated rats received similar surgical operation without removal of the olfactory bulb. Seven days after the operation, the rats were randomly assigned to the treatment groups according to hyperemotionality score (Kelly et al., 1997), and then lurasidone (3 mg/kg, 2 weeks), imipramine (10 mg/kg, 1 week), or vehicle were administered once a day. After the treatment, the rats were placed on an open field, and their locomotor activities were evaluated by counting the lines crossed for 5 min.

Behavioral Tests That Predict EPS Liability

Catalepsy Test. SD rats or mice were used. One hour after the administration of drugs forepaws of animals were placed on a stainless-steel bar. If the animals kept this position for 30 s or longer catalepsy was judged to be positive. Three to five groups of six rats or 10 mice were used to calculate the ED50 value that induces catalepsy in 50% of animals tested.

Pole Test. The experiments were performed according to the method of Ohno et al. (1994). Mice were administered drugs or vehicle. One hour after the administration, mice were placed headward-up at the top of a wooden pole. Then, the time to descend to the floor (Ttotal) was measured. The maximum observation period was 90 s. The minimum effective dose (MED) to increase the Ttotal values was determined by using three to five groups of 14 to 30 mice.

Muscle Relaxation. Mice were given drugs or vehicle. After 1 h, the forepaws were placed on a wire stretched horizontally at a height of 30 cm. Three trials were performed sequentially, and if the mouse did not place its hind paws on the wire within 15 s in two trials or more muscle relaxation was judged to be positive. Three or four groups of 10 mice were used to determine the ED50 value that induces muscle relaxation in 50% of the animals.

Potentiation of Hexobarbital-Induced Anesthesia. Mice were given drugs or vehicle. One hour later, hexobarbital (70 mg/kg i.p.) was administered, and the duration of the loss of righting reflexes was measured. If the duration was twice or more the mean duration of the vehicle group potentiation of hexobarbital-induced anesthesia was judged to be positive. From the incidence rate of the enhancement at each dose, the ED50 that enhances the anesthesia in 50% of the animals was calculated by using four or five groups of 9 or 10 mice. The maximal observation period was set at 3 h.

Effect on Motor Coordination. One day before the experiment, mice were placed on a rota-rod (a 3-cm-diameter rod supported horizontally and rotated at 6 rpm) with their head against the direction of rotation. Mice that could stay on the rod for 2 min or more were selected. On the day of the experiment, those mice were subjected to the same test, and only those that could stay on the rod for 1 min or more were used. One hour after the administration of drugs or vehicle each mouse was placed on the rota-rod again. If the mouse did not stay on the rod for 1 min or more inhibition of motor coordination was judged to be positive. Three or four groups of 10 mice were used to determine the ED50 value that induces the incidence rate of motor coordination in 50% of the animals.

Statistical Analysis

Data are expressed as mean ± S.E.M., MED, or ED50 with 95% confidence limits. The ED50 values were calculated by the method of Litchfield and Wilcoxon (1949). To assess the significance in differences among the multiple groups, one-way analysis of variance followed by Dunnett’s multiple comparison test (for a parametric analysis), or Kruskal-Wallis followed by Steel’s multiple comparison test (for a nonparametric analysis) were used.

Results

In Vitro Receptor Binding Profile

As shown in Table 2, in vitro receptor binding experiments revealed that lurasidone demonstrates affinity for dopamine D2 and 5-HT2A receptors higher than other tested antipsychotics. In contrast to other agents, lurasidone also displayed high affinity for 5-HT7, 5-HT1A, and noradrenaline a2C receptors (Ki values, 0.495, 6.75, and 10.8 nM, respectively). Lurasidone had lower affinity for noradrenergic a1 and a2A receptors (Ki values 47.9 and 40.7 nM, respectively) and only negligible affinities for histamine H1 and muscarinic receptors (IC50 values >1000 nM). In contrast, olanzapine and clozapine showed high affinities for a1, H1, and muscarinic receptors, and risperidone showed potent affinities for a1 and H1 receptors. Haloperidol also displayed a marked affinity for the a1 receptor.

