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Review article

Lurasidone: The 2016 update on the pharmacology, efficacy and safety profile

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ABSTRACT

The aim of this paper was to review the up-to-date evidence base on pharmacology and clinical properties of lurasidone.

Lurasidone is an atypical antipsychotic, approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia and bipolar depression. Lurasidone exhibits both an antipsychotic and antidepressant action. Based on its pharmacodynamics profile, it is believed that the drug's clinical action is mediated mainly through the D_2, 5-HT_{2A} and 5-HT_7 receptors inhibition.

In patients with schizophrenia the recommended dose range is 40–80 mg/day. In bipolar depression broader dosage ranges (20–120 mg/day) were found to be effective. In terms of side effects, higher rates of akathisia, parkinsonism and hyperprolactinemia were observed in individuals receiving lurasidone (as compared to patients treated with other atypical antipsychotics). On the other hand, treatment with lurasidone yields relatively lower risk for developing sedation or overweight/obesity.

Contents

Introduction

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) criteria, psychotic disorders can be defined as a heterogeneous group of severe mental health issues,

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characterized by delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms. The diagnostic class 'Schizophrenia spectrum and other psychotic disorders' encompasses a broad range of categories: schizophrenia, schizoaffective disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, substance/medication-induced psychotic disorder, psychotic disorder due to another medical condition, and schizotypal (personality) disorder [1]. Psychotic episodes may also highlight severe exacerbations of bipolar disorder (BD) and major depressive disorder (MDD).

Psychotic disorders pose a significant public health challenge worldwide. According to the World Health Organization (WHO), over 26 million individuals suffer from schizophrenia [2], and in the recent Global Burden of Disease 2010 study schizophrenia was found to be at the forefront of the most debilitating health issues [3,4]. Nowadays, atypical antipsychotic drugs form the mainstay of treatment for schizophrenia and BD [5,6]. Yet, given both the small between-agent differences in efficacy and the significant tolerability limitations [7,8], there is an ongoing need for new pharmacotherapeutic options. Also, a wider choice of antipsychotics would make it easier for a clinician to tailor the treatment to individual patient's values and preferences [2,9]. Consequently, in recent years the US Food and Drug Administration (FDA) granted license to six novel antipsychotics/antipsychotic formulations: iloperidone, lurasidone, asenapine, oral paliperidone, paliperidone palmitate long-acting injection (LAI), and olanzapine LAI [10,11]. Several trials on the latest developed antipsychotic agents (pomaglumetad methionil and bitopertin) were recently completed [12–16].

The aim of this paper was to summarize the state-of-the-art knowledge on lurasidone, regarding both pharmacological properties of the drug and its clinical utility. Following the principles of the Evidence-Based Medicine (EBM), the efficacy and safety profile of lurasidone was outlined on the basis of randomized controlled trials (RCTs) [17,18] and systematic reviews of RCTs [19]. The eligible studies were identified by searching web-based databases (PubMed/MEDLINE and Cochrane Library), using the following search terms: lurasidone; antipsychotic*; bipolar*; schizophr*; and depress*. The reference lists from retrieved articles were also reviewed. The experimental pharmacology studies were found in the PubMed/MEDLINE database.

Pharmacology

Lurasidone hydrochloride (HCl) belongs to the class of benzothiazol derivatives and is chemically identified as (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 (Fig. 1).

The mechanism of action of lurasidone (just like other antipsychotics) is not fully understood [20]. However, based on its receptor profile, it is believed that the efficacy of lurasidone is mediated mainly through antagonist activity at the dopamine D_2, and the 5-hydroxytryptamine (5-HT, serotonin) receptors: 5-HT_{2A} and 5-HT_7 [21].

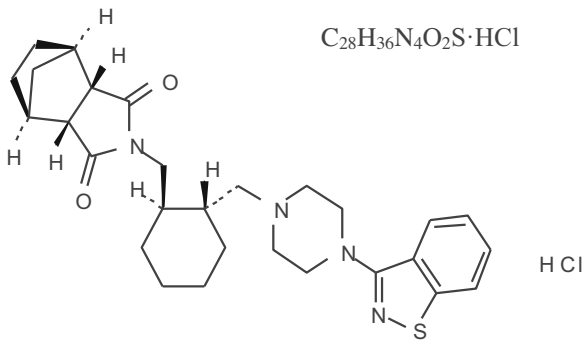

Fig. 1. The structural and molecular formula of lurasidone HCl (molecular weight: 529.14).

