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REVIEW

Lurasidone for the treatment of schizophrenia in adult and paediatric populations

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Abstract

Schizophrenia is a common debilitating disorder characterized by significant impairments in how reality is perceived, combined with behavioural changes. In this review, we describe the lurasidone development programme for adult and paediatric patients. Both the pharmacokinetic and pharmacodynamic characteristics of lurasidone are revisited. In addition, pivotal clinical studies conducted on both adults and children are summarized. Several clinical cases, which demonstrate the role of lurasidone in real-world practice, are also presented. Current clinical guidelines recommend lurasidone as the first-line treatment in the acute and long-term management of schizophrenia in both adult and paediatric populations.

Keywords: case studies, clinical trials, lurasidone, real-world data, schizophrenia.

Citation

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Introduction

Schizophrenia is a mental health condition characterized by an impaired perception of reality and significant behaviour changes.[1] It is a multifactorial disorder with contributions from genetic, environmental and psychosocial factors.[2] Worldwide, schizophrenia affects around 24 million people,[1] is in the top 15 causes of disability[1–3] and is associated with a high economic burden.[4–7] In addition, individuals with schizophrenia have a reduced life expectancy compared with the general population (13.8 and 11.8 life years lost for males and females, respectively).[8] Excess mortality is not solely explained by the increased risk of death by suicide and other injuries; indeed, cardiovascular disease is the leading preventable cause of early deaths in those with severe mental illness.[9]

The disease is characterized by significant impairments in how reality is perceived as well as behavioural changes related to delusions, hallucinations, disorganized thinking and behaviour (positive symptoms), negative symptoms (e.g. apathy and social withdrawal), alteration in movements, and limitations in cognitive or thinking skills (cognitive symptoms).[1] However, the main impact of the burden of schizophrenia on the individual is the pervasive impact on functioning and quality of life: personal, family, occupational and social spheres are profoundly affected in most of patients.[10] It can be treated effectively using pharmacological (broadly classified as typical and atypical antipsychotics[11]) and psychosocial therapies.[12] However, current treatments of schizophrenia have significant limitations. Firstly, they are efficient for only about half of patients, enabling them independent life.[12]

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Secondly, they ameliorate mainly positive symptoms (e.g. hallucinations and thought disorders, which are the core of the disease), but negative (e.g. flat affect and social withdrawal) and cognitive (e.g. learning and attention disorders) symptoms remain untreated.[13] Thirdly, they involve severe neurological and metabolic side effects and may lead to sexual dysfunction or agranulocytosis (clozapine).[14]

This article reviews current treatment guidelines for schizophrenia and, specifically, the key clinical trials regarding lurasidone, the only antipsychotic indicated for adolescents ≥13 years of age and for the treatment of depressive episodes associated with bipolar I disorder. Finally, real-world data regarding the use of lurasidone in clinical practice are discussed. During the preparation of this article, GPP guidelines for industry-sponsored biomedical research were followed.

Ethics statement

All data presented in this article were deidentified to ensure patient confidentiality. The patients provided consent for anonymized use of clinical data.

Treatment guidelines for schizophrenia

Treatment and psychosocial interventions, together with prevention, are the tools of health professionals to reduce this high burden; nevertheless, despite of recent developments of new pharmacological agents for schizophrenia and the proposal of new therapeutic targets, their use is associated with significant restrictions.[15,16] Patient treatment pathways and treatment choices are determined based on illness acuity/severity, past treatment response, tolerability, balancing efficacy and adverse effect profiles, in agreement with patients' preferences and adherence patterns.[17] Although there are no unified European recommendations, several professional international and national organizations have published guidelines for the treatment of adult patients, including the World Federation of Societies of Biological Psychiatry,[18,19] the American Psychiatric Association,[20] the National Institute for Health and Care Excellence,[21] the British Association of Psychopharmacology,[22,23] and the German Guidelines released by the Global Public Policy Network.[24]

The main goals of treatment during the acute phase include harm prevention, disturbed behaviour control, reduction of the severity of psychosis, identification and eradication of factors associated with disease occurrence and achievement of a rapid return to the best level of daily functioning and social relationships.[18,25] During both initial stabilization and maintenance phases, the main treatment goals include symptom amelioration, consolidation, maintenance of remission, recovery promotion as well as improvement of daily functioning, quality of life and monitoring for adverse events.[19,25] In recent years, promising new treatments (lurasidone, brexiprazole and cariprazine) for schizophrenia in adults have been approved in Europe but only one for the treatment of adolescents (lurasidone).[26] These three treatments were selected for study in this systematic literature review due to their shared safety profile and recent market approval.

Lurasidone

Lurasidone is an atypical antipsychotic drug approved for the treatment of schizophrenia in adults (2010 by FDA, 2014 by EMA) and in adolescents ≥13 years of age (2015 by FDA, 2020 by EMA). Lurasidone is the only antipsychotic with the indication for this age range (aripiprazole and paliperidone have the indication for adolescents ≥15 years of age).[27] In addition, lurasidone is also indicated for the treatment of depressive episodes associated with bipolar I disorder in the United States.[28]

Chemical properties and pharmacodynamics

Lurasidone is a benzisothiazol derivative, atypical antipsychotic. Whilst it shows a potent binding affinity for dopamine D_2, 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$), 5-HT$_7$, 5-HT$_{1A}$ and noradrenaline α_{2C} receptors, affinity for noradrenaline α_1, α_{2A} and 5-HT$_{2C}$ receptors is weak, whilst the affinity for histamine H_1 and muscarinic acetylcholine receptors is negligible. In vitro functional assays have shown the antagonistic effect of lurasidone for D_2 and 5-HT$_7$ receptors, whilst it has a partial agonistic effect at the 5-HT$_{1A}$ receptor subtype[29] (Figure 1).