Relative potency ratio of Ki values to dopamine D2 receptor, which is one of the main targets of antipsychotic effects, are indicated in parentheses in Table 2. This ratio suggests that lurasidone acts primarily at 5-HT7, 5-HT2A, and 5-HT1A receptors in addition to dopamine D2 receptor. Clozapine has shown relative potency ratio at 5-HT1A, 5-HT2A, and 5-HT7 receptors similar to lurasidone. Lurasidone has higher affinity (generally both absolute and relative to D2) than risperidone, olanzapine, clozapine, or haloperidol at 5-HT7, 5-HT1A, and a2C receptor types.
Pharmacological Profile of Lurasidone

**TABLE 2**

Comparison of receptor binding profiles between lurasidone and other antipsychotic agents

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Binding Affinity, Kᵦ[^a]</th>
<th>nM</th>
<th>Lurasidone</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Clozapine</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine D₂</td>
<td>1.68 ± 0.09</td>
<td></td>
<td>2.91 ± 0.16</td>
<td>14.4 ± 3.2</td>
<td>108 ± 27</td>
<td>3.25 ± 0.42</td>
<td></td>
</tr>
<tr>
<td>5-HT₁A</td>
<td>6.75 ± 0.97 (4.0)</td>
<td></td>
<td>262 ± 21 (90)</td>
<td>&gt;1000[^b]</td>
<td>123 ± 5 (1.1)</td>
<td>&gt;1000[^b]</td>
<td></td>
</tr>
<tr>
<td>5-HT₂A</td>
<td>2.03 ± 0.46 (1.2)</td>
<td></td>
<td>0.205 ± 0.066 (0.070)</td>
<td>5.78 ± 0.89 (0.40)</td>
<td>9.17 ± 1.46 (0.085)</td>
<td>84.7 ± 13.1 (269)</td>
<td></td>
</tr>
<tr>
<td>5-HT₅</td>
<td>0.495 ± 0.090 (0.29)</td>
<td></td>
<td>0.72 ± 0.42 (0.93)</td>
<td>n.t.</td>
<td>21 ± 0.3 (0.039)</td>
<td>&gt;1000[^b]</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline α₁</td>
<td>47.9 ± 7.8 (29)</td>
<td></td>
<td>1.42 ± 0.09 (0.49)</td>
<td>22.1 ± 7.7 (1.5)</td>
<td>17.5 ± 5.0 (0.16)</td>
<td>17.9 ± 1.5 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline α₂A</td>
<td>40.7 ± 7.7 (24)</td>
<td></td>
<td>13.7 ± 1.1 (4.7)</td>
<td>n.t.</td>
<td>147 ± 14 (1.4)</td>
<td>&gt;1000[^b]</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline α₂C</td>
<td>10.8 ± 0.64 (6.4)</td>
<td></td>
<td>11.0 ± 1.4 (3.8)</td>
<td>n.t.</td>
<td>15.5 ± 2.0 (0.14)</td>
<td>&gt;1000[^b]</td>
<td></td>
</tr>
<tr>
<td>Histamine H₁</td>
<td>&gt;1000[^b] (&gt;500)</td>
<td></td>
<td>3.46 ± 0.17 (1.2)</td>
<td>3.83 ± 0.52 (0.27)</td>
<td>2.02 ± 0.20 (0.019)</td>
<td>330 ± 22 (100)</td>
<td></td>
</tr>
<tr>
<td>Muscarinic</td>
<td>&gt;1000[^b] (&gt;500)</td>
<td></td>
<td>&gt;1000[^b] (&gt;240)</td>
<td>7.6 ± 1.3 (0.53)</td>
<td>4.9 ± 2.0 (0.045)</td>
<td>&gt;1000[^b]</td>
<td></td>
</tr>
</tbody>
</table>

n.t., not tested.

[^a]: Each number in parentheses is indicated as relative potency ratio of Kᵦ of receptor to that of dopamine D₂ receptor.

[^b]: IC₅₀ value.