Pharmacodynamics. Receptor binding profile

Lurasidone is a full antagonist at the dopamine D_2 (Ki = 0.994 nM) and 5-hydroxytryptamine (5-HT, serotonin) 5-HT_{2A} receptors (Ki = 0.47 nM) [22]. The *in vitro* binding studies revealed that lurasidone exhibits similarly high affinity for these two receptors and is higher than conventional (haloperidol) or other atypical (risperidone, olanzapine, clozapine) antipsychotics. In contrast to the other neuroleptics, lurasidone also possesses high binding affinity for 5-HT_7 (Ki = 0.495 nM), 5-HT_{1A} (Ki = 6.38 nM), α_{2C}-adrenergic (Ki = 10.8 nM), and D_3 (Ki = 15.7 nM) receptors. Simultaneously, the compound shows reduced affinity for the human D_4 (Ki = 29.7 nM), α_1 (Ki = 35.7 nM), and α_{2A}-adrenergic (Ki = 40.7 nM) receptors [23]. Moreover, lurasidone have only weak affinity for the D_1 (Ki = 262 nM) and 5-HT_{2c} (Ki = 415 nM) receptors, and no or negligible affinity for the histamine H_1, muscarinic M_1, and other receptors (e.g. 5-HT_3, 5-HT_4, adenosine A_1, A_2, AMPA, and NMDA) [22]. Ishibashi et al. [22], based on the relative potency ratio of the Ki values to dopamine D_2 receptor (main target of antipsychotic effects), suggested that lurasidone acts primarily at the 5-HT_7, 5-HT_{2A}, and 5-HT_{1A} receptors in addition to the dopamine D_2 receptor. Also, the *in vitro* functional study demonstrated that lurasidone is a D_2, 5-HT_{2A} and 5-HT_7 antagonist, as well as a 5-HT_{1A} receptor partial agonist (E_{max} = 33%). The receptor occupancy studies using positron emission tomography imaging confirmed that the D_2 receptor occupancy ratio following the intake of lurasidone at the dose of 40 mg/day is equal to 60–80%. This D_2 receptor blockade is the likely precondition for the antipsychotic efficacy [24].

The activity on the 5-HT_7, 5-HT_{1A} and α_{2C}-adrenergic receptors is hypothesized to enhance cognition, and the 5-HT_7 is being studied for its potential role in mood regulation and sensory processing [25–27]. Lurasidone's low activity on the α_1-adrenergic, histaminergic H_1, and muscarinic receptors suggest lower risk of orthostatic hypotension, H_1-mediated sedation and weight gain, and H_1- and M_1-mediated cognitive blunting [22,28]. The lack of affinity for other receptors, as well as transporter proteins (e.g. dopamine or serotonin transporter), significantly reduces the likelihood of further side effects. As discussed in section "Human (clinical) studies", clinical trials provided validation to some of those hypotheses (with the notable exception of sedation) [8].

Pharmacokinetics

The pharmacokinetic profile of lurasidone

Lurasidone is rapidly absorbed from the gastrointestinal tract, reaching peak concentrations in blood within 1–3 h (T_{max}), following either single or repeated oral intake. The steady-state concentration is reached after 7 days administration, and the course of absorption depends on the dose of drug. For the lurasidone doses at the range of 20–160 mg/day, the area under the curve (AUC) and maximum concentration (C_{max}) show a linear increase in direct proportion to the dose [29]. Food is another important factor affecting the absorption of lurasidone. As recommended by the FDA, lurasidone should be taken with a meal with the caloric value of at least 350 kcal [24]. In the study comparing the pharmacokinetics of lurasidone (steady-state concentration of 120 mg/kg) it was shown that in the group of patients receiving lurasidone with food, the parameters of AUC and C_{max} increased 2–3 times, respectively, in comparison with a group of patients who took the drug in the fasted state [30].