This unique receptor profile provides lurasidone with very advantageous properties, including reduction in negative symptoms (high affinity; serotonin 5-HT$_{2a}$ antagonist); improvement in cognition and circadian rhythm regulation (high affinity; serotonin 5-HT$_7$ antagonist); improvement in depressive symptoms (moderate affinity; serotonin 5-HT$_{1a}$ partial agonist); reduced drowsiness and somnolence (moderate affinity; α_{2a} adrenergic agonist); and no sedation, weight gain or cholinergic effects (low or no affinity; muscarinic M_1 and histamine H_1 receptors).[29,31]

Pharmacokinetics

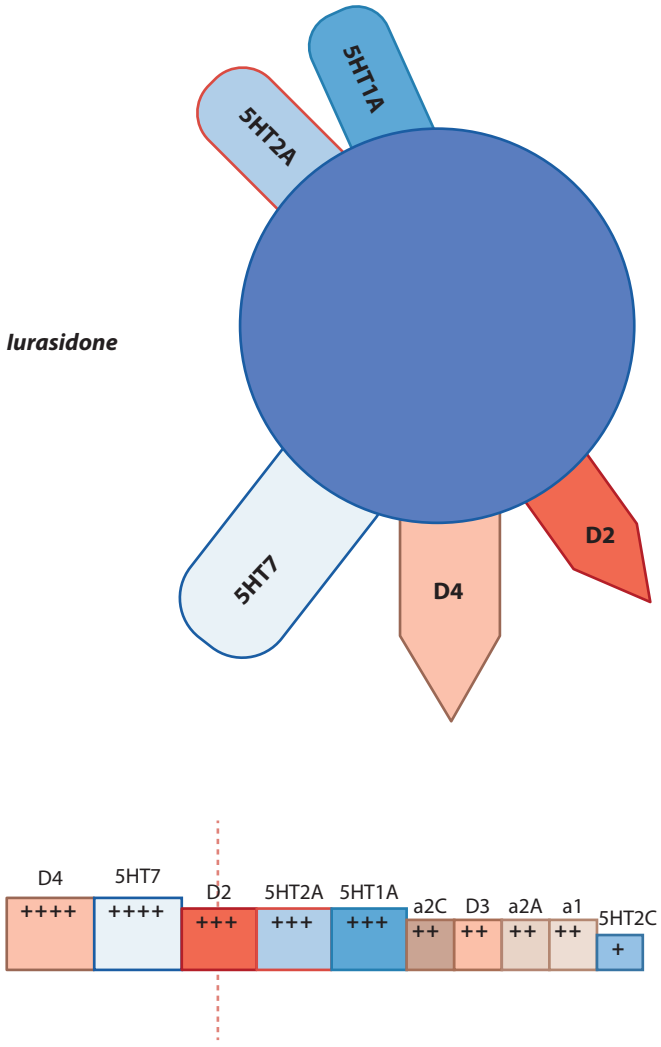
Lurasidone's pharmacokinetics are dose dependent and its activity is mainly related to the parent drug (Table 1).[28]

Clinical studies

Adult population

The main characteristics of the key clinical trials of lurasidone for the treatment of schizophrenia in the adult population are summarized in Table 2.[32–36] The efficacy of lurasidone for the treatment of schizophrenia was estab-

Figure 1. Pharmacological and binding profile of lurasidone.



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lished in five short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.4 years, range 18–72) who met DSM-IV criteria for schizophrenia.[33–37] An active-control arm (olanzapine or quetiapine extended release) was included in two studies to assess assay sensitivity. Two studies were conducted in the United States and three were multiregional (North America, Europe, Asia and South America) (Table 3).[33–37]

Early-onset response

Early response (≥20% improvement at 2 weeks) has been shown to be a predictor for late response.[37] For non-responders, current treatment strategies include dose escalation, dose change and dose increase.[38–40] Thus, a study conducted by Loebel et al.[41] was a double-blind, placebo-controlled study in hospitalized patients with acute schizophrenia (DSM-IV-TR criteria). Patients were randomly assigned to double-blind treatment with lurasidone (20 mg/d lurasidone, *n*=101; 80 mg/d, *n*=199) or placebo (*n*=112). Non-responders to lurasidone 80 mg/d (Positive and Negative Syndrome Scale (PANSS) score decrease <20%) at 2 weeks were rerandomized to lurasidone 80 mg/d or 160 mg/d for the remaining 4 weeks of the study. The primary outcome measure was changed from baseline to week 6 in PANSS total score. The results of the study showed that, in non-responders to lurasidone 80 mg/d (*n*=95), dose increase to 160 mg/d at week 2 significantly reduced PANSS total score at week 6 study endpoint compared with continuing 80 mg/d (−16.6 *versus* −8.9; $p<0.05$). This study provided evidence that early non-responders with schizophrenia may benefit from an increase in lurasidone dose. Significantly greater improvement in schizophrenia symptoms was found after lurasidone dose escalation compared with continuation of the initial dose.[41]

Table 1. Lurasidone: pharmacokinetics.[28]

