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Lurasidone in adolescents and adults with schizophrenia: from clinical trials to real-world clinical practice

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ABSTRACT

Introduction: Lurasidone is an atypical antipsychotic agent approved in the European Union for the treatment of schizophrenia in adults and adolescents (13–17 years). Clinical trials have shown a generally favorable balance between efficacy and tolerability.

Areas covered: This paper provides a review and commentary regarding the use of lurasidone in adults and adolescents with schizophrenia. The available information about efficacy, tolerability, dosing, and switching is analyzed, highlighting the strategies that may be most useful in real-world clinical practice. Virtual case studies, designed based on the authors' clinical experience with real-world patients, are provided.

Expert opinion: Lurasidone is efficacious in adolescents and adults in a wide range of symptoms of schizophrenia. Choosing the right dose for each patient and combining lurasidone with other medications is key to treatment success. Lurasidone has proven effective both in adolescents and adults in treating the acute phase of schizophrenia and reducing the risk of relapse. It has shown a relatively favorable tolerability profile, with minimal effects on metabolic parameters and prolactin levels.

1. Introduction

Schizophrenia is a severe mental disorder, which affects approximately 24 million people or 1 in 300 people (0.32%) worldwide, with a peak of onset in the adolescent age and a complex etiopathology [1,2]. Schizophrenia is associated with a significant level of personal and societal burden, and therefore requires an appropriate and integrated management plan [3,4]. It has been widely accepted that the optimal management of a patient with schizophrenia should be personalized and based on the clinical characterization of the individual case, including the assessment of the severity of positive and negative symptoms [5], the type of onset [6], the presence of suicidal ideation [7], the level of neurocognition and of social functioning [8], antecedent and concomitant psychiatric conditions [9], the presence of physical comorbidities [10], the lack of efficacy or incomplete adherence with

previous pharmacological treatments, the family history and the presence of protective factors [11].

All these aspects should be carefully evaluated in order to develop a tailored management plan and to promote patients journey to recovery [12]. In order to personalize the treatment plan, different pharmacological and non-pharmacological interventions can be selected and integrated. In recent years, several new antipsychotic agents have been developed and approved including cariprazine, brexipiprazole, and lurasidone. In particular, lurasidone (LUR) has been approved by the European Medicines Agency (EMA) for the treatment of schizophrenia in adults and adolescents (13 to 17 years) and by the Food and Drugs Administration (FDA) for the treatment of schizophrenia and for bipolar disorder [13]. LUR's efficacy for treating

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schizophrenia was established in short- and long-term controlled studies in adult and adolescent patients with schizophrenia [14]. As a result of this, we provide a clinical opinion and guidance about the use of LUR, supported by: 1) a review of LUR's pharmacokinetic and pharmacodynamic properties; 2) a review of the available literature focusing on the efficacy and tolerability of LUR in the treatment of both acute and stable schizophrenia; 3) our experience with LUR use in clinical practice.

2. Pharmacological profile of LUR

LUR is a benzisothiazole with high binding affinity (0.99, 0.47, and 0.50 nM, respectively) for the dopamine D2, serotonin 5-HT2A, and serotonin 5-HT7 receptors [15]. LUR is a full antagonist at D2, 5-HT2A, and 5-HT7 receptors [15,16] and also blocks α2c-adrenergic and α2a-adrenergic receptors, with a binding affinity of 10.80 and 40.70 nM, respectively. It is also a partial agonist at the 5-HT1A receptor with a binding affinity of 6.38 nM.

Compared to other atypical antipsychotics, LUR shows the highest binding affinity for the 5-HT7 receptor, which may have a role in regulating circadian rhythms and sleep, thermoregulation, learning and memory, and endocrine regulation [17].

Full antagonism at the D_2 receptors in the mesolimbic pathway is believed to be correlated to the beneficial effects on positive symptoms of schizophrenia, such as hallucinations and delusions. Moreover, lurasidone is an antagonist for serotonin 5-HT_{2A} receptor. By this activity, it disinhibits the dopamine neuron, and therefore increases the release of dopamine, which competes with the antipsychotic in the D_2 antagonistic action at D_2 receptors. This mechanism of action reduces the antagonistic binding in several dopaminergic pathways and it is associated with the better tolerability profile of lurasidone [18–22]. In particular, by targeting the nigrostriatal pathway, it reduces extrapyramidal symptoms. In the tuberoinfundibular pathway, this reduces hyperprolactinemia. In the mesocortical pathway and in the prefrontal cortex, it improves the negative,

