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REVIEW & CASE SERIES

Towards full recovery with lurasidone: effective doses in the treatment of agitation, affective, positive, and cognitive symptoms in schizophrenia and of dual psychosis

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Abstract

The management of schizophrenia necessitates a comprehensive treatment paradigm that considers individual patient nuances and the efficacy of lurasidone in addressing schizophrenia symptoms, particularly at elevated dosages. Numerous randomized trials have affirmed the efficacy of lurasidone across various dimensions of schizophrenia, demonstrating marked enhancements in positive, negative and cognitive symptoms compared to a placebo. In addition, lurasidone exhibits potential in ameliorating agitation amongst acutely ill patients, showcasing greater efficacy at higher doses. However, despite the favourable outcomes observed with higher lurasidone doses, routine clinical practice often opts for lower doses, potentially limiting its maximal therapeutic impact. Furthermore, lurasidone also shows efficacy in reducing post-psychotic depression in dual psychosis. Moreover, practical insights into lurasidone usage encompass swift dose escalation within a 1–5-day span and recommended combination strategies with other medications such as benzodiazepines for insomnia or agitation, beta-blockers for akathisia, and antihistamines or antimuscarinic drugs for patients transitioning rapidly from antipsychotics with substantial antihistamine and/or anticholinergic effects. Finally, a series of clinical cases is presented, highlighting benefits of lurasidone in terms of cognitive function, functional recovery and other therapeutic aspects for the management of schizophrenia.

Keywords: agitation, case studies, lurasidone, post-psychotic depression, schizophrenia.

Citation

Guarro Carreras MT, Jiménez Suárez L, Lago García L, Montes Reula L, Neyra del Rosario A, Rodríguez Batista FA, Velasco Santos M, Prados-Ojeda JL, Diaz-Marsà M, Martín-Carrasco M, Cardenas A. Towards full recovery with lurasidone: effective doses in the treatment of agitation, affective, positive, and cognitive symptoms in schizophrenia and of dual psychosis. *Drugs Context*. 2024;13:2024-4-4. https://doi.org/10.7573/dic.2024-4-4

Introduction

Schizophrenia affects approximately 24 million people globally, accounting for 1 in every 300 individuals (0.32%). Its onset during adolescence adds complexity to its already intricate aetiology.[1,2] Given the immense personal and societal toll associated with schizophrenia, a comprehensive and integrated management plan is imperative.[3,4] Experts widely advocate for an individualized approach to managing schizophrenia, rooted in the unique clinical characteristics of each case. This involves assessing positive and negative symptoms, onset type, suicidal tendencies, neurocognitive status, social

functioning, comorbidities, past treatment responses or adherence, family history, and protective factors.[5–12] Considering these elements meticulously aids in tailoring an effective management strategy, fostering patient recovery.[13]

Lurasidone, an atypical antipsychotic and benzisothiazole derivative, exhibits strong binding affinity for dopamine D2, 5-hydroxytryptamine 2A (5-HT_{2A}), 5-HT_7, 5-HT_{1A}, and noradrenaline α2C receptors. It shows weak affinity for noradrenaline α1, α2A and 5-HT_{2C} receptors and negligible affinity for histamine H1 and muscarinic acetylcholine receptors. In vitro functional assays indicate that lurasidone acts as an antagonist at D2 and 5-HT_7 receptors, whilst it functions as a partial agonist at the 5-HT_{1A} receptor subtype.[14]

The beneficial effects on positive schizophrenia symptoms, such as hallucinations and delusions, are thought to result from complete antagonism at the D2 receptors in the mesolimbic pathway. Lurasidone also acts as an antagonist at the serotonin 5-HT_{2A} receptor, reducing antagonistic interactions in various dopaminergic pathways, which contributes to its better tolerability. Specifically, targeting the nigrostriatal pathway helps decrease extrapyramidal symptoms, whilst acting in the tuberoinfundibular pathway lowers hyperprolactinaemia. In the mesocortical pathway and prefrontal cortex, this action improves negative, affective and cognitive symptoms. The antagonism at 5-HT_{2A} receptors also reduces serotonergic excitation of cortical pyramidal cells, thereby improving positive schizophrenia symptoms. Additionally, the antagonism of lurasidone at the 5-HT_7 receptor enhances learning and memory and reduces cognitive deficits and depressive symptoms. Finally, its partial agonism at the 5-HT_{1A} receptor may further contribute to its antidepressant properties (Table 1).[15–17]

Lurasidone can be considered a multidimensional drug and is recommended for use across all ages, for both sexes and at any stage of the disease. Switching from previous treatments often occurs due to lack of effectiveness or poor adherence/tolerability. Lurasidone is recognized as one of the most well-tolerated antipsychotics, suitable for patients with various comorbidities, although some dose-dependent adverse effects have been described (akathisia is the most common side-effect but it can usually be managed by reducing the dose). It offers a wide range of dosages, facilitating dose escalation, with the maximum dose (148 mg) typically used for acute phase treatment. The rate of discontinuation due to poor tolerability, low compliance or drug interactions is minimal.

Lurasidone has minimal sedative effects but can be combined with sedatives like benzodiazepines for agitated patients. The primary reason for switching to other therapies is the need for long-acting formulations, particularly for patients with low adherence or suicide risk.[18–21]

Table 1. 5-HT receptor affinity and effects.[15–17]

Receptor, activity	Effects
D_2, full antagonism	Improvement in positive symptoms (hallucinations and delusions)
Serotonin 5-HT_{2A}, antagonism	Better tolerability profile (reduction in extrapyramidal symptoms; reduction in hyperprolactinaemia); improvement in negative, affective and cognitive symptoms; improvement in positive symptoms
5-HT_7, antagonism	Improvement in cognitive deficits (favourable effects in learning and memory) and depressive symptoms
$5HT_1$, partial agonism	Improvement in depressive symptoms

Its positive impact extends to managing acute phases and reducing relapse risk. In addition, a favourable tolerability profile of lurasidone, including negligible effects on weight, prolactin levels and metabolic parameters, has been reported.[12,22,23] Lurasidone should be taken once daily with a meal. If taken without food, it is expected that the exposure to lurasidone will be considerably reduced compared to when taken with food.[22]

Approved by the FDA in 2010 and the EMA in 2014 for adult schizophrenia treatment and later endorsed by the FDA in 2015 and the EMA in 2020 for adolescents aged 13 or older, lurasidone has demonstrated its effectiveness through randomized, placebo-controlled trials.[24–28]

Post-psychotic depression (PPD) significantly influences early psychosis prognosis.[29] Substance-induced psychosis heightens the risk of subsequent unipolar depression or anxiety disorders.[30] Whilst most antipsychotics lack antidepressant efficacy in patients with psychosis, certain medications, such as lurasidone or clozapine, stand out for their potential to treat depressive symptoms associated with schizophrenia.[31]

This review explores the effectiveness of high doses of lurasidone in managing all schizophrenia symptoms

and its role in addressing PPD in dual psychosis cases. Additionally, it delves into real-world insights on the clinical application of lurasidone. During the preparation of this article, GPP guidelines for industry-sponsored biomedical research were followed.