Pharmacokinetic parameters	Characteristics
Absorption and distribution	Dose proportional, within a total daily dose range of 20–160 mg Peak serum concentrations are reached in approximately 1–3 hours (9–19% of an administered dose is absorbed) Following administration of 40 mg of lurasidone the mean (%CV) apparent volume of distribution is 6173 (17.2) Lurasidone is highly bound (~99%) to serum proteins Steady-state concentrations are reached within 7 days of starting treatment Following administration of 40 mg, the mean (%CV) elimination half-life was 18 (7) hours
Effect of food in absorption	Lurasidone mean C_{max} and AUC are 3-fold and 2-fold when administered with food compared to fasting conditions Lurasidone exposure was not affected by either meal size or fat content
Metabolism and elimination	Its activity is mainly related to the parent drug Lurasidone is metabolized mainly via CYP3A4 Major biotransformation pathways: oxidative N-dealkylation, hydroxylation of norbornane ring and S-oxidation Two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220) Total excretion in urine and faeces combined is approximately 89% (80% recovered in faeces and 9% recovered in urine) Following administration of 40 mg of lurasidone, the mean (%CV) apparent clearance was 3902 (18.0) mL/min

Table 2. Main characteristics of the key clinical trials of lurasidone for treatment of schizophrenia in adult population.[28]

Main characteristics	Description
Type of study	Double-blind, randomized, fixed-dose, placebo-controlled study
Duration	6 weeks
Study periods	Screening (up to 14 days) Single-blind placebo washout (3–7 days of prior antipsychotic medication) Double-blind treatment (6 weeks)
Hospital admission	2–4 week hospital admission was required for patients with acute exacerbation of schizophrenia
Instruments used for assessing psychiatric signs and symptoms	1. Positive and Negative Syndrome Scale (PANSS): Multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210. 2. Brief Psychiatric Rating Scale derived (BPRSd): Multi-item inventory primarily focusing on positive symptoms of schizophrenia. It consists of 18 items rated on a scale of 1 (not present) to 7 (severe). BPRSd scores may range from 18 to 126. 3. The Clinical Global Impression Severity scale (CGI-S): Clinician-rated scale that measures the subject's current illness state on a 1- to 7-point scale. *The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared with placebo changes for the drug and control groups.

Table 3. Lurasidone in schizophrenic adult population.[32–36]

Study	Description	Results
Study 1	Type: placebo-controlled trial Number of patients: 145 Doses: two fixed doses of lurasidone (40 or 120 mg/day) *versus* placebo Duration: 6 weeks	Both doses were significantly superior to placebo on the BPRSd total score, as well as the CGI-S score at endpoint
Study 2	Type: placebo-controlled trial Number of patients: 180 Doses: two fixed doses of lurasidone (80 mg/day) *versus* placebo Duration: 6 weeks	Lurasidone was superior to placebo on the BPRSd total score and the CGI-S score at endpoint
Study 3	Type: placebo-controlled trial Number of patients: 473 Doses: two fixed doses of lurasidone (40 or 120 mg/day) and active control (olanzapine) *versus* placebo Duration: 6 weeks	Both lurasidone doses and the active control at endpoint were superior to placebo on the PANSS total score and the CGI-S
Study 4	Type: placebo-controlled trial Number of patients: 489 Doses: three fixed doses of lurasidone (40, 80 or 120 mg/day) *versus* placebo Duration: 6 weeks	Only the 80 mg/day dose of lurasidone at endpoint was superior to placebo on the PANSS total score and the CGI-S
Study 5	Type: placebo-controlled trial Number of patients: 482 Doses: two fixed doses of lurasidone (80 or 160 mg/day) and an active control (quetiapine extended release) *versus* placebo Duration: 6 weeks	Both lurasidone doses and the active control at endpoint were superior to placebo on the PANSS total score and the CGI-S

BPRSd, Brief Psychiatric Rating Scale derived; CGI-S, Clinical Global Impression Severity scale; PANSS, Positive and Negative Syndrome Scale.

Long-term safety and tolerability of lurasidone

The long-term safety and tolerability of lurasidone for the treatment of adult patients with schizophrenia have been evaluated in a large, randomized trial.[42] A total of 629 patients were randomized to receive either once-daily, flexibly dosed lurasidone (40–120 mg) (n=427) or risperidone (2–6 mg) (n=202) for 12 months. The results of the study showed that prolonged treatment with lurasidone was safe and well tolerated, with minimal effects on weight, metabolic variables and prolactin levels. On the contrary, treatment with risperidone was associated with significantly greater effects on weight, measures of glycaemic control and prolactin levels. The three most frequent side effects in the lurasidone group include nausea, insomnia and sedation. All side effects were considered mild. On the other hand, the three most frequent side effects in the risperidone group were increased weight, somnolence and headache.[42]

With regards to weight gain, a pooled analysis of studies in patients with schizophrenia receiving long-term treatment showed low potential for clinically significant weight gain in patients with schizophrenia treated continuously with lurasidone for 12 months.[43] The same positive effect has been confirmed with real-world data. The results of a study conducted on 15,323 adults suggest that lurasidone has a lower risk of clinically relevant weight gain and a higher chance of clinically relevant weight loss than other commonly used antipsychotics.[44] Two other real-world studies have also shown the higher adherence to treatment and the lower rate of hospital admissions associated with lurasidone treatment, compared with other antipsychotic treatments,[45,46] with an associated improvement in quality of life.[47]

In addition, recent practical guidelines on the use of lurasidone for the treatment of adult patients with schizophrenia as well as the results from a meta-analysis have confirmed the role of lurasidone in both the acute and maintenance phases of treatment for schizophrenia in adults.[48,49] Extensive evidence from the lurasidone clinical development programme has suggested that lurasidone is as effective as other atypical agents, possibly with the exception of clozapine, and can be used as a first-line treatment in the acute setting and in patients who have previously failed to respond to other atypical antipsychotics, with a better safety profile.[48,49]

