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REVIEW

Clinical potential of lurasidone in the management of schizophrenia

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Abstract: Lurasidone is a new second-generation antipsychotic approved in October 2010 by the Food and Drug Administration for the treatment of schizophrenia. Like other second-generation antipsychotics, lurasidone is a powerful antagonist of D_2 dopamine and $5HT_{2A}$ serotonin receptors, but differs from the other second-generation antipsychotics in its action profile for certain receptors. Lurasidone is the second-generation antipsychotic with the greatest affinity for $5HT_7$ receptors and has a high affinity for $5HT_{1A}$ serotonin receptors, compatible with favorable effects on cognitive function and an antidepressant action. By contrast, lurasidone has a low affinity for α_1 and α_{2C}-adrenergic and $5HT_{2C}$ serotonin receptors, and no affinity for histaminergic H_1 or muscarinic M_1 receptors, suggesting a better tolerability profile than the other second-generation antipsychotics. Lurasidone has demonstrated its efficacy in several short-term trials in acute schizophrenia, promptly and significantly reducing total Positive and Negative Syndrome Scale and Brief Psychiatric Rating Scale scores compared with placebo. Several long-term studies are in progress to assess its efficacy in the maintenance treatment of schizophrenic patients. The efficacy of lurasidone with regard to cognitive functions and depressive symptoms seems good, but requires further work. Lurasidone differs from the other second-generation antipsychotics by having a good tolerability profile, in particular for cardiometabolic tolerability. However, it seems to have a significant although moderate link with the occurrence of akathisia, extrapyramidal symptoms, and hyperprolactinemia at the start of treatment. This tolerance profile greatly broadens the scope of second-generation antipsychotics and so supports the view of some authors that the term "second-generation antipsychotic" is now outdated. Other therapeutic perspectives of lurasidone are assessed here, in particular bipolar depression.

Keywords: lurasidone, second-generation antipsychotic, schizophrenia, efficacy, safety

Management issues in schizophrenia

Schizophrenia is a serious chronic mental illness that appears in late adolescence or early adulthood, and affects about 1% of the world's population.[1] It is a heterogeneous condition characterized by positive and negative symptoms, and is often associated with cognitive disorders and symptoms of depression.

Pharmacological treatment is based essentially on antipsychotics. These drugs are central to care because they offer the only efficacious treatment for most of the symptoms. They allow both treatment of acute phases and the prevention of relapses.

Clozapine, introduced into the US in 1988, differed from classical neuroleptics not only in its greater efficacy but also, more importantly, by having markedly reduced neurological effects.[2] With this compound as leader, the atypical antipsychotics appeared at the end of the 1990s. However, atypicalness is a catch-all classification that is extremely

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difficult to exploit operationally. The atypical antipsychotics form a heterogeneous group that have a pharmacodynamic action on neurotransmission that is different from that of the neuroleptics, with involvement of other neurotransmission systems, few or no induced extrapyramidal effects, and stronger activity on negative schizophrenic symptoms.[3] This very loose definition prompted a new terminology, ie, the terms "first-generation" and "second-generation" antipsychotics, which have been in use since 2004.

The second-generation antipsychotics are recommended in various guidelines as first-line treatment in view of their better neurological tolerability, and their greater efficacy on negative, cognitive, and depressive symptoms.[4–7] They include the chemical entities amisulpride, aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine.

The superiority of second-generation antipsychotics over first-generation antipsychotics has been the subject of much debate, based on several meta-analyses published since 2000. Some authors are not convinced of the superiority of second-generation antipsychotics and point to the poor methodological quality of the comparative trials in terms of evaluation criteria, dropouts, and choice and dose of comparator.[8,9] A more recent meta-analysis singled out four second-generation antipsychotics that displayed greater overall efficacy compared with first-generation antipsychotics, namely clozapine, amisulpride, risperidone, and olanzapine. The other second-generation antipsychotics were no more efficacious than the older first-generation antipsychotics, even for negative symptoms.[10]