Methods

A literature search was carried out using PubMed from 2007 to 2024 with the following key words: "Lurasidone", "schizophrenia", "psychosis", "depression", "cognition", "pooled analysis", "agitation", "cannabis" and "alcohol".

Review

Efficacy of high-dose lurasidone in treating schizophrenia symptoms

Research conducted by Loebel et al. examined the efficacy of lurasidone across five schizophrenia symptom dimensions,[32] pooling results from five randomized, double-blind, placebo-controlled, 6-week trials involving 1029 patients with acute schizophrenia exacerbation.[24–28] The evaluation utilized the five-factor model developed by Marder et al. to gauge changes in the Positive and Negative Syndrome Scale (PANSS) factors.[33] Compared to the placebo group (n=496), lurasidone (n=1029, pooled doses) significantly improved the PANSS total score at week 6 (−22.6 *versus* −12.8; p<0.001; effect size 0.45). Notably, all factor scores showed significant improvement (p<0.001 for each): positive symptoms (−8.4 *versus* −6.0; effect size 0.43), negative symptoms (−5.2 *versus* −3.3; effect size 0.33), disorganized thought (−4.9 *versus* −2.8; effect size 0.42), hostility/excitement (−2.7 *versus* −1.6; effect size 0.31), and depression/anxiety (−3.2 *versus* −2.3; effect size 0.31). Initial differences from placebo were observed as early as week 1 for positive symptoms, disorganized thought and hostility/excitement. However, it took 2 weeks for improvement in the remaining factors (except for the 120 mg/day dose) (Figure 1). Lurasidone (all doses pooled) demonstrated effect sizes ranging from 0.31 to 0.43 for the five factors between 40 mg/day and 120 mg/day doses. The efficacy was notably higher for the 160 mg/day dose across all PANSS factors. In daily practice, however, lurasidone is typically administered at low to medium doses, starting at 37 mg once daily.[22] Table 2 summarizes lurasidone dose equivalents in the EU and the USA.[34]

Table 2. Lurasidone dose equivalents in the EU and the USA.[34]

USA doses (mg, HCl salt)	EU doses (mg, active moiety)
20	18.5
40	37
60	56[a]
80	74
120	111[a]
160[b]	148[a]

[a]Tablet strength not available in the EU.
[b]Tablet strength not available in the USA.

Efficacy of high-dose lurasidone for the management of agitation in acutely ill patients

Agitation commonly occurs amongst patients with schizophrenia, notably in acute psychiatric settings during illness exacerbation.[35] This distressing symptom often contributes to hospital admissions.[36] Moreover, it has been linked to an increased risk of suicide in this patient population.[37] Agitation may manifest in various behavioural forms, ranging from non-aggressive actions like pacing or hand wringing to more aggressive behaviours such as screaming or threatening others.[38,39]

Allen et al. analysed the impact of lurasidone on agitation in hospitalized patients with schizophrenia experiencing acute exacerbations.[40] Data pooled from five randomized, double-blind, placebo-controlled, 6-week studies of lurasidone were analysed (Table 3).[24–28] These patients, aged 18–75 years, exhibited acute psychotic symptoms (as indicated by CGI-S scores ≥4 and PANSS total scores ≥80), with specific criteria on PANSS items.

The primary focus of this analysis was agitation, measured by the PANSS–Excited Component, a composite score comprising excitement, hostility, tension, uncooperativeness and poor impulse control. Amongst patients with higher baseline agitation levels (PANSS–Excited Component score ≥14), lurasidone exhibited significant improvement *versus* placebo at day 3/4 (−1.6 *versus* −1.0; p<0.05), day 7 (−2.3 *versus* −1.6; p<0.05), and the week 6 endpoint (−5.5 *versus* −3.8; p<0.001; effect size 0.43). Even in patients with lower baseline agitation, lurasidone demonstrated notable improvement from day 7 (−0.8 *versus* −0.1; p<0.01) through week 6 (−1.9 *versus* −0.9; p<0.001; effect size 0.31). Higher doses of lurasidone proved to be more effective, especially in patients with severe agitation at the study's onset.

Srisurapanont et al. conducted a comprehensive meta-analysis to evaluate the dose–response effects of lurasidone in acute schizophrenia. The aim of the study was to compare the therapeutic and adverse effects of

Figure 1. Week 6: Positive and Negative Syndrome Scale (PANSS) factor score effect size.

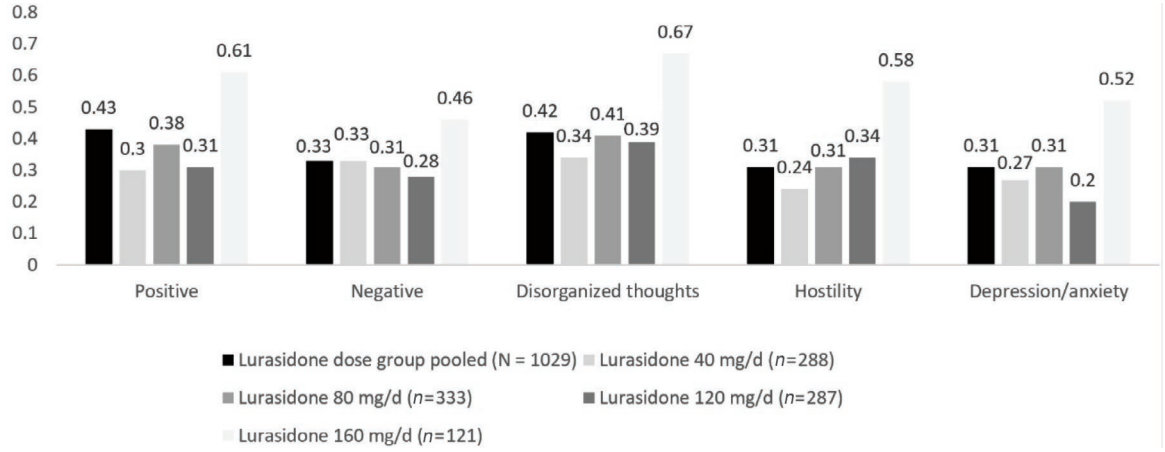


Table 3. Summary of the studies included in the pooled analysis by Alan et al.[24–27,40]

