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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].

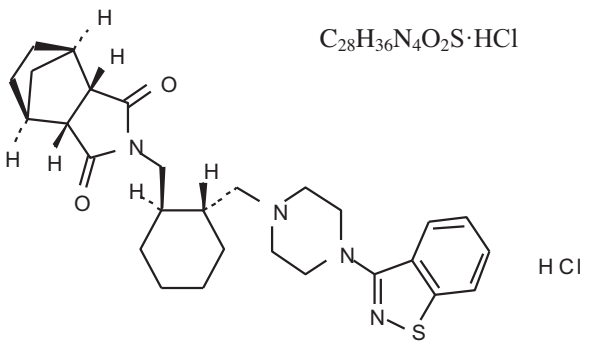

Fig. 1. The structural and molecular formula of lurasidone HCl (molecular weight: 529.14).

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].