This difference in efficacy among the second-generation antipsychotics was confirmed in a meta-analysis of head-to-head comparisons of second-generation antipsychotics. Olanzapine was found to be more efficacious than aripiprazole, quetiapine, risperidone, and ziprasidone, and of similar efficacy to amisulpride and clozapine.[11] This difference among second-generation antipsychotics showed up mainly in the Positive and Negative Syndrome scale (PANSS) positive symptom subscores, and was small in the PANSS negative symptom subscores. CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness) and CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) gave similar results, except that clozapine stood apart from both first-generation antipsychotics and other second-generation antipsychotics.[12,13]

Concerning tolerability, whereas second-generation antipsychotics induced much weaker neurological side effects, they induced metabolic (weight gain, hyperglycemia, and dyslipidemia) and cardiac side effects (QT prolongation) requiring regular monitoring. Differences were also found among the second-generation antipsychotics. Although inducing fewer extrapyramidal effects compared with first-generation antipsychotics, risperidone was associated with greater use of antiparkinsonian medication than clozapine, olanzapine, quetiapine, and ziprasidone.[14] Also, concerning metabolic side effects, olanzapine and clozapine produced more weight gain than all the other second-generation antipsychotics, and olanzapine produced a higher rise in cholesterol than aripiprazole, risperidone, and ziprasidone.[15]

Overall, these recent data confirm that second-generation antipsychotics are not a homogeneous group, that each second-generation antipsychotic possesses distinct pharmacodynamic properties, and that consequently any new member may be of therapeutic interest. Lurasidone is a second-generation antipsychotic that was approved by the Food and Drug Administration (FDA) in October 2010 for the treatment of schizophrenia. Here we present the data available for this new agent concerning its pharmacological properties, efficacy, and tolerability in schizophrenic patients, and show the position of lurisadone with respect to the other second-generation antipsychotics.

Data sources

A literature search using the keywords "lurasidone" and "schizophrenia" was undertaken using the databases PubMed and EMBASE to find all the relevant studies published in English. Additional references were identified from http://www.fda.gov and http://clinicaltrials.gov.[16] Data were also collected from product user information.[17] Searches were last updated on March 12, 2011.

Pharmacology and drug interactions

Pharmacological profile

Lurasidone is a benzoisothiazol derivative (SM-13496; (3a*R*,4*S*,7*R*,7a*S*)-2-[(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl] cyclohexylmethyl] hexahydro-4, 7-methano-2*H*-isoindole-1,3-dione hydrochloride).

Like the other second-generation antipsychotics, lurasidone is a powerful antagonist of the dopamine D_2 and serotonin $5HT_{2A}$ receptors, with a strong affinity for the $5HT_{2A}$ receptor (K_i = 0.470–0.357 nM) and very high selectivity for the D_2 receptor (K_i = 0.329–0.994 nM) 264, 16, and 30 times greater, respectively, compared with D_1, D_3, and D_4 receptors.[16] In a preliminary trial using positron emission

tomodensitometry in 21 healthy subjects, it was shown that the degree of occupation of D_2 receptors at lurasidone dosages of 10, 20, 40, 60, and 80 mg ranged from 41.3% to 43.3%, 51% to 54.8%, 63.1% to 67.5%, 77.4% to 84.3%, and 72.9% to 78.9%, respectively. An antipsychotic response, for which an occupation of 60%–80% of the receptors is required, could thus be expected from 40 mg/day.[18]

Lurasidone differs from other second-generation antipsychotics in its action profile for certain receptors. In vitro studies have shown that lurasidone is the second-generation antipsychotic that shows the greatest affinity for $5HT_7$ receptors (K_i = 0.495–2.10 nM) and a high affinity for $5HT_{1A}$ receptors.[16,19] $5HT_7$ receptors are abundant in the thalamic and hypothalamic regions involved in the regulation of sleep, and in the cortical areas and the regions of the hippocampus and raphe nuclei involved in memory and mood regulation.[20,21] Therefore, via these two receptors, lurasidone should have favorable effects on memory and cognitive functions, together with an antidepressive and anxiolytic action.[22]