Lurasidone had only weak affinity for dopamine D₁ and 5-HT₂C receptors (Kᵦ, 262 and 415 nM, respectively), and negligible affinity for 19 other receptors or two uptake sites including 5-HT₅, 5-HT₆, noradrenaline β₁, β₂, adenosine A₁, A₂a, cholecystokin CCK₆, CCK₇, serotonin 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, 5-HT₇, 5-HT₈, and 5-HT₁A receptors. Results are expressed as a percentage of stimulation of dopamine. B, antagonism of 3[^S]GTPγS binding to the membrane preparations for dopamine D₂ receptors by itself (data not shown), but it antagonized dopamine-stimulated[^S]GTPγS binding in a concentration-dependent manner with a Kᵦ value of 2.8 ± 1.1 nM. Lurasidone also did not affect intracellular cAMP accumulation in CHO/h5-HT₇ cells alone (data not shown), but it antagonized 5-HT-stimulated cAMP accumulation in the cells with a Kᵦ value of 2.6 ± 0.6 nM. However, lurasidone partially stimulated[^S]GTPγS binding to the membrane preparation for human 5-HT₁A receptors with a maximum effect of 33% (versus 10 μM 5-HT).

**In Vitro Functional Studies**

To evaluate the intrinsic activities of lurasidone for dopamine D₂, 5-HT₇, and 5-HT₁A receptors, the effects of lurasidone on the intracellular signal in the recombinant receptors were investigated (Fig. 2). Lurasidone did not increase[^S]GTPγS binding to the membrane preparations for dopamine D₂ receptors by itself (data not shown), but it antagonized dopamine-stimulated[^S]GTPγS binding in a concentration-dependent manner with a Kᵦ value of 2.8 ± 1.1 nM. Lurasidone also did not affect intracellular cAMP accumulation in CHO/h5-HT₇ cells alone (data not shown), but it antagonized 5-HT-stimulated cAMP accumulation in the cells with a Kᵦ value of 2.6 ± 0.6 nM. However, lurasidone partially stimulated[^S]GTPγS binding to the membrane preparation for human 5-HT₁A receptors with a maximum effect of 33% (versus 10 μM 5-HT).

**Dopamine Turnover in Frontal Cortex and Striatum in Rats.** The effect of lurasidone on dopamine turnover, which is defined as the ratio of dopamine metabolite to dopamine, in rat frontal cortex and striatum was compared with that of haloperidol or clozapine (Fig. 3). Lurasidone dose-dependently increased the ratio of DOPAC/dopamine in both regions, but it showed a preferential effect on the frontal cortex compared with the striatum, especially at higher doses. Clozapine also showed a similar tendency. On the other hand, haloperidol induced a preferential effect on the striatum compared with lurasidone (Fig. 3).

**Behavioral Studies**

**Evidence of Antipsychotic Mechanisms.** Lurasidone and other antipsychotics dose-dependently inhibited dopamine D₂ receptor-mediated behaviors such as MAP-induced hyperactivity in rats, APO-induced stereotyped behavior in rats, and APO-induced climbing behavior in mice (Table 3). In these experiments, lurasidone (ED₅₀ values 2.3–5.0 mg/kg) showed a comparable potency with olanzapine (ED₅₀ values 1.1–5.1 mg/kg), higher potency than clozapine (ED₅₀ values 9.5–290 mg/kg), and slightly lower potency than haloperidol (ED₅₀ values 0.44–17.9 mg/kg). Risperidone showed more potent efficacy in APO-induced climbing in mice compared with lurasidone, equivalent potency in the MAP-induced hyperactivity test, and less potent efficacy in the APO-induced stereotyped behavior test. The inhibitory actions of lurasidone on MAP-induced hyperactivity persisted for more than 8 h, and the ED₅₀ values of the action at 1, 2, 4, and 8 h after the treatment were 2.3, 0.87, 1.6, and 5.0 mg/kg, respectively (data not shown).

Lurasidone (1–10 mg/kg) dose-dependently inhibited CAR in rats, and the ED₅₀ values were 6.3 mg/kg (Table 3). In
contrast, the inhibitory effects of lurasidone on escape behavior at these doses were weak (data not shown), indicating that the drug selectively inhibited CAR. The potency order of the CAR test of the drugs tested in the present study was consistent with that of the D2 receptor-mediated behavior test; lurasidone showed slightly lower potency than haloperidol and risperidone, but higher potency than clozapine. Lurasidone dose-dependently inhibited TRY-induced forepaw clonic seizure and p-CAMP-induced hyperthermia with ED50 values of 5.6 and 3.0 mg/kg, respectively (Table 3). Risperidone, olanzapine, or clozapine also showed dose-dependent inhibitory effects in these tests. The potency of antiserotonergic activity of lurasidone was higher than that of haloperidol, but slightly lower than that of risperidone or olanzapine.