Study number	Study medication	Number of patients
Study 1[25] (phase II), 15 USA sites	Lurasidone 40 mg/day	49
	Lurasidone 120 mg/day	47
	Placebo	49
Study 2[40] (phase II), 22 USA sites	Lurasidone 80 mg/day	90
	Placebo	90
Study 3[26] (phase III), multinational, 48 sites (21 USA sites)	Lurasidone 40 mg/day	121
	Lurasidone 80 mg/day	118
	Lurasidone 120 mg/day	123
	Placebo	124
Study 4[24] (phase III), multinational, 52 sites	Lurasidone 40 mg/day	118
	Lurasidone 120 mg/day	118
	Placebo	114
	Olanzapine 15 mg/day	121
Study 5[27] (phase III), multinational, 63 sites (24 USA sites)	Lurasidone 80 mg/day	115
	Lurasidone 160 mg/day	121
	Placebo	120
	Quetiapine 600 mg/day	116

different lurasidone doses as well as other antipsychotics and placebo.[41] The study encompassed the analysis of ten 4–16-week, fixed-dose, randomized controlled trials involving adults with acute schizophrenia.[24–28,42–46] Various lurasidone doses (20, 40, 80, 120 and 160 mg/day) were explored across ten trials involving a total of 3366 patients. The results showed that a high dose of lurasidone (160 mg/day) achieved significantly greater reductions in PANSS total scores compared to lower doses (mean differences ranged from −7.63 to −12.25). Additionally, participants receiving lurasidone at 160 mg/day and 80 mg/day exhibited significantly lower all-cause dropout rates compared to those on placebo. The analysis suggested that the half-maximal effective doses for reducing PANSS total, PANSS positive, and Montgomery Asberg Depression rating scale (MADRS) scores might surpass 80 mg/day. As per the analysis, lurasidone at 160 mg/day emerged as the most efficacious and acceptable dose for acute schizophrenia.

However, a real-world evidence retrospective study conducted in Spain (Retrolur Study) showed that, despite the

positive results obtained with high doses of lurasidone, in daily clinical practice, lower doses were most commonly used. In this study, conducted by Mora et al., patients were enrolled between 1 September 2019 and 31 March 2022 in four participating hospitals.[47] The study used EHRead®[48], an innovative technology that applies natural language processing and machine learning to extract, organize and analyse the unstructured clinical information jotted down by health professionals in patients' electronic medical records from the participating hospitals. A total of 272 patients were included in the study (60.3% women and 39.7% men), with a mean age (SD) of 45.9 (13.1) years (5.1% between 18 and 25 years of age; 40.1% between 25 and 45 years of age; 47.8% between 45 and 65 years of age; and 7% >65 years of age). Figure 2 summarizes the baseline demographic and clinical characteristics as well as the dose of lurasidone prescribed at baseline, the maximum dose during lurasidone treatment period, and the reduction in psychiatric signs and symptoms. As noted in Figure 2, the percentage of patients receiving high doses was very low (between 0.9% and 1.2%) compared to the percentage of patients receiving low and medium doses (37 mg, range 37.8–48.1%; 74 mg, 25.9–41.5%). It was concluded in the study that, in addition to low dosages, delays in treatment initiation and combination with other antipsychotics may have masked the full potential of lurasidone use.

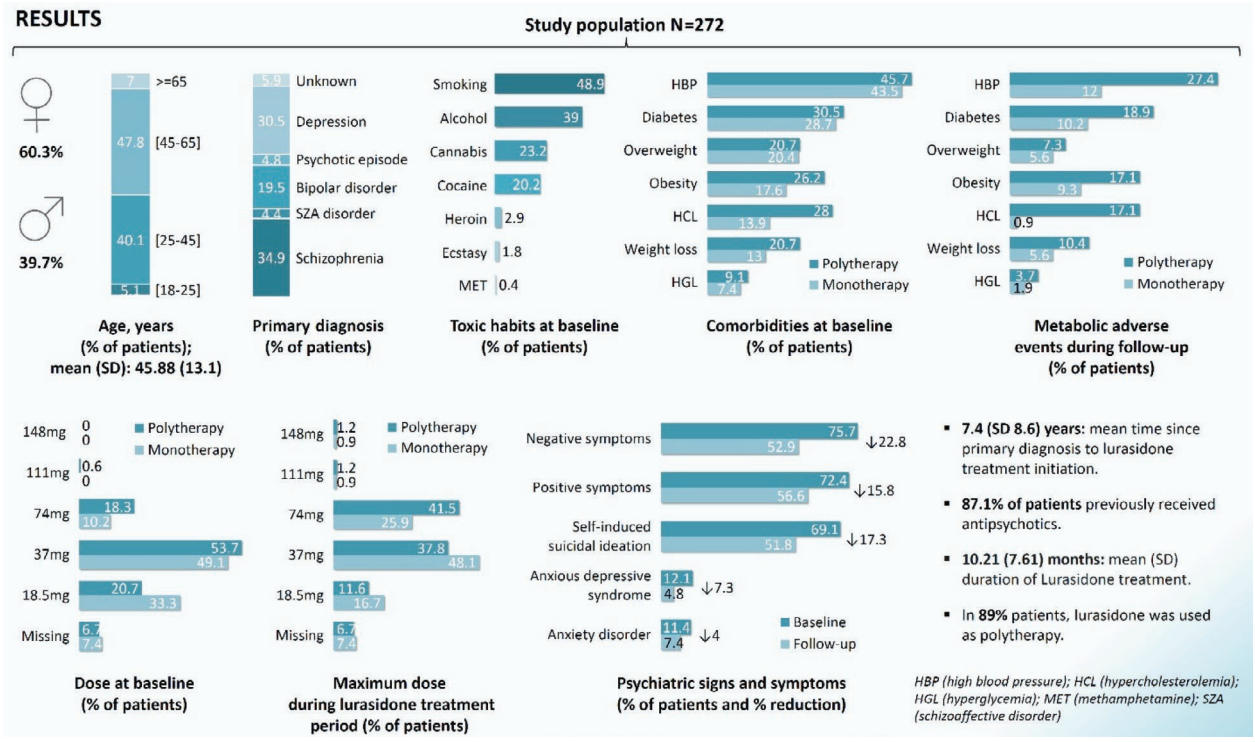
It is therefore important to emphasize that lurasidone dosage can be increased beyond 74 mg for patients who may need it, such as those with acute conditions or dual diagnoses. In these cases, the dosage can go up to 148 mg, as this is known to best control agitation and is the most effective across all domains of the PANSS scale.

Efficacy of lurasidone in reducing PPD in dual psychosis

The term 'post-psychotic depression' refers to the phase subsequent to the acute phase of schizophrenia and its definition has evolved throughout time, from "future rejection and hopelessness as a way of reacting after a psychotic experience" to "post-psychotic collapse"[49,50]. Guerrero-Jiménez et al.[50] highlighted the evolving perspective on schizophrenia, remarking, "While our attention historically focused on hallucinatory delusions, recent years have underscored the emotional facet as integral to psychotic patients' recovery process".