In contrast with its high affinity for the $5HT_7$ and $5HT_{1A}$ receptors, lurasidone has a moderate affinity for α_{2C}-adrenergic receptors, a very weak affinity for α_1-adrenergic and serotonin $5HT_{2C}$ receptors, and no affinity for histaminergic H_1 or muscarinic M_1 receptors.[16,19] Through its action on these different receptors, lurasidone should have a better tolerability profile than the other antipsychotics, in particular less risk of orthostatic hypertension (α_{2C} and α_1 receptors), less weight gain (H_1 and $5HT_{2C}$ receptors), less sedative effect (H_1 and M_1 receptors) and fewer anticholinergic effects (M_1 receptors).[18]

In vivo studies in animal models have shown that, compared with other antipsychotic drugs, lurasidone carries a low risk for extrapyramidal symptoms or central nervous system depressive effects (motor coordination, muscle relaxation, anesthesia potentiation, bradykinesia, and catalepsy).[19]

Pharmacokinetics

Lurasidone is rapidly absorbed after oral administration, reaching peak concentrations (T_{max}) in 1–3 hours.[17] Absorption is dose-dependent. For dosages in the range of 20–160 mg/day, the area under the curve (AUC) and peak concentration (C_{max}) increase linearly with the absorbed dose.[17] Absorption is apparently favored by eating, as could be observed for ziprazidone. About 9%–19% of the dose administered is absorbed with no associated food intake, whereas AUC and C_{max} are increased three-fold when at least 350 calories of food is ingested concomitantly. Eating has no effect on T_{max}.[17]

Steady-state is reached within seven days. For a lurasidone dose of 40 mg, a distribution volume estimated at 6173 L and a clearance of 3902 mL/min have been reported.[17] The mean elimination half-life in trials including healthy subjects given a single dose of 100 mg/day was 12.2–18.3 hours, reaching 36 hours after nine days. The mean half-life in schizophrenic patients with single doses of 120–160 mg/day was 28.8–37.4 hours.[18]

The lurasidone molecule binds very strongly to plasma proteins (99.8%), in particular to albumin and α1-glycoprotein.[23] Lurasidone is metabolized in the liver, principally by the cytochrome P450 (CYP) isoenzyme, CYP3A4, into three active and two inactive metabolites. The main active metabolite, ID-14283, an exohydroxy metabolite, is rapidly detected in the serum, with a C_{max} value equal to 26% of the starting material. It has a comparable pharmacological profile, but a shorter life (7.48–10 hours) than lurasidone. The other two metabolites, ID-14326 and ID-11614, are present at extremely low levels of 3% and 1%, respectively.[18]

Lurasidone crosses the placental barrier.[16] Approximately 89% is excreted in urine and stools. After administration of [^{14}C]-lurasidone, 80% of the radioactivity was found in stools and 9% in urine.[17]

C_{max} and AUC values increased in patients with mild, moderate, or severe renal and hepatic insufficiency, suggesting that dosages should be adapted in these subjects.[17] There seems to be no impact of race or age on the pharmacokinetics. Blood assays carried out in psychotic patients aged 65–85 years taking lurasidone 20 mg/day showed concentrations identical to those in young subjects.[17]

Drug interactions

Because of hepatic metabolism of lurasidone by CYP3A4, there is a risk of drug interaction if lurasidone is taken concomitantly with inhibitors or inducers of this enzyme (diltiazem, ketoconazole, or erythromycin).[17,18,23] Because lurasidone is not metabolized by CYP2D6, coprescription with inhibitors of CYP2D6, such as fluoxetine, paroxetine, and quinidine, needs no dosage adaptation. Lurasidone is not a substrate for P glycoprotein. No drug interactions have been observed when lurasidone is coprescribed with P glycoprotein substrates such as digoxin, or CYP3A4 substrates such as midazolam, oral contraceptives, or lithium.[17,18] The high plasma protein-binding power of lurasidone, especially towards albumin and α1-glycoprotein, should be taken into account to avert certain drug interactions, in particular in undernourished subjects or the elderly.