Concurrently, it was determined that the dietary fat content does not affect the pharmacokinetics of lurasidone [29]. Moreover, on the analysis of absolute volume of distribution parameter (VD) for the lurasidone dose of 40 mg is estimated at 6173 l [31]. Research also determined the biological half-life of lurasidone. In the group of healthy subjects it was found that the mean half-life of lurasidone was 12.2–18.3 h following administration of a single dose of 100 mg/day, and the corresponding value in patients with schizophrenia was equal to 28.8–37.4 h after single doses of 120–160 mg/day [25].

Lurasidone is strongly bound to plasma proteins (99.8%), notably to albumin and α_1-glycoprotein [28]. The drug is primarily metabolized in the liver by the cytochrome P450 (CYP) isoenzyme CYP3A4. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation. Lurasidone is broken down into three active metabolites (ID-14283, ID-14326, and ID-14614; Fig. 2) and two inactive metabolites (ID-20219 and ID-20220), present systemically at levels >10% [31,32]. The main active metabolite, ID-14283, 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 h) than lurasidone. In turn, the two other metabolites (ID-14326 and ID-14614) are detected at extremely low levels (3% and 1%, respectively) [31,32].

Lurasidone crosses the placental barrier, and in 89% this drug is excreted from the body with urine and feces. Increased values of C_{max} and AUC were found in patients with mild to severe renal or hepatic impairment [23].

Pharmacokinetic interactions and toxicity

Lurasidone is a substrate for the cytochrome P450 enzyme CYP3A4 [33].

In general, lurasidone should not be co-administered with potent inducers or inhibitors of CYP3A4 [28]. Chiu et al. [34] showed that concomitant ketoconazole administration conditioned a 6.8-fold increase in lurasidone's C_{max}, and a 9.3-fold increase in lurasidone's AUC. On the contrary, the administration of rifampicin led to a decrease in the drug's C_{max} and AUC. Application of lurasidone with haloperidol and diazepam did not induce changes in the level of plasma protein binding [23]. Similarly, administration of oral contraceptives containing ethinyl estradiol and norelgestromin with lurasidone (40 mg/day) did not induce significant changes in C_{max} and AUC of this drug [29]. In patients with schizophrenia or schizoaffective disorder research did not show significant interactions between lurasidone (120 mg) and lithium (600 mg, twice daily) [29]. Notably, in patients receiving a moderate inhibitor of CYP3A4 (e.g. erythromycin or fluconazole) the 80 mg/day is deemed the maximum daily dose of lurasidone [34].

In clinical terms, however, no significant pharmacokinetic interactions have been observed thus far. The recent evidence-based review by Madhusoodanan et al. found no severe (i.e. acute life threatening), moderate (implying efficacy issues) or mild (leading to non-serious adverse events) interactions involving lurasidone. Nevertheless, it was confirmed that the co-administration of lurasidone and either ketoconazole or ritonavir may induce an increase in plasma concentration of the antipsychotic drug. The authors provided no data indicative for interactions between lurasidone and commonly co-prescribed serotonergic medications [33].

While apparently no cases of lurasidone overdose have been reported [35], it is suggested that the toxic effects may involve orthostatic hypotension, CNS depression, tachycardia and (perhaps) QTc prolongation [36].

Animal (preclinical) studies

A growing body of evidence suggests that lurasidone exhibits an antipsychotic, antidepressant, and also anxiolytic efficacy in preclinical studies.

The antipsychotic activity of lurasidone was investigated in a large behavioral study in rodents performed by Ishibashi et al. [22]. Like other neuroleptics (e.g. olanzapine, risperidone), lurasidone inhibited dose-dependently dopamine D2 receptor-mediated behaviors such as apomorphine (APO)-induced stereotyped behavior and methamphetamine (MAP)-induced hyperactivity in rats or APO-induced climbing behavior in mice. Moreover, in a dose-dependent manner, lurasidone (1–10 mg/kg) inhibited conditioned avoidance response, tryptamine (TRY)-induced forepaw clonic seizure and p-chloroamphetamine (p-CAMP)-induced hyperthermia in rats [22].