Improvement in cognitive ability, learning and memory associated with lurasidone

Schizophrenia causes cognitive alterations as well as positive, negative and disorganized symptomatology.[50] Alterations in cognitive functioning correlate with impaired daily functional capacity.[51] Improvement in cognitive impairment is one of the most important challenges in the treatment of schizophrenia.[50] Lurasidone's receptor profile suggests its potential to exert a pro-cognitive action through the blockade of serotonin receptors 5-HT_7 and 5-HT_{1A}.[52] Lurasidone significantly improved response rates in animal models of cognitive ability, learning and memory (Table 4).[53–59] The same positive effects have been also reported in a double-blind placebo-controlled study that evaluated change in cognitive performance and functional capacity in patients with schizophrenia treated with lurasidone and quetiapine XR over a 6-week period, followed by a 6-month extension. The results of the study showed significantly better cognitive performance associated with lurasidone treatment.[60] Lurasidone's pro-cognitive effects have also been observed in patients diagnosed with bipolar depression.[61]

Paediatric population

The main clinical features of adolescent schizophrenia include functional impairment, reduced average IQ, insidious start, family history of mental diseases/schizophrenia, predominance of negative symptoms, severe disease and chronicity.[62] The characteristics of the two pivotal 6-week duration studies are summarized in Table 5.[63,64] The results of a meta-analysis that compared lurasidone with eight antipsychotic drugs (aripiprazole, asenapine, clozapine, olanzapine, paliperidone extended release (ER), quetiapine, risperidone and ziprasidone) for the treatment of schizophrenia in adolescents showed that lurasidone was numerically more effective on the PANSS score compared with ziprasidone, asenapine, paliperidone ER and aripiprazole.[65] With regards to the Clinical Global Impression Severity scale (CGI-S) score, lurasidone was found to be more effective than asenapine, aripiprazole, ziprasidone and quetiapine. In addition, lurasidone was associated with less weight gain compared with quetiapine, olanzapine, risperidone, asenapine, and paliperidone ER and had fewer treatment discontinuations compared with aripiprazole and paliperidone ER. No significant differences in the presence of extrapyramidal symptoms between the active treatments were reported.[65] With regards to young adults, Costamagna et al.[66] conducted a pooled analysis of six studies that included 6-week, double-blind, placebo-controlled trials with lurasidone in fixed doses of 40, 80, 120 or 160 mg in 537 patients, with ages ranging from 13 to 25 years. Lurasidone was significantly superior to placebo on the PANSS total score and CGI-S score. In addition, treatment with lurasidone was well tolerated and safe.

Table 4. Improvement in cognitive ability, learning and memory associated with lurasidone treatment in animal models.[33–37]

Animal model	Outcome after treatment with lurasidone
Passive avoidance conditioning	Prevention of impairment of passive avoidance conditioning induced by scopolamine and MK-801
Passive avoidance conditioning	Reversal of the MK-801 effect: role of 5-HT_7
Morris Water Maze	Prevention of spatial memory impairment with the glutamate receptor antagonist MK-801
Recovery of objects with deviation	Enhanced food reward retrieval in executive function tasks requiring suppression of impulsive responses in primates
Recognition of novel objects	Reversed impairment associated with in phencyclidine-modulated by 5-HT_{1A} and 5-HT_7

Real-world data regarding the use of lurasidone in the adult population in Spain

Very limited real-world data regarding the use of lurasidone in clinical practice are available. The below real-life cases illustrate how lurasidone can be used to treat adult patients with psychotic episodes, depressive episodes associated with schizophrenia, late diagnosis of schizophrenia and finally iatrogenic psychosis. These cases were selected through a contest, where an expert committee evaluated the cases presented following specific criteria with regards to quality and scientific interest, these being the ones with the highest scientific quality.

Case #1. Lurasidone for a psychotic episode

Reason for consultation

A 36-year-old patient was transferred to the emergency department for the third time in a week due to delusional harm ideation with an invasion of the affective sphere and repercussions on the behavioural level, associating experiences of derealization and external control without awareness of the disease. The patient presented with self-inflicted injuries on her arm.

Table 5. Lurasidone in schizophrenic paediatric population.[53–59]

Study	Description	Results
Study 1	Type: placebo-controlled trial Number of patients: 327 Age: 13–17 years Doses: two fixed doses of lurasidone (40 or 80 mg/d) *versus* placebo Duration: 6 weeks Study periods: Screening (up to 14 days) Single-blind placebo washout (3–7 days of prior antipsychotic medication) Double-blind treatment (6 weeks)	Both doses were significantly superior to placebo on the PANSS, CGI-S, CGAS and PQ-LES-Q scores at endpoint A significantly higher proportion of patients met responder criteria on lurasidone 40 and 80 mg/day *versus* placebo (63.9% and 65.1% *versus* 42.0%; $p<0.001$) Lurasidone was generally well tolerated, with few effects on weight and metabolic parameters
Study 2	Study 1 extension study Patients who completed study 1 were enrolled in a 2-year, open-label, flexible dose (20–80 mg/d) lurasidone treatment *versus* placebo study Number of patients: 271 (181 lurasidone; 90 placebo)	The mean daily dose of lurasidone averaged across the 104-week open-label treatment period was 57.0 mg/d Lurasidone was significantly superior to placebo on the PANSS, CGI-S, CGAS and PQ-LES-Q scores at endpoint Long-term lurasidone treatment was associated with minimal effects on body weight, lipids, glycaemic indices and prolactin

BPRSd, Brief Psychiatric Rating Scale derived; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression Severity scale; PANSS, Positive and Negative Syndrome Scale; PQ-LES-Q, Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

Physical and psychopathological examinations and tests

Physical exam

Normal.