affective, and cognitive symptoms. Also, the antagonism at 5-HT_{2A} receptors mitigates the serotonergic excitation of the cortical pyramidal cells. This results in a reduction of glutamate release, which in turn may reduce the dopaminergic activity in the mesolimbic pathway and thereby the positive symptoms of schizophrenia [18–22]. LUR's antagonism at the 5-HT7 receptor may contribute to the favorable effects in learning and memory and, more in general, improve the cognitive deficits and the depressive symptoms [23,24]. The partial agonism at the 5-HT1A may contribute, as well, to the antidepressant properties of LUR [16].

However, some lurasidone side effects commonly found in clinical trials include extrapyramidal symptoms/akathisia and anxiety, which could be due to the blockage of D2 and 5-HT2A receptors that confers the property of atypical antipsychotic to lurasidone. The antagonism at the 5-HT7 receptor and partial agonism at the 5-HT1A – which contributes to the antidepressant properties of lurasidone – could explain headache and nausea.

3. Overview of clinical trials of LUR

In the period 2009–2022, several clinical trials have been conducted with a specific focus on the use of LUR in patients with schizophrenia. The following keywords were entered in PubMed, ISI Web of Knowledge, Scopus and Medline: 'schizophrenia,' 'lurasidone,' 'adolescent,' 'pregnancy,' 'substance use,' 'efficacy,' 'tolerability,' 'side effects.' Using this procedure, 820 papers were identified (see Figure 1, supplementary material). After evaluation of abstracts and full texts, we selected 31 papers (Tables 1 and 2); of these, the majority (N = 28) included adult patients (aged 18–75 years), while three papers included adolescent samples (aged 13–17 years).

3.1. Efficacy in adult patients with schizophrenia

According to the results of the network meta-analysis by Huhn et al. [30] focusing on studies for the acute treatment of adults with multi-episode schizophrenia, lurasidone is associated with a significant decrease in overall symptoms of −0.36 Standardized Mean Difference (SMD) with a 95% Confidence Interval (95% CI) ranging from −0.48 to −0.24. Furthermore, treatment with lurasidone is associated with −0.33 SMD (95% CI = −0.45 to −0.20) on positive symptoms, with −0.29 SMD (95% CI = −0.39 to −0.18) on negative symptoms, with −0.20 SMD (95% CI = −0.32 to −0.09) on depressive symptoms, with −0.44 SMD (95% CI = −0.72 to −0.16) on social functioning. The Risk Ratio (RR) for all cause of discontinuation was of 0.88, with a Credible Interval (CrI) ranging from 0.80 to 0.96.