The schizophrenia-related cognitive impairment (e.g. learning and memory deficits) is likely caused by hypofunction of the N-methyl-D-aspartate receptor (NMDAR). This hypothesis is strongly supported by numerous studies showing that NMDAR antagonists (e.g. phencyclidine, ketamine or MK-801/dizocilpine) produce prolonged deficits in cognitive functioning. Therefore the above-mentioned compounds are now widely used to model the symptoms of schizophrenia in animals [37]. Preclinical studies showed that lurasidone potently reversed learning deficits (as well

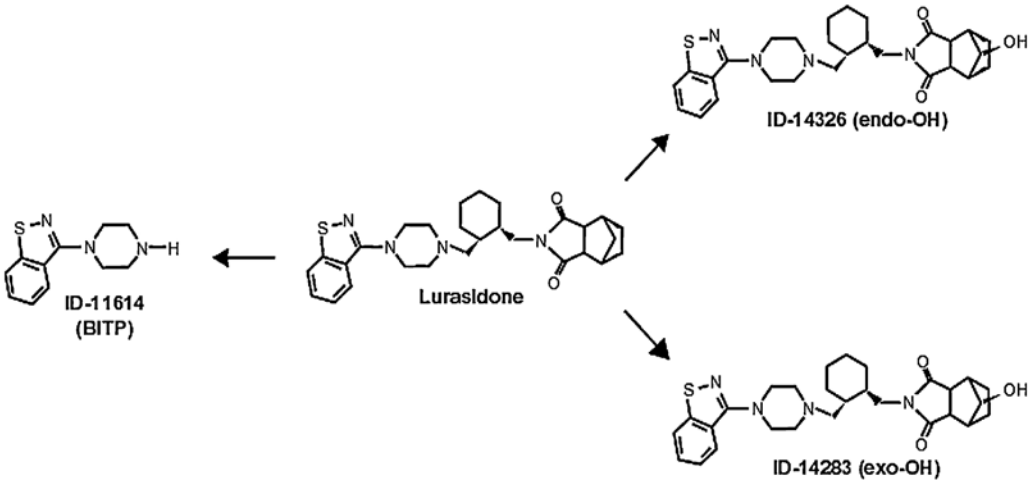

Fig. 2. Chemical structure of the main metabolites of lurasidone; BITP = 1-(1,2-benzisothiazol-3-yl)-piperazine.
Adapted from Caccia et al. [29].

as memory impairment) induced by MK-801 in the most common tasks used to assess spatial learning and memory ability in rodents [38,39]. Ishiyama et al. [38] indicated that administration of lurasidone 1 h before the training session significantly and dose-dependently (only at the dose of 3 mg/kg, but not at the dose of 1 mg/kg, *po*) reversed the MK-801-induced impairment of the passive-avoidance response in rats, such as reduction of the step-through latency or the percent of animals avoiding in the test session. A similar effect was also observed, when lurasidone (0.3 mg/kg, not 0.1 mg/kg, *iv*) was given 10 min after the training session. These findings suggest that lurasidone acted, at least partially, by restoring the memory consolidation process disrupted by MK-801 [38].

Significant effectiveness of lurasidone in reversing the MK-801-induced behavior was also confirmed by Enomoto et al. [39] in the Morris water maze (MWM) and the radial-arm maze (RAM) tests. In the MWM test, lurasidone (1 and 3 mg/kg, *po*) potently decreased the escape latency, swimming distance (but not swimming speed) and frequency of diving behavior in the MK-801 treated rats. While in the RAM test lurasidone (in either investigated dosage level), potently reversed MK-801-induced reference memory impairment and moderately but not significantly attenuated MK-801-induced working memory impairment [39]. The above-mentioned data also suggest that lurasidone may be more effective than other antipsychotics (risperidone, clozapine and aripiprazole) in reversing the MK-801-induced behavior [38,39]. Lurasidone also improves cognition associated with executive function (evaluated by the object retrieval with detours [ORD] task) in naive marmosets (non-human primates). Unlike other antipsychotics (olanzapine, haloperidol, clozapine, olanzapine, quetiapine), the drug of interest increased (in a dose-dependent manner) marmosets' success rates in the difficult trial with significant effect at 10 mg/kg [40]. Apart from that lurasidone reversed novel object recognition (NOR) deficit induced by subchronic administration of phencyclidine (PCP; a noncompetitive antagonist of NMDAR) [41]. It was shown that 7-days lurasidone (1 mg/kg) administration, following the washout period of subchronic PCP, produces a prolonged (up to 3 weeks) reversal of the deficit in NOR induced by subchronic PCP. Moreover, lurasidone at the dose of 1 mg/kg (but not at the dose of 0.1 mg/kg) used as a co-treatment with PCP during the initial PCP treatment period, prevented the subchronic PCP-induced NOR deficit when tested at the day 22 [41].