Psychopathological exam

The patient was aware and oriented, with a neglected appearance and impoverished contact; directed, concrete and coherent speech; delusional content of harm, with no systematization; nocturnal predominant achoasma; hypothymia reactive to the situation. Previous complaints of asthenia and apathy, without abandonment of daily activities, a tendency to isolation, ideas of guilt, ruin or handicap, nor was there a decrease in hedonic capacity. No phobias or obsessive symptoms. Increase in tobacco consumption. No other toxic habits. Decreased intake without clear hyporexia and almost complete insomnia. The patient was aware of her current condition.

Differential and final diagnosis

Initial diagnosis

Unspecified psychotic episode.

Differential diagnosis

During the initial follow-up, the possibility of a delusional disorder was assessed due to some delirious idea of harm that did not affect her daily activities. The possibility of depressive-type schizoaffective disorder was also assessed and ruled out due to a history of depressive anxiety disorder. However, there were no major affective symptoms during most of the active phase of the disease. For months, the patient maintained apathy, lack of drive for activity, affective flattening, hypohedonia and cognitive difficulties such as loss of concentration and memory that significantly limited her capabilities.

Final diagnosis

Schizophrenia.

Treatment

The patient received olanzapine 20 mg during hospital admission for 2 weeks with no improvement. Treatment was then switched to risperidone 3 mg with attenuation but no disappearance of positive symptoms. The dose was subsequently increased to 6 mg. The patient presented marked pharmacological impregnation, psychomotor retardation, rigidity and a feeling of dullness. The dose was reduced to 4 mg without achieving complete remission of the side effects and experienced marked negative symptoms. The patient was discharged after a month with a multidisciplinary follow-up.

Follow-up

During follow-up, a predominance of negative symptoms was observed, with the inability to carry out essential

daily activities associated with complaints of drowsiness, dullness, stiffness and weight gain. The patient developed hyperprolactinaemia, hypertriglyceridaemia and a decrease in HDL cholesterol associated with a weight increase of 4 kg. Risperidone was discontinued, and treatment with quetiapine 300 mg and fluoxetine 40 mg was initiated. The addition of fluoxetine was based on the reasoning that sub-depressive symptoms could partially cause the negative symptoms. After 2 months, no improvement was observed. Treatment was then switched to aripiprazole 10 mg, with good initial tolerance and subsequent relapse of positive symptoms, marked akathisia and maintenance of weight gain. It was then decided to start treatment with lurasidone (74 mg). The patient presented akathisia during the first few days but rapidly resolved. Hypnotic treatment was also added. A year and a half later, the patient remained stable, having lost 9 kg and having experienced a significant improvement in her quality of life.

Treatment rationale

The treatment switch aimed to reduce the side effects experienced by the patient, as they are, along with the disease itself, the leading cause of increased morbidity and mortality in patients with schizophrenia.[67,68] Given the persistence of negative and cognitive symptoms and the presence of metabolic syndrome, treatment with lurasidone monotherapy was started, as it is an antipsychotic that does not cause drowsiness and has proven efficacy in the treatment of affective and cognitive symptoms as well as improvement of metabolic levels.[34,69]

Case #2: Lurasidone for schizophrenia with depressive symptoms

Reason for consultation

A 47-year-old man, diagnosed with schizophrenia for more than 10 years, with persistent psychotic symptoms and refractory to treatment, presented with associated depressive symptoms that significantly interfered with his daily life for approximately 3 weeks. Autolytic ideation and active psychotic symptomatology were reported.

Physical, psychopathological exams and complementary tests

Physical exam

Normal.

Psychopathological exam

On admission, the patient was aware, globally oriented, approachable and collaborative. Core obesity; dystonic contact; preserved emotional reactivity, marked cognitive rigidity; no psychomotor restlessness; high levels of anxiety secondary to thought content; normoprosexia; spontaneous, verbose speech; language with tone and fluency within normality but monochord tonality. Hypothymia with endogenous pattern of 3 weeks of evolution, marked anhedonia and apatoabulia. Increased social isolation and loss of self-care. Ideas of despair and tedium of life. History of messianic delusions. Highly structured active autolytic ideation. Mixed type insomnia. Hyporexia with weight loss. Good disease awareness.

Differential and final diagnosis

Differential diagnosis

Patient diagnosed with schizophrenia presenting with psychotic and depressive symptoms. His current psychotic symptomatology met criteria A of the DSM-V1, leading to the diagnosis of an episode of schizophrenia decompensation. Delusional disorder was ruled out by the presence of a history of hallucinations and disorganized behaviour. Schizoaffective disorder was ruled out given that, according to the DSM-V1 criteria, affective episodes should occur during a significant part of the illness, and this was the first time that this clinic was described (previous suicidal behaviour was secondary to delusional clinic). A depressive episode with psychotic symptoms was ruled out because the delusions only appeared alongside a depressed mood. On the other hand, the negative symptoms (energy, anhedonia and blunted affect) did not seem to cause the condition due to frank hypothymia, hopelessness, increased social isolation, hyporexia with weight loss that constitute the description of a major depressive episode.

Final diagnosis

Episode of decompensated schizophrenia, concurrent with a severe depressive episode.