Anxiolytic- and Antidepressant-Like Actions

**Vogel’s Conflict Test.** Lurasidone (0.3–30 mg/kg) dose-dependently and significantly increased the number of shocks received by rats in the Vogel’s conflict test with MED of 10 mg/kg (p < 0.01; Fig. 4A). Lurasidone (3–100 mg/kg) did not affect spontaneous water drinking in a separate experiment without shocks (data not shown).

**Social Interaction Test.** Lurasidone (0.1–6 mg/kg) prolonged the time spent in social interaction, and this prolongation was significant at 1 and 3 mg/kg (p < 0.01 and 0.05, respectively) compared with the control group (Fig. 4B). Lurasidone did not affect spontaneous locomotor activity at doses used in this test (data not shown).

**Olfactory Bullectomy Model.** The olfactory bullectomy model in rats is known as a useful animal model of depression. In the present study, olfactory bullectomy treatment increased the average numbers of line crosses per 5 min compared with sham-operated rats. Chronic treatment with the antidepressant imipramine (10 mg/kg, 1 week) significantly suppressed olfactory bullectomy-induced hyperactivity (p < 0.01; Fig. 5A). As with imipramine, chronic treatment of lurasidone (3 mg/kg, 2 weeks)

### Table 3

<table>
<thead>
<tr>
<th>Drugs</th>
<th>MAP-Induced Hyperactivity in Rats</th>
<th>APO-Induced Stereotyped Behavior in Rats</th>
<th>APO-Induced Climping Behavior in Mice</th>
<th>Conditioned Avoidance Response in Rats</th>
<th>TRY-Induced Clonic Seizure in Rats</th>
<th>p-CAMP-Induced Hyperthermia in Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
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<tr>
<td>Risperidone</td>
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<tr>
<td>Olanzapine</td>
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<td>Clozapine</td>
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</table>

### Fig. 3

Effect of lurasidone and other antipsychotics on dopamine turnover in rats; comparison in the frontal cortex and striatum. The ratios of DOPAC, a dopamine metabolite, to dopamine (DA) after administration of lurasidone (left), haloperidol (right), and clozapine (center) are represented as the points (C, frontal cortex; ●, striatum) with vertical bars (mean ± S.E.M. of six rats). **, p < 0.01: significantly different from vehicle control (Dunnett’s test). #, p < 0.05; ##, p < 0.01: significantly different from the value in the striatum (Student’s t-test).
significantly suppressed hyperactivity behavior ($p < 0.001$; Fig. 5B). Neither treatment affected the line cross in sham-operated rats (Fig. 5).

**EPS Liability**

**Catalepsy Test.** Lurasidone at doses up to 1000 mg/kg did not induce catalepsy in either rats or mice (Table 4). In contrast, haloperidol, risperidone, and olanzapine dose-dependently induced catalepsy, and potencies of catalepsy induction of these drugs were much higher than those of lurasidone. Clozapine induced practically no catalepsy at doses up to 300 mg/kg in rats, but higher doses could not be tested because of marked muscle relaxation. Higher doses of olanzapine (>10 mg/kg) and clozapine (>30 mg/kg) could not be tested in mice for the same reason.

**Induction of Bradykinesia (Pole Test).** We have previously shown that antipsychotics specifically induce bradykinesia as indexed by prolongation of the pole-descending time of mice in the pole test, and these indices are well correlated with propensity of EPS (Ohno et al., 1994). As shown in Table 4, lurasidone showed no significant effects on the pole-descending time at doses up to 1000 mg/kg. Risperidone (0.3–10 mg/kg), olanzapine (3–10 mg/kg), and haloperidol (0.3–10 mg/kg) increased the time in a dose-dependent manner with MEDs of 3, 10, and 1 mg/kg, respectively. Clozapine did not prolong the descending time at doses up to 30 mg/kg, but could not be evaluated at higher doses because of severe muscle relaxation and impaired motor coordination.