Other studies demonstrated that efficacy of lurasidone to reverse MK-801 or PCP-induced cognitive dysfunction may be related to its effect on 5-HT7 and 5-HT1A or some nicotinic acetylcholine receptors subtypes [41–45].

Treatment with lurasidone was also associated with significant improvement in the Vogel's conflict and social interaction tests, which are widely used for early behavioral screening of anxiolytic or antidepressant (respectively) drugs activity [22]. Apart from the screening tests, in order to study the potential antidepressant activity of new compounds, animal models of depression are most frequently used. Olfactory bulbectomy (OB) is a widely accepted model of agitated depression, which causes an increase in locomotor activity in animals. As shown by Ishibashi et al. [22], chronic lurasidone (3 mg/kg for 2 weeks) administration significantly suppressed OB-induced hyperactivity behavior and this effect was similar to that observed after imipramine treatment (10 mg/kg, 1 week). Lurasidone can also modulate behavioral and molecular changes in the chronic mild stress (CMS) in rats. Luoni and colleagues [46] demonstrated that 5-weeks lurasidone (3 mg/kg) treatment during CMS exposure improved anhedonia in stressed rats and restored brain-derived neurotrophic factor (BDNF) mRNA level in the prefrontal cortex. Furthermore, chronic lurasidone treatment normalized CMS-induced defects of Psd95 and Gfap and some modulators of protein translation (e.g. mTOR and eEF2) [46]. Another study has also shown that lurasidone was able to normalize the CMS-induced changes of clock gene expression (and related proteins) in the nuclear compartment of the prefrontal cortex and hippocampus [47]. Antidepressant activity (reduced immobility time) of lurasidone was also demonstrated in both the tail suspension (only at the dose of 0.3 mg/kg; not in lower or higher doses) and forced swim (dose range of 0.3–1 mg/kg) tests in wild-type 5-$HT_7^{+/+}$ mice but not in 5-$HT_7^{-/-}$ knockout mice. Likewise, in the repeated open-space swim test (an animal model of chronic depression) lurasidone was able to reverse the despair induced by a repeated swimming session. All these results strongly suggest that the antidepressant effect of lurasidone requires functional 5-HT_7 receptors and that lurasidone can act as a 5-HT_7 antagonist [48]. Similar observations were also made in the serotonin transporter knockout (SERT KO) rats. 3-weeks treatment with lurasidone (10 mg/kg) increased fear extinction in the $SERT^{-/-}$ knockout rats, as opposed to the wild-type ($SERT^{+/+}$) controls. These changes were associated with normalization of the reduced expression of Gadd45β (GABAergic marker), as well as up-regulation of BDNF transcription in the prefrontal cortex [49]. In adult male C57Bl/6 J mice, oral administration of 3 and 10-mg/kg lurasidone as well as of 20-mg/kg fluoxetine during 21 days, reduced the latency to feed in the novelty-induced hypophagia test. Furthermore, lurasidone significantly reduced locomotor activity (average of velocity and total track length) in open field test, but only at a dose of 10 mg/kg. These behavioral changes were associated with a decrease in the NMDA receptor subunits (especially NR2A, NR1) and PSD-95 protein levels in the hippocampus and prefrontal cortex [50]. As described earlier, lurasidone exerted a modulating effect on BDNF. In the prefrontal cortex BDNF (exon IV) as well as Arc mRNA levels was elevated after 21-days administration of lurasidone (10 mg/kg) and exposure to acute swim stress [51]. The modulatory effect of lurasidone on BDNF level was also demonstrated in the Sprague-Dawley rat exposed to prenatal stress [52]. Likewise, co-treatment with lurasidone (3 mg/kg) and the mood stabilizer valproic acid (300 mg/kg) for 21 days increased BDNF expression and further modulated histone deacetylases (HDAC2 and HDAC5) in the hippocampus. These findings suggest that some of transcriptional