Treatment

Treatment with sertraline at a dose of 200 mg was maintained titration of benzodiazepines (clorazepate) for acute control of insomnia and anxiety was increased. Regarding antipsychotic treatment, risperidone and paliperidone were suspended due to the lack of control of psychotic symptoms and their possible influence on the level of negative symptoms. Moreover, aripiprazole was started with no response at the affective and psychotic level of symptoms and development of akathisia was reported. Lurasidone was then initiated with significant improvement at the level of affective and delusional symptomatology, conducting a progressive ascending titration with good tolerance.

Follow-up

During hospital admission, a slowly favourable evolution was reported. From the effective point of view, a disposition towards euthymia was achieved, with recovery of the hedonic capacity and vital plans. The autolytic ideation completely disappeared. In addition, the delusional verbalizations receded, with a certain self-referentiality

persisting as the only psychotic symptom, without behavioural or emotional repercussions. The stabilization process was maintained at the outpatient level (up to 6 months after hospital discharge), reaching euthymia. An increase in social relations and leisure activities that had been restricted for years was reported.

Treatment rationale

A clinical case of a patient diagnosed with schizophrenia with multiple episodes of decompensation who presented with messianic delusions and affective symptomatology is presented. Given the lack of response to risperidone and paliperidone and the possible influence on the affective symptoms (worsening of negative symptoms due to intense D2 blockade),[70] the switch was initially decided for aripiprazole, with no response. In these circumstances, the switch to lurasidone was based on a series of scientific evidence: there are indications that lurasidone is more effective in reducing depressive symptoms than other antipsychotics. At the receptor level, it is a D_2 and $5HT_{2A}$ antagonist. However, its distinctive characteristics come from its $5HT_7$ antagonism and partial $5HT_{1A}$ agonism and lower affinity than other antipsychotics to $5HT_{2C}$, histaminergic, adrenergic and muscarinic receptors, which explain its fewer side effects. The effect on the $5HT_7$ receptor, together with the partial agonism of $5HT_{1A}$, could translate into an improvement at the level of memory, learning, motivation and cognition as well as recovery at the level of affective and negative symptoms, meaning an improvement in quality of life and functional recovery of patients.[69–71] Lurasidone has been included amongst the antipsychotics with lower metabolic risk, improving the weight gain associated with other antipsychotic treatments. In addition, the increase in prolactin is slightly and significantly lower compared with risperidone.[69,71,72]

Case #3: Lurasidone for late diagnosed schizophrenia

Reason for consultation

A 53-year-old woman with recurrent major depressive disorder and cluster A and C personality traits (DSM-V criteria) presented to the clinic 1 day urgently due to active, severe suicidal ideation and psychotic symptoms.

Physical and psychopathological exams and complementary tests

Physical exam

Normal.

Psychopathological exam

The patient complained about significant anguish secondary to delusional ideation of harm in the workplace and self-referentiality, of insidious establishment in the previous weeks, when the patient gave a delusional meaning to daily events. She also presented auditory hallucinations. She has experienced insomnia for the last 3 days and verbalized ideas of structured and planned suicide. Given the risk of suicide and the presence of psychotic symptoms, she was referred for urgent admission to the Acute Care Unit. Blood tests, ECG and head CT, performed during admission, were strictly normal.

Differential and final diagnosis

Differential diagnosis

1. Major depressive episode with psychotic symptoms in a patient with cluster A and C personality traits. This diagnosis since there was no frankly depressed affect; the suicidal ideation was secondary to the psychotic symptoms and not to the presence of clinical symptoms.
2. Onset of cognitive impairment added to previous diagnoses: despite cognitive complaints and specific difficulties in work performance, functioning in basic and instrumental activities of daily living was adequate; however, given the family history of dementia, a neuropsychological examination was performed to rule out the onset of primary degenerative dementia.

Final diagnosis

Paranoid schizophrenia. For years, the patient had been treated as a patient with a recurrent depressive disorder and paranoid personality traits that were exacerbated during periods of elevated stress. However, reviewing the medical record, the patient had presented at least three prior psychotic episodes, with characteristics similar to the current one. The patient had previously minimized and rationalized these episodes, making them difficult to identify. The poor adjustment of the patient in different areas of her life (personal, family, interpersonal and work), subtle cognitive failures and a marked restriction of emotional expressiveness, with a lack of spontaneity and naturalness in interpersonal contact, supported the diagnosis of primary psychotic disorder.

Treatment

On admission, treatment was scheduled with quetiapine 400 mg (0-0-1), venlafaxine 150 mg (1-0-0) and bromazepam 3 mg (1-1-1). During admission, the antidepressant and the antipsychotic were modified, and she was discharged with lurasidone 74 mg (1-0-1), bromazepam 1.5 mg (1-0-1), clomipramine 75 mg (0-0-1) and trazodone 100 mg (0-0-1).

Follow-up

After hospital discharge, she resumed outpatient follow-up with a complete biopsychosocial approach. Although delusional symptoms and hallucinations subsided, flat affect and habitual aprosodic speech persisted,

maintaining euthymic subjective symptoms. She had a good night's rest and tolerated lurasidone treatment well, with no relevant side effects. Given the difficulties in her current job, both due to her cognitive complaints and the need for social interaction with colleagues and customers an assessment of the degree of disability was processed to request a change of position within the company.