PPD significantly exacerbates the prognosis during the initial stages of psychoses.[50] Notably, substance-induced psychosis stands out as a risk factor for subsequent unipolar depression or anxiety disorders following the primary psychotic episode.[30] The challenges in distinguishing PPD render it a clinically prevalent issue, increasing the risk of

Figure 2. Baseline characteristics and preliminary results of Retrolur study.[47]



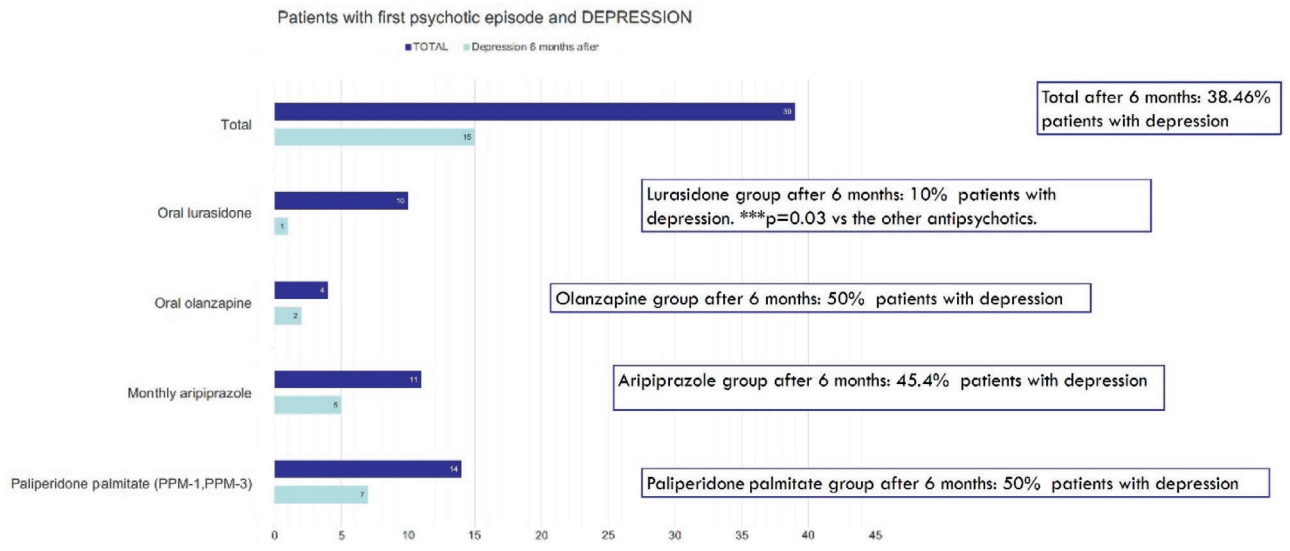
suicide and impairing mental faculties. Although treatment with antipsychotics for PPD is desirable, there remains no consensus on the most efficacious antipsychotics.[51] The efficacy of antipsychotics in addressing depressive symptoms in psychotic patients is limited, with lurasidone and clozapine emerging as notable exceptions.[31]

The effectiveness of lurasidone in mitigating PPD in dual psychosis was the focus of a recent observational prospective study conducted in Spain.[52] The study assessed PPD in 39 individuals who experienced a single psychotic episode induced by substances at 6 months following the episode, using the Montgomery-Asberg Depression rating scale. The patients received outpatient treatment, and their psychotic symptoms were evaluated using the Brief Psychiatric Rating Scale. The presence of depressive disorder (score exceeding 12 points) was examined concerning the prescribed antipsychotic in monotherapy. The average age of the participants was 20.1 (SD 2.4) years, with a majority being men (67%). Preceding the psychotic episode, 80% used cannabis, 10% used cocaine, and the remaining used both substances. At the evaluation time, all participants were abstinent, confirmed by negative urinalysis for substances. Treatment consisted of 14 patients receiving once-monthly paliperidone palmitate (mean dose 98.5 mg/month, SD 5.6), 11 patients on once-monthly aripiprazole (mean dose 400 mg/month), 4 patients on oral olanzapine (mean dose 12.5 mg/day, SD 2.3) and 10 patients on oral lurasidone (mean dose 82 mg/day, SD 5.7). The mean score on the Brief Psychiatric Rating Scale was 6.8 (SD 1.2) points. Overall, 38.46% of the population of the study demonstrated depression 6 months after the initial psychotic episode using the Montgomery-Asberg Depression rating scale. The percentage of patients that exhibited depression after treatment was significantly lower in the lurasidone arm *versus* the other treatments (10% *versus* 45.4% with aripiprazole and 50% with paliperidone palmitate and olanzapine; $p<0.03$) (Figure 3).

Assessing tolerability, two patients on olanzapine exhibited significant weight gain (>5% of total body weight), whilst three patients on once-monthly paliperidone palmitate experienced hyperprolactinaemia and associated sexual dysfunction. Conversely, no notable adverse effects were observed in the group receiving once-monthly aripiprazole or lurasidone. The findings suggest a potential association between the antidepressant efficacy of lurasidone and the prevention of PPD in the subset of patients experiencing induced psychosis. The alleviation of depressive symptoms may contribute to enhanced functional recovery and reduction in suicidal tendencies linked with depression. These findings were also reported in a recent case report by Oguchi et al. outlining the case of a young male patient in his 20s with schizophrenia who developed PPD, including despair, overwhelming loss, humiliation and suicidal thoughts during paliperidone treatment. Upon transitioning to lurasidone, the depressive symptoms vanished without relapse, thereby enhancing social functioning.[51]

The efficacy of lurasidone in cannabis-induced psychosis has recently been shown. Ricci et al. analysed the efficacy of lurasidone in four patients receiving treatment for their first cannabis-induced psychotic episode.[53] The clinical picture of psychosis improved in all patients. In addition to the positive and negative symptoms disappearing, recovery also concerned the resumption of functioning in relation to disruptive

Figure 3. Percentage of patients with depression after 6 months of treatment.[51]



behaviour. Lurasidone was used to treat each patient, with a daily target dose ranging from 74 to 128 mg. There were no noteworthy side-effects noted.[53]

Recommendations for the use of combination treatment

Fiorillo et al. recently provided a clinical opinion and guidance about the use of lurasidone supported by a review of its pharmacokinetic and pharmacodynamic properties as well as efficacy and tolerability.[12] Lurasidone is effective in managing acute schizophrenia phases and preventing relapse. Known for its favourable tolerability profile with minimal impact on metabolic parameters, weight and prolactin levels, lurasidone has demonstrated efficacy across various schizophrenia symptoms, including positive, negative and cognitive aspects, making it a promising choice for personalized schizophrenia treatment.[3] The prudent selection of doses for individual patients and the temporary integration of lurasidone with other medications, like benzodiazepines for insomnia or agitation, beta-blockers for akathisia, antihistamines, or antimuscarinic drugs for patients swiftly transitioning from antipsychotics with significant antihistamine and/or anticholinergic properties, are critical for treatment efficacy.[54–59]

The standard dose initiation of lurasidone is at 37 mg daily, advised to be taken with a meal providing a minimum of 350 calories. Subsequently, the daily dosage can be escalated to 74 mg for adolescents and 148 mg for adults, guided by clinician discretion. In practice, dosage elevation by 37 mg every 1–5 days, based on symptom severity and tolerability, is common. Patients displaying good tolerability but inadequate symptom control at lower doses often benefit from higher lurasidone doses. Patients with pronounced positive symptoms or agitation frequently require the full 148 mg/day dosage, except in cases of significant dose-related side-effects. Nonetheless, considering their clinical experience, Fiorillo et al. recommended administering at least 74 mg daily for adolescents and up to 148 mg for adults to facilitate complete remission of positive, negative and cognitive symptoms.[12]