Table 1
Dose equivalents for lurasidone. Adapted from Leucht et al. [58].[a,b]

	Olanzapine 1 mg/day	Risperidone 1 mg/day	Haloperidol 1 mg/day	Chlorpromazine 100 mg/day
Lurasidone equivalents				
Primary analysis	5.33 mg/day	20 mg/day	10 mg/day	16 mg/day
Sensitivity analysis[c]	4 mg/day	10 mg/day	8.9 mg/day	14.2 mg/day

[a] A systematic review of randomized controlled trials on second-generation antipsychotics or haloperidol in adults with schizophrenia or schizoaffective disorder.
[b] The following populations were excluded from the analysis: adolescents, elderly, first-episode patients, stable patients, patients with predominant negative symptoms, patients diagnosed with treatment-resistant schizophrenia.
[c] Sensitivity analysis answers the question if the result changes according to minor variations in the data and methodology of the study. The authors followed the FDA rules, requiring data from ≥2 positive trials to run the sensitivity analysis.

changes caused by lurasidone may be sustained by epigenetic mechanisms [53].

Human (clinical) studies

Schizophrenia

Lurasidone gained the FDA approval for the treatment of schizophrenia in 2010, with the recommended starting dose of 40 mg/day. The top recommended dose was set at 80 mg/day [23]. Yet, in some short-term, industry-sponsored trials lurasidone was also found to be effective at higher portions (120–160 mg/day) [54–57]. Overall, the current evidence base suggests that 40 mg/day is the minimum effective dose of lurasidone [58]. Its dose equivalents to olanzapine, risperidone, haloperidol and chlorpromazine are provided in Table 1.

The most comprehensive to date review of lurasidone's efficacy and safety in acute treatment of schizophrenia was provided in the network meta-analysis by Leucht et al. [8]. Accordingly, while lurasidone is more effective than placebo (standardized mean difference [SMD] = −0.33 [95% confidence interval (CI): −0.45 to −0.21], denoting moderate effect size), it lags behind clozapine, amisulpride, olanzapine, risperidone, and paliperidone – both in terms of efficacy and acceptability (as reflected by the risk of withdrawing from treatment). At the same time, lurasidone yields similar efficacy and acceptability to zotepine, haloperidol, quetiapine, aripiprazole, sertindole, ziprasidone, chlorpromazine, asenapine, and iloperidone (see Table 2).

In comparison with placebo, lurasidone is more likely to cause extrapyramidal side-effects (odds ratio [OR] = 2.46; 95% CI: 1.55–3.72), hyperprolactinemia (SMD = 0.34; 95% CI: 0.11–0.57), and sedation (OR = 2.45; 95% CI: 1.31–4.24). On the other hand, patients receiving lurasidone were less likely to cease the treatment (OR = 0.77; 95% CI: 0.61–0.96), and – notably – the drug did not differ from placebo in terms of the risk for QTc prolongation (SMD = −0.10; 95% CI: −0.21 to 0.01) and weight gain (SMD = 0.10; 95% CI: −0.02 to 0.21) [8].

The evidence base regarding the longer-term efficacy of lurasidone remains sparse. However, there are some early data to suggest that patients receiving prolonged treatment with lurasidone may enjoy sustained improvement with relatively few side effects (mainly akathisia and somnolence, occurring in about 10% of the subjects) [59]. Having compared lurasidone to quetiapine extended release [60] in a sample of 292 patients with schizophrenia enrolled in a non-inferiority RCT, Loebel et al. [61] found similar rates of relapse over a one-year period. In two extension trials the six-month therapy with lurasidone appeared to be safe and effective [62,63], yet the results were highly susceptible to performance- and detection bias (due to the open-label design of the studies) [64].

Bipolar disorder

Lurasidone is also approved for the treatment of bipolar depression [23], both in monotherapy and as adjunctive therapy with lithium or valproate [65–67].