**Induction of Muscle Rigidity (Paw Test).** FRT in the rat paw test is thought to be a useful index for the prediction of EPS risk of antipsychotics (Ellenbroek, et al., 1987). Lurasidone had no effect on FRT at doses up to 300 mg/kg in the paw test. At dose of 1000 mg/kg lurasidone slightly increased FRT, but the effect was not statistically significant. In contrast, risperidone (1–30 mg/kg), olanzapine (3–100 mg/kg), clozapine (10–300 mg/kg), and haloperidol (1–30 mg/kg) prolonged FRT in a dose-dependent manner. MEDs of these antipsychotics are indicated in Table 4.

**Safety Ratio.** Table 4 also summarizes the potency ratio of EPS signs evaluated here to that of D₂ antagonism (i.e., inhibition of MAP hyperactivity in rats or that of APO climbing behavior in mice). The ratio of lurasidone was calculated to more than 430 in rats and 240 in mice, but the ratio of the other antipsychotics was between 1.1 and 21 (except for unfixed values).

**Other CNS Actions**

**Potentiation of Hexobarbital-Induced Anesthesia.** Lurasidone at relatively high doses (700–1000 mg/kg) slightly prolonged the duration of loss of righting reflexes elicited by hexobarbital (anesthesia) in a dose-dependent manner. However, even at a dose of 1000 mg/kg, only 4 of 10 mice showed an anesthesia duration at least twice or more the mean duration of the control group (ED₅₀ >1000 mg/kg; Table 5). Other antipsychotics also potentiated the anesthesia time at even relatively low doses, and their ED₅₀ values were 1.5 mg/kg for risperidone, 8.3 mg/kg for olanzapine, 8.2 mg/kg for clozapine, and 11 mg/kg for haloperidol (Table 5).

**Induction of Muscle Relaxation.** Lurasidone failed to induce muscle relaxation even at a dose of 1000 mg/kg (one positive in 10 mice; ED₅₀ >1000 mg/kg; Table 5). However, other antipsychotics dose-dependently induced muscle relaxation in mice; the ED₅₀ values were 11 mg/kg for risperidone, 11 mg/kg for olanzapine, 32 mg/kg for clozapine, and 33 mg/kg for haloperidol (Table 5).

**Impairment of Motor Coordination.** Lurasidone impaired motor coordination at relatively high doses (100–700 mg/kg) with an ED₅₀ value of 250 mg/kg (Table 5). Risperidone, olanzapine, clozapine, and haloperidol impaired motor

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**Table 4**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Catalepsy Test in Rats</th>
<th>Paw Test in Rats</th>
<th>Catalepsy Test in Mice</th>
<th>Pole Test in Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ED₅₀ mg/kg</td>
<td>MED mg/kg</td>
<td>ED₅₀ mg/kg</td>
<td>MED mg/kg</td>
</tr>
<tr>
<td></td>
<td>Ratio</td>
<td>Ratio</td>
<td>Ratio</td>
<td>Ratio</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>&gt;1000</td>
<td>&gt;430</td>
<td>&gt;1000</td>
<td>&gt;240</td>
</tr>
<tr>
<td>Risperidone</td>
<td>20 (9.3–43)</td>
<td>11</td>
<td>30</td>
<td>6.1</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>29 (11–74)</td>
<td>8.5</td>
<td>30</td>
<td>9.1</td>
</tr>
<tr>
<td>Clozapine</td>
<td>&gt;1000</td>
<td>&gt;46</td>
<td>&gt;30</td>
<td>9.0</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>12 (6.8–23)</td>
<td>14</td>
<td>150</td>
<td>4.6</td>
</tr>
</tbody>
</table>

**Ratio is calculated as the potency ratio of EPS measure to that of D₂ antagonism (i.e., inhibition of MAP hyperactivity in rats and APO climbing behavior in mice).**
coordination with ED\textsubscript{50} values of 1.8, 5.2, 8.7, and 2.7 mg/kg, respectively (Table 5).

**Antinoradrenergic Action.** To evaluate the noradrenaline \(\alpha\)-blocking action of lurasidone, we examined ptosis induction in mice. Lurasidone at relatively higher doses (100-1000 mg/kg) induced ptosis in a dose-dependent manner. Ptosis was observed in 5 of 10 mice tested at 1000 mg/kg lurasidone, and the ED\textsubscript{50} value was estimated to be approximately 1000 mg/kg (Table 5). In contrast, risperidone, olanzapine, and haloperidol significantly induced ptosis with ED\textsubscript{50} values of 0.68, 9.2, and 6.3 mg/kg, respectively (Table 5).