In studies including patients with acute exacerbation of schizophrenia – defined as scoring at PANSS total score ≥80; or score ≥4 on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, suspiciousness, or unusual thought content, at both screening and baseline; or scoring a 4 or higher at CGI-S – LUR provided effective treatment in terms of significant reduction of symptoms' severity, with minimal effects on weight and metabolic parameters [22; 26–34]. Fixed dosages of 80 mg/day (US dose
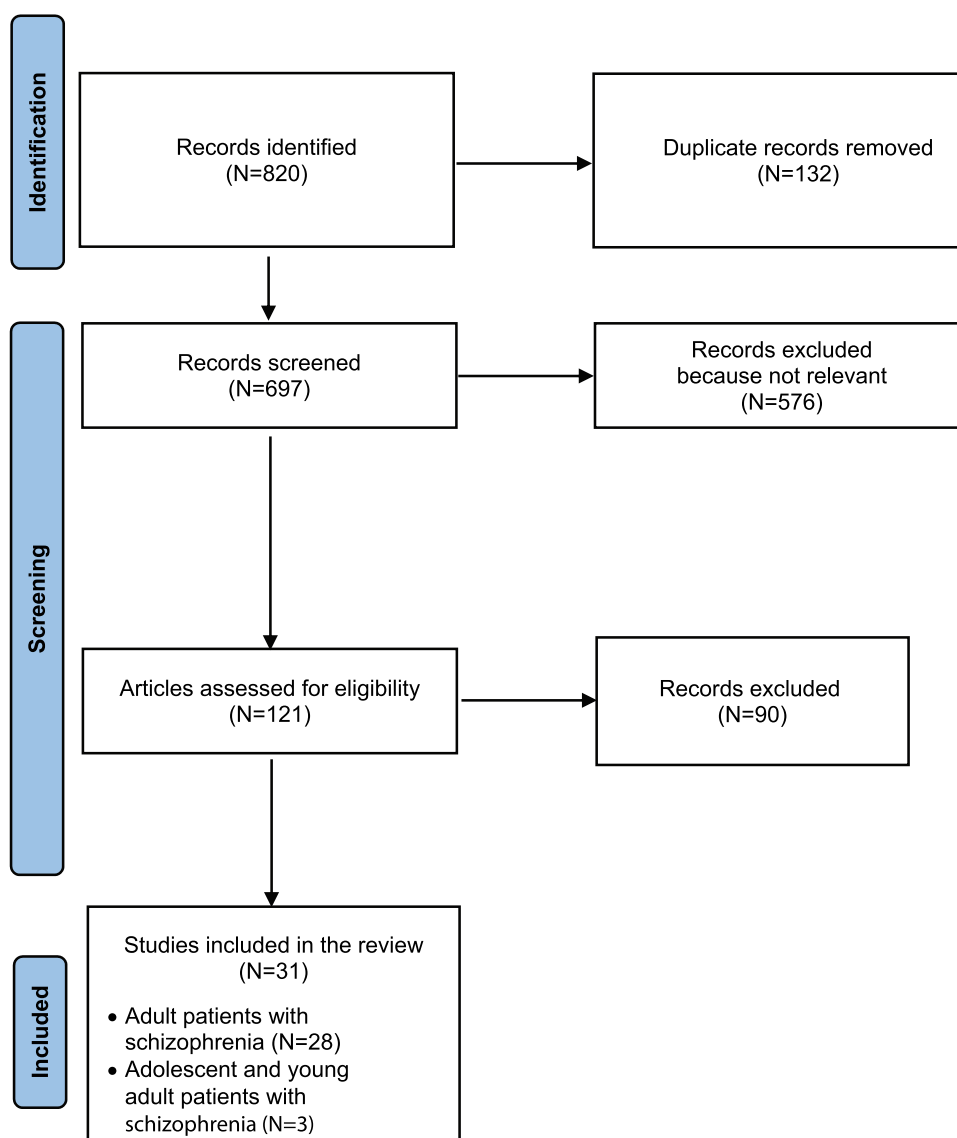
Figure 1. PRISMA flow diagram of of studies selection.

based on LUR hydrochloride salt, corresponding to 74 mg/day of EU dose, based on LUR active moiety) and 160 mg/day (US dose based on LUR hydrochloride salt, corresponding to 148 mg/day of EU doses, based on active moiety) of LUR were effective and well tolerated [31,32].

Studies including stable patients – defined as patients with no change in antipsychotic medications for at least six weeks before screening; no hospitalization for psychiatric illness for at least eight weeks before screening; and <4 severity rating on PANSS items of delusions, conceptual disorganization, hallucinations, and unusual thought content [31–35] – found a significant improvement in symptoms severity at PANSS scale from baseline to (at least) week 6 of treatment in patients receiving LUR 40–80 mg/day (US dose based on HCl salt, corresponding to 37–74 mg/day of EU dose, based as active moiety) and 120–160 mg/day (US dose based on HCl salt, corresponding to 111–148 mg/day of EU dose, based as active moiety) compared to placebo.

A pooled analysis of short-term studies [36] confirmed the efficacy of LUR in patients with acute exacerbation across all five symptom dimensions of schizophrenia (positive, negative, disorganized symptoms, hostility/excitement, and depression/anxiety), suggesting also that the most effective dosage is 160 mg/day.

Long-term effectiveness of LUR was evaluated in double-blind relapse-prevention studies. In particular, the first study was a non-inferiority study assessing LUR versus quetiapine in patients responding to a 6 week trial with LUR or quetiapine [32]. In another study, LUR efficacy was assessed versus placebo In patients who maintained clinical stability with 40–80 mg of LUR for ≥12 weeks and then were switched to LUR maintenance or placebo [37] In one post-hoc analysis of results of a double-blind trial comparing LUR versus risperidone and an additional 6-month open-label extension study where all patients received LUR [34] were identified. In all cases, LUR was found to be effective in the maintenance treatment of patients with schizophrenia. Moreover, stability was maintained for up to three months with LUR. In a retrospective claims database study, LUR was associated with a significant reduction in all-cause and mental health-

Table 1. Clinical trials on LUR in adult population (N = 23).