In the recent network meta-analysis of short- to medium-term RCTs (4–16 weeks) regarding pharmacotherapies for bipolar depression in adults, Taylor et al. [68] concluded that lurasidone monotherapy yields similar efficacy to olanzapine, valproate, quetiapine, selective serotonin reuptake inhibitors (SSRI), lithium, and tricyclic antidepressants (TCA). Also, the ostensibly different dosing regimens for lurasidone (20–120 mg/day and 80–120 mg/day) were comparatively effective. However, due to acceptability issues, the authors supported the combined use of olanzapine and

Table 2
Summary of data comparing the relative efficacy and tolerability of lurasidone *versus* other antipsychotics in the acute treatment of schizophrenia.

Outcome #1: Mean overall change in symptoms		
Lower efficacy	Similar efficacy	Higher efficacy
–	• Zotepine • Haloperidol • Quetiapine • Aripiprazole • Sertindole • Ziprasidone • Chlorpromazine • Asenapine • Iloperidone	• Clozapine • Amisulpride • Olanzapine • Risperidone • Paliperidone
Outcome #2: Acceptability (all-cause discontinuation)		
Worse acceptability	Similar acceptability	Better acceptability
–	• Zotepine • Haloperidol • Quetiapine • Aripiprazole • Sertindole • Ziprasidone • Chlorpromazine • Asenapine • Iloperidone	• Clozapine • Amisulpride • Olanzapine • Risperidone • Paliperidone
Higher risk	Similar risk	Lower risk
Outcome #3: Weight gain		
• Paliperidone • Risperidone • Quetiapine • Sertindole • Chlorpromazine • Iloperidone • Clozapine • Zotepine • Olanzapine	• Aripiprazole • Amisulpride • Asenapine	–
Outcome #4: Extrapyramidal side-effects		
–	• Ziprasidone • Amisulpride • Asenapine • Paliperidone • Risperidone • Chlorpromazine • Iloperidone • Zotepine	• Haloperidol • Aripiprazole • Quetiapine • Sertindole • Clozapine • Olanzapine
Outcome #5: Hyperprolactinemia		
• Haloperidol • Risperidone • Paliperidone	• Asenapine • Olanzapine • Chlorpromazine • Iloperidone • Ziprasidone	• Aripiprazole • Quetiapine
Outcome #6: QTc prolongation		
• Sertindole • Haloperidol • Risperidone • Amisulpride • Quetiapine • Asenapine • Olanzapine • Iloperidone • Ziprasidone	• Aripiprazole • Paliperidone	–
Outcome #7: Sedation		
–	• Amisulpride • Risperidone • Paliperidone • Sertindole • Iloperidone • Aripiprazole • Haloperidol • Asenapine • Olanzapine • Quetiapine • Ziprasidone	• Clozapine • Chlorpromazine • Zotepine

Adapted from Leucht et al. [8].

fluoxetine as the optimal treatment for bipolar depression (for details, see Table 3).

In the recent update of the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: 'lurasidone monotherapy and the combination of lurasidone or lamotrigine plus lithium or divalproex have been added as second-line options' for the treatment of bipolar depression (from: Yatham et al. [6], cited verbatim).

As suggested in the placebo-controlled, double-blind RCT encompassing depressed patients with BD type I, lurasidone exhibits significant anxiolytic properties. Noticeable improvement in quality of life was also observed in the lurasidone sample. The authors set the starting dose of the drug at 20 mg/day. In general, the treatment was well tolerated. The most common adverse effects reported by the patients were: nausea, sedation, vomiting, and extrapyramidal symptoms. The majority of adverse effects were reported as mild or moderate. Less than 10% of adverse symptoms were described as severe [66].

In another placebo-controlled RCT Loebel et al. [69] examined the effects of lurasidone adjunctive therapy with either lithium or valproate in patients with BD type I. As compared to the placebo group, patients receiving lurasidone at the mean daily dose of 31.8 mg (range: 20–60 mg) or 82.0 mg (range: 80–120 mg) had greater improvements in depressive symptoms starting from week 3 through week 6. Additionally, there was a significant reduction in anxiety symptoms, and improvement of patient-rated functional impairment and quality of life. Moreover, the adjunctive lurasidone therapy was well tolerated and the discontinuation rate due to adverse effects was comparable to placebo. Also, the risk of treatment-emergent hypomania or mania was comparable to the placebo group and was lower than the switch risk of standard antidepressant BD treatment.