**Anticholinergic Action.** Lurasidone did not inhibit oxotremorine-induced tremor even at a dose of 1000 mg/kg (Table 5). However, olanzapine significantly inhibited oxotremorine-induced tremor with a ED\textsubscript{50} value of 4.9 mg/kg. Haloperidol also inhibited the tremor induced by oxotremorine, but its potency was relatively low (ED\textsubscript{50} value 23 mg/kg).

### Discussion

The present study evaluated the receptor binding affinities, functional activities, and behavioral pharmacological characteristics of lurasidone in various animal models. The current results demonstrate that lurasidone possesses potent antipsychotic-, anxiolytic-like, and antidepressant-like activity with a low propensity for EPS, motor impairment, and CNS depressant side effects.

In vitro receptor binding experiments in the present study have shown \(K_i\) values in typical and atypical antipsychotics, which were comparable with those in previous reports (e.g., Kroeze et al., 2003). The present study reveals that lurasidone has potent affinity for dopamine D\textsubscript{2} and 5-HT\textsubscript{2A} receptors; however, unlike most second-generation antipsychotics, it completely lacks binding affinity for histamine H\textsubscript{1} and muscarinic receptors. Olanzapine, risperidone, and clozapine have higher affinity for the histamine H\textsubscript{1} receptor, and olanzapine and clozapine have significant binding affinity for the muscarinic receptor. Histamine H\textsubscript{1} receptor blockade has been implicated as a key mechanism in weight gain induced by second-generation antipsychotics (Kroeze et al., 2003). Muscarinic M\textsubscript{1} receptor blockade is associated with cognitive deficits (Terry and Mahadik, 2007), which may be especially severe in vulnerable populations such as the elderly. Furthermore, lurasidone also has weak binding affinity for the 5-HT\textsubscript{2C} receptor that has been implicated in weight gain caused by atypical antipsychotics (Reynolds et al., 2006).

### Results from Recent Clinical Trials

Results from recent clinical trials have confirmed that lurasidone has minimal effects on weight (Meyer et al., 2009). Lurasidone possesses potent 5-HT\textsubscript{7} and 5-HT\textsubscript{1A} receptor binding affinities. Functional activity studies suggest that lurasidone acts as an antagonist at 5-HT\textsubscript{7} receptors and a partial agonist at 5-HT\textsubscript{1A} receptors. 5-HT\textsubscript{7} receptors are highly expressed in the hippocampus, which is involved in learning and memory, and selective 5-HT\textsubscript{7} antagonists, such as SB-269970 [(2R)-1-[(3-hydroxyphenyl)sulfonyl]-2-(2-(4-methyl-1-piperidinyl)ethyl]pyrroldine], improved reference memory in animals (Gasbarri et al., 2008). Indeed, we previously demonstrated that lurasidone markedly reversed MK-801-induced memory dysfunction in the rat passive avoidance model (Ishiyama et al., 2007), Morris water maze test, and radial maze test (Enomoto et al., 2008). Because the efficacy of lurasidone for procognitive effects in these tests seems greater than the other antipsychotics, it is possible that lurasidone may have procognitive effects in patients with schizophrenia. Contrary to the above speculation, there are other studies suggesting that the function of 5-HT\textsubscript{7} receptor is essential in contextual fear learning (Roberts et al., 2004a) or allocentric spatial memory information processing (Sarkisyan and Hedlund, 2009) in mice. Although these studies demonstrated that 5-HT\textsubscript{7} receptor gene knockout or 5-HT\textsubscript{7} receptor antagonist action has the potential to impair some cognitive function in mice, the evidence does not exclude the possibility that 5-HT\textsubscript{7} receptor antagonist action becomes beneficial for cognitive function that is originally impaired by the disease or drugs such as MK-801, as reported previously (Meneses, 2004). Furthermore, lurasidone has binding activities not only for 5-HT\textsubscript{7} receptor but also for 5-HT\textsubscript{1A} and noradrenaline \(\alpha\)-receptors, which have also been implicated as potentially relevant to cognitive function (Björklund et al., 2000; Meltzer et al., 2003). Clinical studies are currently underway to characterize the capacity of lurasidone to enhance cognition in patients with schizophrenia.

