**Supplementary Material**

**Iloperidone**

Iloperidone (piperidinyl-benzisoxazole) is a molecule derived from risperidone (1,2) (see figure 1). In 2009, the FDA approved this AAP for the treatment of the acute phase of schizophrenia in adults (3,4) and it is recommended until the stabilization phase (5). The therapeutic effect of this drug is associated with the agonism of the 5-HT1A, 5-HT2A,5-HT2C, 5-HT6, 5-HT7, D1-4, α-2A, and H1receptors (see Table 1) (6–11). It is metabolized primarily by carbonyl reduction, hydroxylation mediated by CYP2D6, and O-demethylation (mediated by CYP3A4). There are two predominant metabolites, P95 and the active metabolite P88.

As other AAPs, iloperidone is able to alter the serum levels of PRL (12) due to its affinity for DA receptors (6) and it seems the effect of this drug on PRL depends on the consumption time and the dose, yet there is evidence that shows no changes in PRL levels during iloperidone consumption (13). In contrast, there is a case report of HPRL with galactorrhea in a middle-aged woman treated with iloperidone (8 mg/day) for three months (14). A study showed decreased PRL in serum (24 mg/day) among 86 patients with schizophrenia after 25 weeks of treatment (15). Three prospective trials (n = 1,943) with three different iloperidone dose ranges (4–8, 10–14, and 20–24 mg/day) for six weeks showed that low and medium doses (4–8 and 10–14 mg/day) decreased serum PRL in patients. However, PRL levels were not detected in patients with high dose (20–24 mg/day) compared with baseline (16). This effect is associated to the interaction between iloperidone and D2 receptors on the tuberoinfundibular pathway, so the DA cannot inhibit PRL secretion in the anterior hypophysis. These changes are associated with genetic factors and drug dose, which explains the results of the studies mentioned above (14,16) (see figure 2).

There are no more reports that exhibit the presence of hormonal alterations induced by iloperidone consumption and there is no evidence showing alterations in the humoral or cellular inflammatory response during iloperidone consumption. Further studies are required to evaluate the effect of this drug on the endocrine function and the impact of its consumption on the inflammatory response and explain the molecular mechanisms involved in the possible alterations.

**Lurasidone**

Lurasidone, a benzothiazole derivative (see figure 1), is used as an AP treatment in adults. This drug gained the FDA approval for the treatment of schizophrenia in 2010 (17) and bipolar depression both in monotherapy and as adjunctive therapy with lithium or valproate in 2013 (18). Lurasidone is metabolized through the CYP3A4 pathway and its consumption with food is recommended for greater efficiency (19). Its metabolism pathways are oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation. This drug is broken down into three active and two inactive metabolites (17).

Lurasidone has a greater affinity for 5-HT7, D2, 5-HT2A, 5-HT1A, and adrenergic α2c receptors. It also has moderate affinity for adrenergic receptors α1 and α2A, weak affinity for D1 and 5-HT2C, and negligible affinity for histamine H1, muscarinic, nicotinic, glutamate, and sigma receptors, as well as dopamine and serotonin transporters (See Table 1) (20).

Although it is reported to induce modest, dose-dependent PRL and HPRL elevations, especially at the beginning of treatment, as well as HPRL in some patients, lurasidone seems to be associated with no clinically meaningful PRL alterations in most cases (21). PRL alterations are associated with the fast dissociation from the D2R and the PRL-sparing properties of APs. Lurasidone is associated with lesser degrees of PRL elevation since it shows a fast D2R dissociation (21). There are a few reports about the effect of this drug on the endocrine system; however, the benign metabolic profile during treatment and its minimal effects on body weight, glucose, and lipid concentrations provide lurasidone with an advantage over other SGAs (22).

Some reports prove the effect of lurasidone consumption in the inflammatory response. One of these alterations is the cell count. Although lurasidone is less likely to cause side effects, a 29-year old patient with bipolar depression developed thrombocytopenia after a 3-month treatment (80 mg/day) (23). A second report linked neutropenia in patients in remission from a manic episode with the use of 40 mg/day of lurasidone (24).

Lurasidone also affects soluble mediators of inflammatory response. It has been proven that patients with bipolar depression treated with 20–60 mg/day (n=161) and 80–120 mg/day (n=162) lurasidone showed a significantly decreased C-reactive protein (CRP) after a 6-week treatment. Although this is not directly related to the effect of the drug upon inflammatory pathways, it is generally accepted that lurasidone plays a regulatory role in central DA levels, promoting depression improvement (25) (see figure 2). In light of the importance of Lurasidone in the immune and endocrine system, additional studies will be needed to take advantage of the clinical potential of this drug.

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