Due to its relatively favourable metabolic risk, lurasidone is often the initial antipsychotic choice for patients at risk of or already with obesity, diabetes, or dyslipidaemia or those requiring an antipsychotic switch. The potent antidopaminergic properties of lurasidone generally mitigate the risk of dopaminergic rebound during the transition. However, the absence of significant antihistamine and anticholinergic properties suggests a gradual cross-taper (or temporary combination with an antihistamine and/or anticholinergic agent) when transitioning patients from highly antihistaminergic or antimuscarinic medications like olanzapine, quetiapine or clozapine to lurasidone.[12] In cases of akathisia, recommendations include (1) reducing lurasidone dosage when viable or (2) combining lurasidone with a benzodiazepine or beta blocker; (3) if severe and unresponsive to the aforementioned interventions, switching to medications less likely to cause akathisia, such as quetiapine or clozapine. In a study administering lurasidone in the evening,[32] 7.4% of patients receiving 148 mg/day reported akathisia. Evening administration, particularly when combined with a benzodiazepine, may yield a more favourable tolerability profile compared to morning dosing. For patients exhibiting temporary agitation or insomnia that could benefit from sedative medications, combination with other treatments, such as benzodiazepines or antihistamines, is recommended, aiming to discontinue these once symptoms are under control. During the transition from antipsychotics with high H1-receptor affinity (e.g. olanzapine or quetiapine) to lurasidone, caution is essential to prevent histaminergic (and/or anticholinergic) withdrawal/rebound symptoms (e.g. activation, agitation or insomnia). Prolonging cross-titration, reducing pre-switch antipsychotic dosage very gradually post-reaching full lurasidone dosage, ideally over a period of at least 1 month or longer, is recommended.[12]

Clinical cases of use of lurasidone in adult population

Real-life cases presented herein illustrate how lurasidone can be used to treat adult patients with cognitive symptoms, to achieve functional recovery and improvement in quality of life with appropriate high-dose treatment to treat depressive episodes associated with schizophrenia as well as first psychotic episodes and dual pathology associated with psychotic disorder.

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

Case 1: schizophrenia and cognition

Reason for consultation

A 55-year-old man diagnosed with paranoid schizophrenia sought outpatient follow-up due to relocation. He had experienced a history of psychotic episodes, presenting auditory hallucinations, delusions and cognitive difficulties since age 18. Medication changes due to side-effects led to symptom recurrence. At the time of consultation, cognitive symptoms included attention and working-memory issues, impacting reading and daily functioning.

Physical and psychopathological exams and complementary tests

Physical exam: grade I obesity.

Psychopathological exam: oriented in the three spheres, remaining calm and collaborative, with normoprosexia in the interview but with subjective perception of hypoprosexia and poor working memory in intellectual activities. Mild ideo-affective impoverishment, without other associated affective alterations. Spontaneous, logical and coherent speech, which does not transduce other formal alterations or the content of thought. No sensory-perceptive alterations. Preserved sleep, predominantly nocturnal hyperphagia and decreased libido. Denied auto-heterolytic ideation. Presented adequate awareness of illness, with preserved judgment of reality and volitional capacity.

Complementary tests: Blood tests showed dyslipidaemia, otherwise normal.

Differential and final diagnosis

Differential diagnosis: the differential diagnosis was made mainly between schizophrenia and delusional disorder because there was no evidence of affective clinical symptoms.

Final diagnosis: it is most likely that the cognitive symptoms are related to schizophrenia and treatment with antipsychotics.

Treatment

In the first consultation, the patient was informed of the existence of new drugs with fewer adverse effects. After jointly assessing the possible risks and benefits of changing the pharmacological regimen, the patient and the family agreed to make such a change. Initial treatment was paliperidone 6 mg/day and olanzapine 5 mg/day, which was progressively replaced by lurasidone 148 mg/day in a single nightly intake. The patient was scheduled for successive consultations every 15 days, making pharmacological adjustments over 5 consultations (Table 4).

Follow-up

During the 5 months of follow-up, the patient did not show delirious or hallucinatory activity and tolerance to the new treatment was very good. On a cognitive level, since the reduction of paliperidone to 3 mg, he reported improvement. This perception gradually increased after completing the treatment change, with improvement in reading speed and ability to concentrate. At the time of writing, he showed great satisfaction with the treatment, because he was better able to enjoy reading. It was necessary to reorganize dietary habits towards healthier ones. Previously, he had very light dinners with a habit of snacking at night. He began to have dinners with an adequate caloric intake that allows adequate absorption of lurasidone. The nocturnal hyperphagia subsided after complete discontinuation of olanzapine. On the other hand, night rest was prolonged to 9 hours a day and improvement was perceived in the sexual sphere.

Treatment rationale

Antipsychotic monotherapy is recommended by different clinical guidelines over polytherapy, such as the Maudsley Prescribing Guidelines,[60] because it presents fewer adverse effects. However, in this case, it is likely that polytherapy was chosen in the past given that the prescribed psychotropic drugs were not tolerated at sufficient doses.

In several studies it has been observed that lurasidone in high doses improves the cognitive performance and functionality of patients with schizophrenia,[61,62] being the main reason why this drug is selected. However, it has a better profile of adverse effects also at the metabolic level and in the sexual sphere, being well tolerated at high doses, which could allow antipsychotic treatment in monotherapy.[63] Furthermore, nocturnal somnolence secondary to treatment was considered beneficial to promote clinical stability because the appearance of

Table 4. Treatment adjustments in Case 1.

Visit	Lurasidone dose	Olanzapine dose	Paliperidone dose
First visit	Lurasidone 18.5 mg Dose increased to 37 mg after 1 week	Olanzapine 5 mg	Paliperidone 6 mg
Second visit	Lurasidone 74 mg	Olanzapine 5 mg	Paliperidone 3 mg
Third visit	Lurasidone 111 mg	Olanzapine 5 mg	
Fourth visit	Lurasidone 148 mg	Olanzapine 2.5 mg	
Fifth visit	Lurasidone 148 mg		

delirious symptoms is preceded by global insomnia for several weeks.

Conclusions

The cognitive dimension of psychosis is progressively gaining relevance in scientific literature. Some studies indicate that the level of functional impairment in schizophrenia or type 1 bipolar disorder, at 1 year of follow-up, correlates with previously observed dysfunctions in verbal memory or vocabulary rather than with the level of positive symptomatology.[64] Likewise, deficits in verbal memory in first psychotic episodes were associated with a worse functional outcome.[65] Moreover, cognitive symptoms are also important on a subjective and personal level.

According to Maslow,[66] human motivation is guided by a series of needs, which are structured hierarchically, making it necessary to satisfy the most basic needs, which are located at the bottom of the pyramid, to qualify for those in higher positions. Therefore, the remission of positive symptoms is not sufficient if the disease itself or the adverse effects of treatment interfere with physical, mental or social well-being. We consider that it is imperative to improve management of patients with schizophrenia to fulfil their vital needs.