In the present study we performed a series of behavioral pharmacological experiments that are well established for investigating in vivo D\textsubscript{2} or 5-HT\textsubscript{2A} receptor blocking activities. All of the antipsychotics (haloperidol, risperidone, olanzapine, and clozapine) investigated in this study were found to be effective in some or all of these tests with ED\textsubscript{50} values that were comparable with those shown previously (e.g., Moore et al., 1992, Rigdon et al., 1996). Lurasidone potently inhibited the dopamine D\textsubscript{2} receptor-mediated behaviors, i.e., MAP-induced hyperactivity in...
lurasidone could improve the symptoms of schizophrenia, seen on the escape response. These findings suggest that lurasidone selectively inhibited the CAR at a dose at which no inhibitory effects were seen on the escape response. These findings suggest that lurasidone could improve the symptoms of schizophrenia, especially the positive symptoms, through blocking dopamine D2 receptors, similar to marketed antipsychotics.

The other cardinal characteristic of second-generation antipsychotic drugs is antagonist activity at 5-HT2A receptors. Lurasidone showed potent binding affinity for 5-HT2A receptors and inhibited the 5-HT2A receptor-mediated behavior at doses equivalent to those required for antidopaminergic actions. In behavioral studies, lurasidone showed the inhibitory effects of 5-hydroxytryptophan-induced wet dog shake and 5-methoxytryptamine-induced head twitch with ED50 values of 2.4 and 3.4 mg/kg, respectively (data on file). These findings indicate that lurasidone has antiserotonergic activity via blockade of 5-HT2A receptors.

In addition to dopamine D2 and serotonin 5-HT2A blocking actions in vivo, we have previously shown that lurasidone has the effects to improve cognitive deficits induced by an NMDA receptor antagonist MK-801 in rats (Ishiyama et al., 2007, Enomoto et al., 2008). Such evidence may imply that lurasidone also has the potential to treat symptoms in schizophrenia through targeting the pathophysiology, such as NMDA receptor hypofunction. Regardless of the mechanisms, randomized, double-blind, placebo-controlled studies (Meyer et al., 2009; Nakamura et al., 2009) have provided consistent results that lurasidone has significant efficacy in treating both the positive and negative symptoms of chronic schizophrenia.

In the present study, we have investigated the antidepressant-like effect of lurasidone by using an olfactory bulbectomy model. Previous studies using preclinical animal models to detect antidepressant-like effects in atypical antipsychotics have been challenging, and atypical antipsychotics are known to be clinically useful for treating symptoms in patients with major depression or bipolar depression. Indeed, a previous report using the learned helplessness paradigm (Ballard et al., 2007) demonstrated that haloperidol, risperidone, olanzapine, and aripiprazole aggravated depressive behavior, whereas quetiapine showed no effect. As a result, it has been proposed that the learned helplessness paradigm may be a model for evaluating antipsychotic-induced dysphoria but not for evaluating the antidepressant effects in antipsychotics. Another study (Bourin et al., 2009) showed that a single treatment with aripiprazole was not effective in reducing immobility in the forced swimming test, although coadministration of serotonin reuptake inhibitor (SSRI) with aripiprazole was found to be effective. Therefore, in this study, rather than using the above paradigms, we tried to use olfactory bulbectomy as another useful animal model for exploring antidepressant-like effects and found that lurasidone demonstrated similar effects like an antidepressant imipramine. Although the present study suggests that lurasidone has an antidepressant-like property, the study is only explorative. Further preclinical and clinical studies are apparently needed to confirm whether lurasidone is truly useful for treating depressive symptoms in patients with psychiatric conditions.