Reference	Study design	Sample size	Inclusion criteria	Phase of the disorder	Outcome measures	Results
[22]	Prospective, multicenter, parallel-group study, with randomly assignment to double-blind treatment	N = 119, LUR (40 mg) N = 118, LUR (120 mg) Olanzapine (15 mg) N = 122, N = 114, Placebo	Hospitalized adult patients aged 18–75 with a DSM-IV diagnosis of schizophrenia and with an illness duration of at least 1 year and to have been hospitalized for ≤2 weeks	An acute exacerbation of psychotic symptoms and, at the screening and baseline visits, to have a CGI-S score ≥4 and a PANSS total score ≥80, including a score ≥4 on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness	PANSS total and subscale scores, the CGI-S, and the Montgomery-Åsberg Depression Rating Scale	The change from baseline to week 6 in PANSS total score was significantly greater for the LUR 40 mg and 120 mg groups compared with the placebo group. The change in PANSS total score was also significantly greater for the olanzapine group
[25]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study over a 6-week period	N = 245, LUR (40 mg/day and 80 mg/ day) N = 233, placebo	Adult patients (aged 18–74 years) diagnosed with schizophrenia according the MINI and the DSM-IV-TR criteria	Exacerbation PANSS tot. score≥80; PANSS item score≥4 on two or more of the following items delusions, conceptual disorganization, hallucinations, suspiciousness, or unusual thought content at both screening and baseline; a score of 4 or higher on CGI-S; an acute exacerbation of positive symptoms for no longer than 2 months prior to the screening visit and marked deterioration of function from baseline; able to be hospitalized	PANSS CGI-S EuroQOL-5 Dimensions-3 Levels (EQ-5D-3 L)	The mean change from baseline to Week 6 in PANSS total score was significantly greater for the LUR group compared to the placebo group
[47]	Randomized controlled trial, with a 2:2:1:2 ratio, for a 6 weeks fixed-dose treatment	N = 460 N = 125, LUR 40 mg/d N = 129, LUR 80 mg/d N = 64, Risperidone 4 mg/d N = 129, Placebo	Hospitalized patients aged 18 to 75 who met DSM-IV criteria for schizophrenia, with a Positive and Negative Syndrome Scale (PANSS) total score ≥ 70	Hospitalized patients	PANSS total score PANSS subscale scores CGI-S scale Criteria for treatment response were greater than or equal to 20% improvement from baseline in the PANSS total score. Safety evaluations included assessment of adverse events, clinical laboratory measures, and electrocardiograms	No significant endpoint differences in PANSS total score were found for LUR or risperidone vs placebo. LUR was safe and well tolerated, with minimal effects on weight and metabolic parameters.
[57]	Prospective, multicenter, parallel-group study, with 6 weeks of double-blind treatment	N = 150 LUR (once-daily 40 mg) N = 155 LUR (once-daily 80 mg) N = 152 placebo	Patients 18 to 74 years of age, DSM-IV-TR criteria for schizophrenia with disorganized, paranoid, or undifferentiated subtypes	Exacerbation of psychotic symptoms within 60 days before screening, with a PANSS total score of ≥80, including a score of ≥4 on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, suspiciousness, and unusual thought content at screening and baseline visits.	PANSS CGI-S Safety evaluations included vital signs, weight, laboratory tests, 12-lead ECG, reported adverse events (AEs), the Drug-induced Extrapyramidal Symptoms Scale, and the Columbia–Suicide Severity Rating Scale	In the ITT population, treatment with LUR was associated with significant improvement in the PANSS total score
[48]	Individual patient data pooled from five randomized, double blind, placebo-controlled, 6-week studies	N = 1030, LUR N = 497, Placebo	Adults aged 18 to 75 years with a diagnosis of schizophrenia (DSM-IV) for at least 1 year	An acute exacerbation of psychotic symptoms, with CGI-S ≥ 4 and a PANSS total score of ≥80, including a score of ≥4 on 2 or more of the following 5 PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness	PANSS CGI-S	LUR provided early and sustained reduction in agitation. Higher doses of LUR were particularly effective in patients with more severe agitation at study baseline.

(Continued)

Table 1. (Continued).