Case 2: schizophrenia, functional recovery and quality of life

Reason for consultation

A 41-year-old woman was referred for anxiety, persistent thoughts of death and unsettling bodily sensations. She reported feeling unwell for months, attributing an ex-partner's illness to guilt from past activities. She maintained daily activities but avoided social interactions due to guilt-related distress. Living with a sister, the patient showed a history of mental health treatment with varied medications but discontinued due to adverse effects like weight gain and mental dullness.

Physical and psychopathological exams and complementary tests

Physical exam: conscious, globally oriented and collaborative. No extrapyramidal symptoms. Overweight. Normotensive.

Psychopathological exam: psychopathological evaluation revealed delusional guilt, auditory hallucinations and feelings of being watched, signalling potential paranoid schizophrenia.

Complementary tests: normal blood count, biochemistry and serology. Prolactin normal, previously elevated. Skull CT normal.

Differential and final diagnosis

Differential diagnosis: due to the patient's symptoms, the following diagnoses were considered: obsessive-compulsive disorder, depressive disorder and psychosis. Together with a torpid evolution, with negative symptoms, the diagnosis of schizophrenia was suggested.

Final diagnosis: paranoid schizophrenia.

Treatment

Treatment was started with lurasidone, gradually increased to 148 mg/day, complemented by clonazepam and flurazepam for adjunctive support.

Follow-up

Initial unease limited interactions, opting for outpatient management for family support. A brief hospital stay led to symptom improvement, notably reduced anxiety, increased social engagement and minimized guilt. Whilst some symptoms persisted, there was gradual progress seen in social activities and emotional resonance.

Treatment rationale

This patient with schizophrenia rejected already used antipsychotics (olanzapine, risperidone, aripiprazole) and presented with secondary depressive symptoms. An effective antipsychotic treatment, with a profile of potential adverse effects appropriate for the patient's situation, was then selected. Lurasidone has been shown to have the same effectiveness as others, with only clozapine being superior.[31] The receptor profile (5-HT_7) suggests favourable antidepressant potential.[16] The antipsychotic used has an adequate profile at the metabolic level,[67] something relevant given the background of the patient. Likewise, it has few extrapyramidal effects. The history of elevated prolactin shows the appropriateness of avoiding powerful dopaminergic blockade, with lurasidone presenting a slight increase in this.[65] Furthermore, the patient expressed wishes to work, having graduated in the past, so an antipsychotic without major deleterious effects at the cognitive level was chosen.[43] The differential diagnosis with obsessive-compulsive symptoms becomes important, because if they were pure obsessive-compulsive symptoms, these could be worse with the use of some antipsychotics by blocking the serotonergic receptors 5-HT_{2C} and 5-HT_{2A}.[68,69] The dose–response relationship justifies the increase in doses compared to those currently used (148 mg/day).[70]

Conclusions

The case underscores the significance of tailoring treatments to enhance functionality and quality of life, with lurasidone showcasing promise in improving cognitive function and minimizing adverse effects, aiding in work performance, and sustaining a better overall condition without significant metabolic or hormonal impacts.

Case 3: schizophrenia with predominant depressive symptoms

Reason for consultation

A 69-year-old woman, diagnosed with paranoid schizophrenia at age 28, presented with worsening symptoms, including depressive manifestations, and family discordance. It started with delusional symptoms at age 26 and progressed to auditory hallucinations, leading to hospitalization and subsequent erratic adherence to treatment. Later, she shifted to long-acting antipsychotic with limited improvement. A recent 10-month decline was marked by social isolation, inactivity and increasing psychotic symptoms. At the time of consultation, the patient experienced guilt and worthlessness, exacerbated by family criticism. Passive suicidal ideation emerged. She was offered inpatient care, declined in favour of outpatient follow-up. Treatment included sertraline, olanzapine and a long-acting antipsychotic.

Physical and psychopathological exams and complementary tests

Physical and psychopathological exam: physical and psychopathological exams revealed depressive symptoms, guilt, isolation and passive suicidal thoughts. Blood tests showed typical parameters with signs of prior pharmacological treatment.

Complementary tests: a blood test was performed with parameters within the normal range except for hypercholesterolaemia and hyperglycaemia.

Differential and final diagnosis

Differential diagnosis: although the patient had been worsening for approximately a year, the clinical history showed a certain progressive deterioration that first forced us to rule out that the current condition was a negative clinical picture associated with paranoid schizophrenia. This option was ruled out given that the patient presented affective resonance appropriate to the story, a tendency to cry, and a feeling of worthlessness and guilt that were not associated with her underlying psychotic symptoms. Given the worsening of psychotic symptoms and delusional ideation of harm and self-referentiality, it could be a case of psychotic decompensation, but those symptoms had been accompanied by a depressed mood, which suggested a major depressive episode that worsened the basic psychotic and delusional symptoms. In relation to the affective symptoms, the patient had not presented recurrent depressive episodes or manifest symptoms that could indicate a schizoaffective disorder.

Final diagnosis: paranoid schizophrenia alongside major depressive disorder.

Treatment

Intramuscular paliperidone palmitate (150 mg/28 days, im), sertraline (200 mg/day) and lurasidone (37 mg/day) were initiated. Adjustments were made to improve mood, reduce irritability and contain psychotic symptoms.

Follow-up

Improved mood and behavioural activation were noted with treatment adjustments. Referral to a day hospital was suggested, which was declined by patient and family. Family dynamics were addressed to reduce criticism. Sertraline dose was reduced due to positive response.

Treatment rationale

This patient was diagnosed with paranoid schizophrenia and presented a major depressive disorder. Given the depressive symptoms, the decision was initially made to start the antidepressant sertraline, maintaining nocturnal olanzapine to alleviate the anxiety and worsening of psychotic symptoms. Given the persistence of affective symptoms as well as weight gain in patients with cardiovascular risk factors, a change from olanzapine to lurasidone was chosen given that this drug has a better metabolic profile with a lower risk of weight gain and metabolic syndrome.[71] On the other hand, there is evidence that lurasidone is more effective in depressive symptoms due to its receptor profile. Specifically, 5-HT_7 antagonism and partial 5-HT_{1A} agonism could translate into improvement in cognition, memory and learning as well as affective and negative symptoms.[71]

Conclusions

In this clinical case, the patient presented with multiple episodes of psychotic decompensation along with a depressive episode. The use of two antipsychotics and an antidepressant was aimed at achieving functional recovery of the patient. Although clinical guidelines recommend antipsychotic monotherapy as much as possible, in this case, due to the patient's lack of awareness of the disease with poor therapeutic adherence combined with poor family support, two antipsychotics were chosen. Lurasidone was selected due to its receptor profile as well as the lower metabolic risk in patients with several cardiovascular risk factors.[18,72]

Case 4: first psychotic episode

Reason for consultation

A 37-year-old woman presented to psychiatric emergency services with behavioural disturbances, disorganization and a sense of strangeness. She initially sought care for insomnia, anxiety and sadness and later progressed to negative ruminations and fears. Consultation history revealed bizarre behaviours and psychotic symptoms, leading to admission. She had no family psychiatric history, had some somatic issues and had recently migrated to Spain.