In addition to the antidepressant-like potential, the present study demonstrated that lurasidone possessed anxiolytic potential in Vogel’s conflict test and the social interaction test. The mechanism underlying the positive results in these behavioral paradigms is unclear. One possibility is lurasidone’s potent inhibitory effect on the 5-HT7 receptor. Recently, 5-HT7 antagonists have received attention as new targets for antidepressant and anxiolytic drugs (Hedlund and Sutcliffe, 2004). 5-HT7, knockout mice exhibit antidepressant-like behavior in the forced swim test and the tail suspension test (Hedlund et al., 2005). Furthermore, selective 5-HT7 antagonists such as SB-269970 show antidepressant- and anxiolytic-like actions, e.g., decrease of immobility time in the tail suspension test, the forced swim test, and the Vogel conflict test (Wesolowska et al., 2006). Because the 5-HT7 receptor is highly expressed in the hippocampus and amygdala, which are involved in anxious states (Hedlund and Sutcliffe, 2004), lurasidone might produce its anxiolytic-like actions by modulating the neural activity in these regions via blockade of 5-HT7 receptors. Biochemical studies have shown that the 5-HT7 receptor is involved in 5-HT release in the dorsal raphe, which is important in the indirect control of serotonergic neurons via the γ-aminobutyric acid type A receptor (Roberts et al., 2004b). Because detailed mechanisms of the anxiolytic- and antidepressant-like actions of 5-HT7 antagonists are still unclear, further investigation is needed.

Another possible mechanism is agonist activity at the 5-HT1A receptor, which is well known to possess anxiolytic- and antidepressant-like activity in rodents and humans (Millan, 2000). Previous studies (e.g., Santarelli et al., 2003) have also suggested that 5-HT1A receptor activation mediates the effects of selective SSRI on the hippocampus neurogenesis, which is considered to underlie the anxiolytic- and antidepressant-like effects of chronic administration with SSRI. As mentioned above, lurasidone is a partial agonist at the 5-HT1A receptor with an \( E_{\text{max}} \) value of 33% of 5-HT. Thus, it is possible that partial activation of 5-HT1A receptor directly by lurasidone induces acute symptomatic or neuropilectic effects to lead to the anxiolytic and antidepressant-like effects. Finally, the \( \alpha_{2C} \) receptor has also been reported to be involved in depression (Sallinen et al., 2007) and may contribute to the effects of lurasidone in animal models of depression.

EPS continues to be a clinically important problem in the treatment of schizophrenia and is an important cause of reduced patient compliance with therapy (Barnes and McPhillips, 1998). In the present study, lurasidone did not induce EPS in various animal behavioral tests at doses up to 1000 mg/kg. In contrast, haloperidol and risperidone induced EPS at relatively low doses. Furthermore, compared with various other antipsychotic drugs, lurasidone showed a markedly higher safety ratio, calculated as the potency ratio of ED50 values for dopamine D2 blocking activity relative to EPS induction. This suggests that lurasidone may have a low risk for EPS.

The precise mechanism for the minimal EPS liability of lurasidone in rodents is not clear. Because 5-HT2A blocking activity might reduce EPS induced by antipsychotics (Ber-
that lurasidone will have a lower propensity for weight gain actions. Furthermore, its in vitro binding profile suggests effects, with few EPS and CNS depressive side effects and behavioral tests, lurasidone produces potent antipsychotic profile compared with several existing antipsychotics. In behavior, lurasidone does not induce anticholinergic side effects, such as amnesia or dry mouth.

In addition to the low risk of EPS, the CNS depressive effects of lurasidone, including potentiation of anesthesia, muscle relaxation, ptosis, and inhibition of motor coordination, were much weaker than those of the other antipsychotics tested. These behavioral changes presumably are mediated by the blocking of histamine H1 receptor or α1 receptor (Skibell et al., 2007), and these results are in agreement with in vitro receptor binding profiles that lurasidone has relatively low affinity for noradrenergic α1 receptor or negligible affinity for histamine H1 receptor. These findings suggested that lurasidone would have fewer risks of cardiovascular side effects, such as orthostatic hypotension, and CNS depressant side effects, such as sedation or somnolence. In addition, lurasidone showed only negligible action in inhibiting oxotremorine-induced tremor in mice (ED50 >1000 mg/kg), indicating that lurasidone does not induce anticholinergic side effects, such as amnesia or dry mouth.

In summary, the present preclinical results demonstrate that lurasidone has pharmacological characteristics of a novel second-generation antipsychotic agent with anxiolytic- and antidepressant-like activity and a more favorable safety profile compared with several existing antipsychotics. In behavioral tests, lurasidone produces potent antipsychotic effects, with few EPS and CNS depressive side effects and minimal α1 blocking and muscarinic acetylcholine blocking actions. Furthermore, its in vitro binding profile suggests that lurasidone will have a lower propensity for weight gain and metabolic dysfunction, while having the potential to improve cognitive deficits associated with schizophrenia.

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References


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