Treatment rationale

Given the patient's characteristics, an effective antipsychotic was needed for the control of positive symptoms that did not produce secondary negative symptoms, without worsening the affective sphere and without a negative impact on cognitive function. Lurasidone was chosen because of its receptor profile that differentiates it from other antipsychotics and is characterized by the following[73]: D_2 antagonism reduces positive psychotic symptoms and stabilizes affective symptoms; 5-HT_{2A} antagonism reinforces the release of dopamine in certain brain areas, reducing motor side effects and improving cognitive and affective symptoms; 5-HT_7 antagonism improves mood, sleep, cognitive deficits and negative symptoms; partial 5-HT_{1A} agonist, antagonistic actions on 5-HT_7 and α_{2A} and α_{2C} receptors improve mood, anxiety and cognition; and it does not have potent actions on D_1, muscarinic M_1 and histaminergic H_1 receptors, leading to less susceptibility to induce cognitive deficiency, weight gain or sedation compared with other antipsychotics.

Case #4: Lurasidone and outpatient management, addressing the metabolic syndrome

Reason for the consultation

The patient presented for this scheduled check-up at an outpatient psychiatry clinic. There was evidence of stable psychopathological terms within the usual psychiatric morbid condition during his appointment. Metabolic syndrome had been addressed in prior visits and two different antipsychotic alternatives were prescribed with no apparent improvement. The patient now presented with alterations in analytical parameters, which, alongside his current physical condition, had led to certain dysfunctionality in his daily tasks.

Physical and psychopathological exam and complementary tests

Physical exam and complementary tests

Physical exam was normal. The patient had progressively gained weight (13 kg) and was attributed to the antipsychotic treatment. However, the patient did not follow any dietary restrictions. The blood test revealed triglycerides levels of 143 mg/dL, with an HDL cholesterol of 38 mg/dL and blood pressure of 140/90 mmHg; fasting glucose was 104 mg/dL. The rest of the parameters did not yield data of interest. All the above parameters increased progressively because the last admission to the mental health hospitalization unit.

Psychopathological exam

The patient was conscious and oriented but frankly psychotic, encountering a certain hypothymia reactive to the delusional symptomatology, expressing discomfort in these matters but without constituting a major affective disorder. Anxiety concerning the delusional theme in the foreground of his speech centred on delusional ideation of harm centred on his family, with abundant delusional interpretations. Auditory hallucinations were also reported. He did not express autolytic ideation. After 7 months of treatment, the patient was approachable and calm in consultation. The contact was syntonic. There were still some symptoms related to apatobulia secondary to the cessation of activity and lack of socio-labour structure. The speech, in general terms, was coherent and structured, adequate in tone and rate, without delusional content in the foreground, despite a particular component of self-referentiality that had been objectified belonging to a matter of the patient's trait. No objectified sensory-perceptive alterations. No autolytic ideation. Pharmacologically preserved biorhythms. Judgment of reality and full volitional capacities.

Differential and final diagnosis

The definitive diagnosis established according to ICD-10 was paranoid schizophrenia.

Treatment

During his first admission to a mental health hospitalization unit, the following treatment was initiated: olanzapine 10 mg and clonazepam 2 mg. Due to the weight gain reported, treatment with olanzapine was progressively decreased and switched to aripiprazole 15 mg but was later suspended due to development of akathisia. Treatment with lurasidone was then initiated.[74,75] An initial dose of 37 mg was then doubled after 7 days of treatment.[76] No secondary effects of interest were observed. The treatment was maintained with good adherence and no evidence of psychopathological alterations in the five subsequent months were reported. In addition, patient was also instructed to follow healthy eating habits. Approximately 6 months after the introduction of lurasidone treatment, the patient had lost about 5 kg, and the abdominal perimeter was reduced by 4 cm. At the analytical level, triglycerides levels were 124 mg/dL, with HDL cholesterol of 49 mg/dL and a blood pressure of 122/86 mmHg; fasting glucose was 92 mg/dL.

Follow-up

The follow-up during the subsequent months did not reflect any psychopathological alterations, though a

possible increase in baseline self-referentiality was observed in the seventh month. However, this coincided with a time of work stress, as the patient resumed his employment and was controlled with a closer follow-up.

Treatment rationale

Due to weight gain, olanzapine treatment was substituted by aripiprazole but had to be suspended due to the development of akathisia. Treatment with lurasidone was then initiated based on its metabolic control property.

Case #5: Iatrogenic psychosis

Reason for the consultation

A 20-year-old female patient with no prior psychiatric history is referred from the Acute Psychiatric Unit for admission to the Crisis Intervention Program of the Psychiatric ambulatory hospital. Ten days before admission, the patient started respiratory symptoms with anosmia, cough and difficulty breathing. PCR results showed COVID-19 infection. Treatment with paracetamol, fluticasone furoate and oral antihistamine was prescribed. In addition, treatment with Miracle Mineral Solution (MMS) was also initiated. Two days after the positive results of the PCR, the patient status worsened, with dyspnoea and respiratory distress. Although the results of the chest X-ray are inconclusive, bronchodilator treatment and oral dexamethasone 4 mg with dose escalation was prescribed. On the fifth day after starting corticosteroid treatment, the patient's dyspnoea improved significantly. The primary care physician abruptly suspended the corticosteroid treatment. Two days later, the patient abruptly began total insomnia and strange behaviour accompanied by delusional symptoms.

Physical and psychopathological exams and complementary tests

Physical exam

Normal. Other tests: blood tests and head CT, performed during admission, were strictly normal.

Psychopathological exam

The patient was alert, conscious, egodystonic contact, perplexed, hypervigilant gaze, speech with little spontaneity, no signs of endogenomorphic affective symptoms, delusions of prejudice, denies sensory-perceptive alterations, maintains appetite, improvement of insomnia with hypnotic treatment, no disease awareness.