Psychopathological exams and complementary tests

Psychopathological exam: patient showed perplexity, self-referentiality, delusional ideation, auditory hallucinations and poor insight.

Complementary tests: a blood test was performed, the results of which were unremarkable. A brain MRI was also performed in which no notable findings were observed.

Differential and final diagnosis

Differential diagnosis: given the anxious and affective symptoms that motivated the first consultation and considering the patient's migration history and unfavourable socioeconomic context, it was initially oriented as an adaptive disorder secondary to environmental stressors. Furthermore, with the prescription of anxiolytic and antidepressant treatment, this condition improved significantly. The subsequent worsening in the form of slowing down, perplexity, catastrophic cognitions and, finally, delusional and self-referential symptoms led us to hypothesize a progression of the adaptive condition to a major depressive disorder with psychotic symptoms. However, the characteristics of these psychotic symptoms allow us to bet on the diagnosis of a first primary psychotic episode. The patient had a feeling of strangeness that she described as living in a movie or a dream, and this was accompanied by self-referentiality in public. Gradually, more complex delusional symptoms were added, such as the belief that her mother had been impersonated (Capgras phenomenon) or that her technological devices were hacked.

Final diagnosis: looking back, the adaptive picture could be considered a plot of psychotic debut. The patient's descriptions coincided, in fact, with some examples from Conrad's classic treatise, with the initial depression and delirious mood being especially notable in our case, as she had verbalized a feeling of strangeness, of being alive in a movie or in a dream.

Treatment

At a pharmacological level in the emergency room, olanzapine 5 mg was started, optimized to 10 mg/day at the beginning of home admission. With this dose, she maintained psychotic symptoms with the same intensity, and family members reported a greater tendency to isolate herself in the room due to pharmacological sedation. For this reason, and considering the affective component of the condition, it was decided to change the antipsychotic to lurasidone up to 74 mg/day and olanzapine was withdrawn. With this change, the sedation that interfered so much with the patient disappeared. Citalopram was maintained throughout the hospitalization given the good initial response and the doubt about the emotional origin of the condition.

Follow-up

After the pharmacological change, a notable improvement in the patient's psychopathological state was observed with adaptation of the contact, appearing less scared and interfered with. Subsequently, a brief clinical deterioration, linked to reduced caloric intake and medication, was observed, followed by a subsequent improvement after dietary adjustments. Finally, given clinical stability obtained and recovery of usual functionality, the patient was discharged to specialized outpatient follow-up for first psychotic episodes.

Treatment rationale

Sometimes, psychiatrists can rush into assigning a diagnosis that will mark the patient's trajectory, partly due to the needs of the health system. Therefore, longitudinal patient follow-up is essential because symptoms can evolve and be redefined in another final diagnosis.[73] In this case, we had to question the aetiological framework that explains the first psychotic episode: an affective disorder or a primary psychotic disorder. Due to time constraints, the choice of antipsychotic had to preserve the two diagnostic options as much as possible. In this sense, lurasidone represented an innovation due to its receptor profile of action because, in addition to the incisive effect on positive symptoms through its antagonism at the dopamine D2 receptor, it acts as a partial agonist at 5-HT_{1A}, which improves the affective and anxiety symptoms. In addition, it is a 5-HT_7 antagonist, which could improve the cognitive symptoms reported by the patient.[15,74] Additionally, lurasidone has very low affinity to muscarinic or histamine receptors, which made it possible to reduce side-effects such as sedation, which in this case was an advantage in the evolution from acute admission.[15]

Conclusions

Some non-specific symptoms, such as anxiety, sadness or apathy, can be part of both a depressive condition and a primary psychosis. In the latter, in addition, they may be the only symptoms that appear in the prodromal phases of the disease. Therefore, the first psychotic episodes with affective symptoms can be difficult to catalogue from the beginning, and only the longitudinal follow-up of the patient will allow definition of the diagnostic translation of these first symptoms. Treatment, however, must be started early because clinical studies have confirmed that delaying the start of medication implies a worse prognosis.[75] In these cases where there is underlying doubt that there may be an emotional component of the condition, it is important to choose a drug that respects this sphere. Lurasidone is

a good pharmacological option that effectively affects psychotic symptoms and preserves this emotional and cognitive sphere.

Case 5: dual psychosis

Reason for consultation

A 42-year-old woman sought psychiatric help after a suicide attempt, presenting with depressive symptoms and auditory hallucinations. Over a 7-month period, she experienced depressive symptoms and auditory hallucinations of criticism from her cousin. She attempted suicide by overdosing on lorazepam. Initial treatment with olanzapine and sertraline showed minimal improvement. Employed as a domestic worker, she resided with her family and denied any prior psychiatric history. No family psychiatric background was reported. She admitted to using cocaine for about 8 months.

Physical and psychopathological exams and complementary tests

Physical and psychopathological exam: initial psychopathological examination showed the patient was alert, conscious and oriented. Attention and memory without alterations. Slightly slowed down at a psychomotor level. Perplexed look. Coherent, linear speech, from which delusional ideas of harm were inferred, as well as auditory hallucinations of contemptuous content locates inside her head. Hypothymia, apathy and tendency to clinophilia. Internal anguish. Fragmented sleep, with inversion of the sleep–wake cycle. Awareness of present illness. She denied autolytic ideation. Impaired judgment of reality.

Complementary tests: in the emergency room, a cranial CT scan was also performed without any findings of acute intracranial pathology. In addition, a blood test was performed, with no biochemical or haematological alterations of interest. However, urine tests confirmed cocaine use.

Differential and final diagnosis

Differential and final diagnosis: although the initial diagnostic orientation was a major depressive disorder with psychotic symptoms or a psychotic condition with predominance of depressive symptoms, the finding of toxins in the urine points us towards leading to a diagnosis of cocaine-induced psychotic (CIP) disorder. Once this fact was known, the patient acknowledged having started using about 8 months ago. The symptoms described would always have appeared in the context of cocaine consumption, subsiding days later. The family also began to be aware of the presence of fluctuations in the intensity of symptoms, in relation to periods of abstinence and intoxication.

Treatment

It was decided to proceed with a multidisciplinary approach in which specialists from the addiction treatment centre intervened to promote the cessation of consumption. At a psychopharmacological level, the regimen of sertraline 100 mg/24 hours in combination with lurasidone 74 mg/24 hours was maintained.

Follow-up

With continuous treatment, the patient showed gradual improvement, achieving abstinence, remission of psychotic symptoms, and mood enhancement. She maintained medication adherence and gained weight.