Efficacy in schizophrenia

The efficacy of lurasidone in acute schizophrenia was assessed in eight trials (Table 1). Six short-term (six-week) randomized, double-blind, placebo-controlled trials (of which three used an active comparator, ie, haloperidol, olanzapine, or quetiapine) in acute schizophrenia, a short-term (three-week) randomized, double-blind controlled trial (versus ziprasidone) in stable outpatients with schizophrenia or schizoaffective disorder, and a short-term (eight-week) randomized, double-blind dose-response study in inpatients and outpatients with schizophrenia.

The primary efficacy endpoint in all the trials was the mean change in PANSS or Brief Psychiatric Rating Scale (BPRS) total score from baseline to endpoint. Secondary endpoints included changes in Clinical Global Impression of Severity (CGI-S) and PANSS subscale scores. One study evaluated cognitive efficacy with a subset of the MATRICS Consensus Cognitive Battery (MCCB) and Schizophrenia Cognition Rating Scale.[24]

Placebo-controlled trials (except for one failed trial) demonstrated antipsychotic efficacy in all primary and secondary efficacy measures in favor of lurasidone 80 mg/day. With the exception of two trials (one failed trial and D1050229), efficacy was found at lurasidone doses of 40, 120, and 160 mg/day.

A pooled analysis based on five PANSS factor scores (positive, negative, disorganized thought, hostility, and depression/anxiety) was performed from four short-term, double-blind, placebo-controlled trials (D1050006, D1050196, D1050229, and D1050231).[25] Despite the inclusion of a trial that did not find lurasidone to be efficacious at 40 or 120 mg/day, pooled data found lurasidone to be significantly better than placebo in improving all five PANSS factor scores. At week 6, changed scores and effect sizes were significant compared with placebo among patients treated with lurasidone at 40 mg, 80 mg, and 120 mg (Table 2).

Significant improvement in the different scores (BPRS, PANSS, and CGI-S) was observed by days 3–7 for the 80–160 mg/day doses.[16,26,27] In a study of stable patients, lurasidone 120 mg/day had an efficacy comparable with that of ziprasidone 160 mg/day, but with an earlier onset of improvement in PANSS total score (by day 7).[28] These trials suggest an early onset of treatment effect for lurasidone.

Trial results did not suggest any additional benefit of lurasidone 120 mg/day over 40 mg/day or 80 mg/day (based on observed mean differences from placebo).[16] Pooled analysis found the treatment effect of lurasidone to be consistent across the dosage range, with no clear superiority of the highest lurasidone dose.[25] No dose-response relationship for lurasidone was found.

A dose-response study of lurasidone 20, 40, and 80 mg/day found that the 40 mg/day and 80 mg/day doses were associated with significant improvements from baseline on the PANSS and BPRS, and were significantly better than 20 mg/day.[29] The starting dose of lurasidone recommended by the FDA is 40 mg once daily, and the maximum dose is 80 mg once daily.

The receptor binding profile of lurasidone, with high affinity for $5HT_7$, $5HT_{1A}$, and α_{2C} receptors, and negligible affinity for muscarinic M_1 and histaminic H_1 receptors, was associated with a potential effect on cognitive function in schizophrenia.[19] Data from placebo-controlled studies demonstrated a significant improvement in the PANSS cognitive symptoms subscale (including conceptual disorganization, poor attention, and difficulty in abstract thinking).[27] However, this subscale has not demonstrated a close correlation with performance-based cognitive tests.[30]

The cognitive effect of lurasidone was evaluated in comparison with ziprasidone in a short-term, randomized, double-blind trial. The outcome measures used were a performance-based cognitive assessment battery with most of the tests coming from the MCCB and an interviewer-rated measure of cognitive functioning, ie, the Schizophrenia Cognition Rating Scale. There were no between-group treatment differences in these ratings, but lurasidone demonstrated significant within-group improvement from baseline on the MCCB composite score ($P = 0.026$) and on the Schizophrenia Cognition Rating Scale ($P < 0.001$), unlike ziprasidone. The very short duration of this trial, using a high dose of lurasidone (120 mg/day) and the use of an incomplete battery of tests set some limits to this study, which now requires further work to evaluate the cognitive effects of lurasidone.