Differential and final diagnosis

Differential diagnosis

1. The abrupt onset without the prodromal symptoms common in a young patient and the rapid resolution of the psychotic symptoms would rule out schizophrenia.
2. The result of a normal cranial CT ruled out an acute neurological cause.
3. Rapid remission of symptoms was achieved with a low dose of antipsychotic treatment.
4. Both the AEMPS (Spanish Agency of Medicines and Medical Products) and the FDA have warned about the danger of MMS, which contains chlorine dioxide, the intake of which can affect different organs and its vapours could cause bronchospasm. Although psychotic episodes have not been described, the toxicity of this type of product in the short and medium term is unknown.
5. Although some cases of psychotic episodes have been described, acute confusional syndrome and anxious-depressive symptoms were the most prevalent pathologies in patients with COVID-19.

Final diagnosis

Psychotic episode induced by abrupt suppression of corticosteroids. The fast remission with a low dose of antipsychotic treatment points towards an induced psychotic picture.

Treatment

The patient remained admitted to the Acute Care Unit for 15 days. Aripiprazole regimen was started with little clinical response. Treatment was then switched to risperidone that had to be discontinued due to the development of extrapyramidal symptoms. Treatment with lurasidone was then initiated at a dose of 37 mg/d, combined with lormetazepam 2 mg for the insomnia.

Follow-up

Based on the improvement reported on insomnia, the hypnotic treatment prescribed during admission was withdrawn. In addition, treatment with lurasidone was progressively reduced to 18.5 mg/d. At the control visits, the patient remained stable and had returned to work.

Rationale for treatment selection

COVID-19 infection can affect brain areas causing neuropsychiatric symptoms such as hallucinations and/or delusions.[77] However, corticosteroid treatment, which is used in severely ill patients to improve the prognosis of respiratory involvement during COVID-19 infection, may also be the cause of some psychotic symptoms.[78] Corticosteroid-induced mental disorders have a prevalence of between 3% and 6%, are more frequent in women, are dose dependent and appear in the first 11 days after starting treatment.[79] Corticosteroid-induced psychotic symptoms have an unpredictable course and, in most cases, do not follow a specific clinical pattern, making diagnosis, approach and treatment difficult.[80] Faced with a sudden onset of psychotic symptoms without prior history in a patient with COVID-19 infection, it is very important to contrast the patient's information with the

family to rule out that it is induced by corticosteroids. In 1985, WHO agreed on the Rational Use of Medicines so that patients receive the appropriate medication for their clinical needs, in the corresponding doses, for an adequate period, and at the lowest possible cost for them and the community.[81] The protocols authorized during the COVID-19 pandemic include early treatment with corticosteroids to improve the prognosis and reduce mortality in seriously ill patients. The patient did not meet severity criteria. Perhaps if the risk to benefit ratio of corticosteroid treatment had been evaluated in the face of the first symptom she presented, she would not have progressed to the psychotic condition that required hospitalization, and which caused a high emotional and financial impact on the patient and family. Once the antipsychotic treatment has started, we must not forget to prescribe the minimum effective dose and for a short period of time until the previous functionality can be recovered. Another issue to reflect on is that, because the start of the pandemic, hardly any face-to-face visits have been made and telephone assistance has been the only contact with health professionals, increasing the risk of unintentional iatrogenesis. In addition, easy access to the Internet has become a double-edged sword by offering alternative therapies that promise solutions, once again increasing the risk of unintentional iatrogenesis also from the family environment. Hospital admission allowed the adequate resolution of the psychotic episode and promoting the recovery of previous functionality in the family as well as in her social and work environment.

Discussion

Despite the limited real-world data about the use of lurasidone in Spain, the above clinical cases series suggest that lurasidone is an effective and well tolerated for treatment of early-onset schizophrenia as well as schizophrenia with predominant depressive symptoms. The frequency of side effects, such as weight gain and metabolic or cardiac abnormalities, was very low as previously shown in randomized clinical trials.[33,34,36,42,63–65,82–87]

This review is aligned with recent consensus publications regarding treatment approaches for first episode and early-phase schizophrenia in adolescents and young adults that state that the pharmacological approach should be taken with particular attention to safety and tolerability aspects of the drug.[88]

Conclusion

Schizophrenia is a common debilitating disorder characterized by significant impairments in how reality is perceived as well as behavioural changes related to delusions, hallucinations, disorganized thinking and behaviour, negative symptoms, alteration in movements and limitations in cognitive or thinking skills. Antipsychotics are the backbone of treatment; nevertheless, their use is associated with significant limitations. Lurasidone is an atypical antipsychotic drug approved for the treatment of schizophrenia in adults and adolescents ≥13 years of age as well as for the treatment of depressive episodes associated with bipolar I disorder (in the United States). Lurasidone has a potent binding affinity for dopamine D_2, 5-hydroxytryptamine$_{2A}$ (5-HT_{2A}), 5-HT_7, 5-HT_{1A} and noradrenaline α_{2C} receptors. Affinity for noradrenaline α_1, α_{2A} and 5-HT_{2C} receptors is weak, whereas affinity for histamine H_1 and muscarinic acetylcholine receptors is negligible. Its receptor profile provides lurasidone with very advantageous properties that include reduction in negative symptoms, improvement in cognition and circadian rhythm regulation, improvement in depressive symptoms, reduced drowsiness and somnolence (moderate affinity, α_{2a} adrenergic agonist), and no sedation, weight gain or cholinergic effects. Lurasidone has a very safe profile, with minimal effects on body weight and low risk for clinically meaningful alterations in glucose, lipids or electrocardiogram parameters, even in early-onset schizophrenia.

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