Treatment rationale

CIP disorder often involved transient psychotic symptoms related to cocaine use. Atypical antipsychotics like lurasidone effectively treat CIP disorder and pre-existing mental disorders in cocaine users. The receptor profile of lurasidone contributed to its efficacy, exhibiting fewer side-effects.[15]

Conclusions

The consumption of substances such as cocaine can cause the appearance of very varied psychiatric symptoms. It is essential to make an adequate differential diagnosis between a primary psychotic disorder and a CIP disorder. Atypical antipsychotics have been effective in the treatment of patients with CIP disorder and drug users with a pre-existing mental disorder. Lurasidone is an atypical antipsychotic that has demonstrated efficacy in the treatment of psychotic, depressive, anxiety and cognition symptoms, with a good safety and tolerability profile.[74–77]

Case 6: schizophrenia and metabolic syndrome

Reason for consultation

A 29-year-old female patient with schizophreniform disorder, type 2 diabetes mellitus and obesity was admitted to the Medium Stay Psychiatry Unit to address lifestyle changes and functional recovery. The patient, diagnosed with schizophrenia, had a history of hospital admissions and stable outpatient follow-ups. However, comorbidities, including metabolic syndrome, exacerbated negative symptoms, leading to a reduced life expectancy. She had a complex medical history involving neurological, mental health and metabolic issues. Known conditions included narcolepsy, chronic interstitial gastritis, obesity and sleep apnoea.

Physical and psychopathological exams and complementary tests

Physical exam: physical examination revealed obesity-related concerns.

Psychopathological exam: the patient was oriented in the three spheres. Collaborative, good eye contact. No anxiety symptoms. Speech without alterations in the form or content of thought. Apathetic clinic, tendency towards clinophilia, anhedonia. Hyperphagia, with impulsive eating behaviours. Appropriate judgment of reality.

Complementary tests: blood analysis showed abnormalities in cholesterol, glucose and triglycerides.

Differential and final diagnosis

Differential diagnosis: the patient had favourable control of psychotic symptoms but with a metabolic and apathetic problem that interfered with her daily life. She presented abdominal obesity, diabetes mellitus, hypercholesterolaemia and respiratory complications, which make medical intervention necessary. The change in pharmacological treatment was evaluated to achieve an improvement in the metabolic syndrome as well as to request new intervention by the Endocrinology Service to review the treatment. This patient had a high cardiovascular risk, with a decrease in quality of life and life expectancy. The concern in mental health about the impact of antipsychotic treatments on the risk of premature mortality is related to the case described.

Final diagnosis: the patient was diagnosed with a schizophrenic disorder that implied the medium- and long-term need for antipsychotic treatment, choosing the most appropriate option considering the characteristics of the patient.

Treatment

Before being admitted in the Medium Stay Unit, the patient was receiving mental health treatment with clozapine (400 mg/day), amisulpride (800 mg/day), trihexyphenidyl (2 mg/day), topiramate (400 mg/day), gabapentin (1200 mg/day) and trazodone (100 mg/day). Treatment for metabolic syndrome included dapagliflozin (10 mg/day), rosuvastatin (20 mg/day) and fenofibrate (145 mg/day). Although a specific treatment for narcolepsy was not initially prescribed, a worsening of the condition was observed. Therefore, it was considered important to ensure and facilitate the daily administration of two naps (one before eating and the other in the middle of the afternoon) to maintain the current level of stability. Treatment was started with modafinil 200 mg/day but the auditory hallucinations were reactivated, and the dose had to be reduced to 100 mg/day with clinical improvement. Treatment was started with lurasidone 37 mg/day considering that it was an antipsychotic with a profile of less metabolic involvement and less interaction on prolactin levels.[78]

Follow-up

Positive outcomes were observed, including weight loss, improved metabolic parameters and decreased prolactin levels with lurasidone. Additional treatments with semaglutide injections were incorporated for further weight management.

Treatment rationale

Patients diagnosed with schizophrenia and schizoaffective disorder have a higher risk of developing metabolic syndrome, which is associated with increased cardiovascular morbidity and mortality.[15] Treatment with some commonly used antipsychotic medications may increase the risk of developing metabolic syndrome.[79–81] In studies conducted on the use of lurasidone, good tolerance is generally described and it is associated with minimal effects on weight, metabolic parameters and prolactin levels.[79–82] Antipsychotics cause an increase in serum prolactin levels.[79,82] Asenapine, olanzapine and ziprasidone have a milder effect on prolactin levels. Lurasidone and quetiapine do not appear to induce an increase in prolactin.[78] Therefore, in the clinical management of hyperprolactinaemia induced by antipsychotics, a change to a drug with a lower impact profile on prolactin can be considered as in the case described.[81,82]

Furthermore, if pharmacological and dietary measures are not sufficient, other more invasive options could be considered, such as the possibility of placing an intragastric balloon. Due to metabolic syndrome, the patient has reduced life expectancy and quality of life and special attention must be given to these factors.

Conclusions

Studies in adults have shown that switching from an antipsychotic drug with a high risk of metabolic syndrome to lurasidone can improve blood glucose concentrations and other metabolism-related parameters.[78–80] Antipsychotic-induced hyperglycaemia is generally considered to be due to insulin resistance.[81] Obesity is caused by an increase in appetite due to effects on the feeding centre through blockade of serotonin 5-HT_{2C} and histamine H1 receptors.[80,81] However, lurasidone has low affinity for these receptors.[78]

Final remarks

- The treatment approach for schizophrenia requires a comprehensive strategy considering individual patient needs and symptomatology.
- Numerous controlled trials have confirmed lurasidone's effectiveness in improving various aspects of schizophrenia, including positive, negative, affective

and cognitive symptomatology, with 148 mg being the most efficacious dose for all symptoms.
- Lurasidone has shown its efficacy in agitation and hostility control in acutely ill patients, displaying increased effectiveness at elevated doses.
- PPD significantly impacts early psychosis outcomes, suggesting that lurasidone may help manage this aspect.
- Additionally, practical guidance on lurasidone usage includes rapid dose escalation over 1–5 days and recommendations for combining it with other medications such as benzodiazepines for insomnia or agitation, beta-blockers for akathisia, and antihistamines or antimuscarinic drugs for patients transitioning quickly from antipsychotics with significant antihistamine and/or anticholinergic effects.

Contributions: All authors contributed equally to the preparation of this manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: JLPO has received honoraria as a consultant and/or advisor to Angelini, Janssen/J&J and Lundbeck. AC is an employee of Angelini Pharma España SLU. All other authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2024/07/dic.2024-4-4-COI.pdf

Acknowledgements: The authors thank Sofia Perea, PharmD, PhD, for her support in writing the manuscript. Editorial assistance was provided by Content Ed Net (Madrid, Spain) with funding from Angelini Pharma España SLU.

Funding declaration: Angelini Pharma España SLU.

Article URL: https://www.drugsincontext.com/towards-full-recovery-with-lurasidone-effective-doses-in-the-treatment-of-agitation-affective-positive-and-cognitive-symptoms-in-schizophrenia-and-dual-psychosis

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Provenance: Submitted; externally peer reviewed.

Submitted: 16 April 2024; **Accepted:** 28 June 2024; **Published:** 5 August 2024.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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