So far, there are no established data on safety and tolerability in neither pediatric nor geriatric patients diagnosed with BD [65].

Table 3
Summary of data comparing the relative efficacy and tolerability of lurasidone *versus* other drug regimens in the treatment of bipolar depression.

Outcome #1: Primary efficacy (change in scores on the MADRS or HAM-D)

Lower efficacy	Similar efficacy	Higher efficacy
–	• Aripiprazole • Lamotrigine • Lithium • MAOI • Olanzapine • Quetiapine • Risperidone • SSRI • TCA • Valproate • Ziprasidone • Olanzapine + fluoxetine • *placebo*	–

Outcome #2: Primary tolerability (switch to mania)

Lower risk	Similar risk	Higher risk
placebo	• Aripiprazole • Lamotrigine • Lithium • MAOI • Olanzapine • Quetiapine • Risperidone • SSRI • TCA • Valproate • Ziprasidone • Olanzapine + fluoxetine	–

Outcome #3: Secondary efficacy (response)

Lower efficacy	Similar efficacy	Higher efficacy
• Aripiprazole • Ziprasidone • Olanzapine • Lamotrigine • Lithium • SSRI • TCA • MAOI • *placebo*	• Quetiapine • Risperidone • Valproate • Olanzapine + fluoxetine	–

Outcome #4: Tolerability (withdrawal)

Lower risk	Similar risk	Higher risk
–	• Aripiprazole • Lamotrigine • Lithium • MAOI • Olanzapine • Quetiapine • Risperidone • SSRI • TCA • Valproate • Ziprasidone • *placebo*	• Olanzapine + fluoxetine

Adapted from Taylor et al. [68].
MAOI, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

Conclusions

In this paper we reviewed the current evidence base on pharmacology and clinical utility of lurasidone in patients with schizophrenia and bipolar depression.

In clinical terms, lurasidone has been found beneficial in treating patients with bipolar depression [6,68]. In subjects with schizophrenia, however, lurasidone seems to belong to a relatively broad range of drugs of moderate efficacy [8]. Nonetheless, it shall be emphasized that lurasidone was found to be effective in patients with schizophrenia suffering from depressive symptoms [56]. The relevance of these finding stems from the fact that depressed mood is an established risk factor for suicide in schizophrenia [70]. Therefore, further studies on the potential antisuicidal effects of lurasidone are warranted.

While the data on the antipsychotic efficacy leave lurasidone behind clozapine, risperidone, paliperidone, olanzapine and amisulpride [8], the side effects profile suggests that the drug may be useful in some specific populations of individuals with schizophrenia. Of note, the risk of sedation and body mass increase is relatively low in patients receiving lurasidone [8,71]. On the other hand, in comparison with numerous other atypical antipsychotics there seem to be higher rates of akathisia, parkinsonism and hyperprolactinemia in subjects treated with the drug of interest [8]. As expected (given lurasidone's low affinity to the α_1-adrenergic receptors), no significant prolongations of QTc interval were observed in subjects receiving lurasidone [72]. Yet, bearing in mind that the risk of sudden cardiac death in individuals receiving atypical antipsychotics is dose-dependent [73], lurasidone needs to be prescribed with caution. It should also be emphasized that the lack of data on lurasidone's safety and effectiveness in special populations (e.g. in the elderly or in the pregnant/postpartum women) leaves a number of significant clinical questions unanswered.

To conclude, more high-quality RCTs on lurasidone need to be conducted. The fact that the majority of data available have been gathered in the course of industry-sponsored trials raises the issue of bias [74]. Furthermore, as pointed out by Patel et al. [10], phase II and III RCTs on new antipsychotics (including lurasidone) are often hampered by poor reporting quality, thus limiting both clinicians'

and policymakers' abilities to make informed decisions pertaining to licensing and prescribing of the drugs.

Conflict of interest

All authors declare no conflict of interest.

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