Secondary analysis of one trial evaluated the efficacy of lurasidone in patients with schizophrenia who were experiencing clinically significant depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS] > 12).[31] Lurasidone-treated patients had significantly improved mean MADRS scores in the total sample ($P = 0.026$) and in the subgroup with MADRS > 12 ($P = 0.04$) compared with placebo (last observation carried forward). This trial is the only one to provide information on the efficacy of lurasidone in the treatment of depressive symptoms associated with schizophrenia. Double-blind Phase III trials are ongoing to confirm this potential benefit in schizophrenic patients with depressive symptoms.

The long-term efficacy of lurasidone in schizophrenia is being assessed from the extension phases of the short-term

Table 1 Summary of completed trials with information available for lurasidone

Authors/Trial number	Trial details	Length	Sample	Randomized (n)	Lurasidone (± active comparator)		Outcome (primary endpoint)
					Dose (mg/day)	n	
Lurasidone dose–response study							
Harvey et al[23]	RCT, DB Dose-response study	8 weeks	Inpatients and outpatients with schizophrenia	195	20	65	Limited information available. LOCF analysis demonstrated that single daily doses of 40 and 80 mg of lurasidone were associated with significant improvement from baseline on the PANSS and BPRS.
					40	72	
					80	58	
Lurasidone versus placebo studies							
D1050006[16]	RCT, DB, PC Efficacy and safety study	6 weeks	Acute schizophrenia	149	40	49	Mean BPRS total (SD) Change from baseline (LOCF) −9.4 (1.58, $P = 0.02$) −11 (1.58, $P = 0.004$) −3.8 (1.57)
					120	47	
					Placebo	49	
Nakamura et al[17] (D1050196)	RCT, DB, PC Efficacy and safety study	6 weeks	Acute schizophrenia	180	80	90	Mean BPRS total (SD) Change from baseline (LOCF) −8.9 (1.32, $P = 0.012$) −4.2 (1.36)
					Placebo	90	
D1050229 PEARL 1[16]	RCT, DB, PC Efficacy and safety study	6 weeks	Acute schizophrenia	500	40	121	Mean PANSS total (SD) Change from baseline (MMRM) −19.2 (1.7, $P = 0.59$) −23.4 (1.8, $P = 0.03$) −20.5 (1.8, $P = 0.39$) −17.0 (1.8)
					80	118	
					120	123	
					Placebo	124	
Lurasidone with active comparator studies							
D1050049[16]	RCT, DB, PC Efficacy study	6 weeks	Acute schizophrenia	356	20	71	Mean BPRS total (SD) Change from baseline (LOCF) −5.0 (1.38, $P = 0.36$) −5.2 (1.44, $P = 0.44$) −8.0 (1.40, $P = 1.00$) −9.8 (1.37, $P = 0.75$) −7.9 (1.38)
					40	67	
					80	71	
					Haloperidol 10	72	
					Placebo	72	
D1050231 PEARL 2[16]	RCT, DB, PC Efficacy and safety study	6 weeks	Acute schizophrenia	478	40	118	This is an inconclusive or failed study. Mean PANSS total (SD) Change from baseline (MMRM) −25.7 (2.0, $P = 0.002$) −23.6 (2.1, $P = 0.022$) −28.7 (1.9, $P < 0.001$) −16.0 (2.1)
					120	118	
					Olanzapine 15	121	
					placebo	114	

(*Continued*)

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