Reference	Study design	Sample size	Inclusion criteria	Phase of the disorder	Outcome measures	Results
[38]	Randomized double blind, placebo-controlled trial. Non-responders were re-randomized to LUR 80 mg/day or LUR 160 mg/day	N = 101, LUR 20 mg, N = 199, LUR 80 mg, N = 112, Placebo	Adult patients aged 18 to 75 years with a diagnosis of schizophrenia (DSM-IV) for at least 1 year	Exacerbation of psychotic symptoms, evaluated as CGI-S score of ≥4 and a PANSS total score of ≥80, including a score of ≥4 on 2 or more of the following 5 PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness	PANSS total score CGI-S score	In non-responders, dose increase to 160 mg was associated with a significant improvement in PANSS score. Patients receiving 20 mg did not demonstrate any significant improvement compared to placebo
[26]	Randomized, 3-week, double-blind, fixed-dose, parallel group study designed to evaluate the safety and tolerability profile of LUR (120 mg/day) and an active comparator (ziprasidone; 160 mg/day)	N = 150, LUR (120 mg) N = 151, Ziprasidone (160 mg)	Adult patients aged 18–70 years of age, with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder with a minimum duration of illness of at least 6 months, but were not currently experiencing an acute exacerbation of psychosis, and had not required inpatient treatment for at least 3 months prior to baseline.	Exacerbation	Safety endpoints consisted of the proportion of patients reporting treatment emergent adverse events, laboratory abnormalities, discontinuation due to adverse events, and serious adverse events	No clinically significant differences between LUR and ziprasidone on key safety parameters. Short-term treatment with LUR and ziprasidone was well tolerated, with no reports of serious adverse events that were treatment related, and a low (7%) rate of adverse events rated as severe on both drugs. Discontinuation due to adverse events occurred in a similar proportion of patients treated with LUR (10.4%) and ziprasidone (11.1%)
[27]	Phase II, randomized, double-blind, placebo-controlled 6-week study	N = 71, LUR (20 mg/day) N = 67, LUR (40 mg/day) N = 71, LUR (80 mg/day) N = 72, Haloperidol (10 mg/day) N = 72, Placebo	Adult patients aged 18–64 years, hospitalized for an acute exacerbation of psychotic symptoms, with a DSM-IV-TR diagnosis of schizophrenia with at least 1-year duration with	Exacerbation evaluated at BPRS total score >42 with a score >4 on at least two items of the positive symptom subscale and CGI-S score >4	BPRS PANSS total and subscale scores CGI-S Montgomery–Åsberg depression rating scale (MADRS) Safety evaluation	None of the LUR groups separated from placebo in this clinical study of patients with acute schizophrenia
[37]	Double-blind, placebo-controlled, randomized, withdrawal study	N = 285 global sample N = 144, LUR N = 141, placebo	Adult patients aged 18–75 years, diagnosed with a DSM-IV-TR diagnosis for schizophrenia and experiencing	An acute exacerbation evaluated at PANSS total score of ≥80 with a score ≥4 on one or more positive subscale items, and a≥4	Time to relapse	The efficacy of LUR for the maintenance treatment of patients with schizophrenia was demonstrated. Maintenance of stability with LUR was feasible over a three-month period.
[72]	Patient-level data were pooled from five similarly designed, 6-week, randomized, double-blind, placebo-controlled, fixed-dose studies	N = 1532 global sample N = 1035, LUR N = 497, Placebo	Adult patients, aged 18–75 years, with a DSM-IV-TR diagnosis for schizophrenia for at least 1 year and were experiencing	An acute exacerbation of psychotic symptoms, with a CGI-S > 4 and a PANSS total score > 80, including a score >4 on two or more on the following five items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness	PANSS at baseline PANSS weekly through Week 6	Improvement with LUR across all five PANSS factors in patients with schizophrenia starting at weeks 1 and 2. Effect sizes for LUR (all doses pooled) for the five factors ranged from 0.31–0.43 and were consistently largest for LUR 160 mg/d

(Continued)

Table 1. (Continued).

Reference	Study design	Sample size	Inclusion criteria	Phase of the disorder	Outcome measures	Results
[31]	Randomized, fixed-dose, double-blind, placebo-controlled, multiregional, parallel-group, 6-week study	N = 500 patients N = 122, LUR (40 mg/day) N = 119, LUR (80 mg/day) N = 124, LUR (120 mg/day) N = 124, Placebo	Adult inpatients, aged 18–75 years, with a DSM-IV diagnosis of schizophrenia	an acute exacerbation of psychotic symptoms (lasting >2 months) and with a CGI-S score >4 and a PANSS total score >80, including a score >4 on two or more of the following five items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness	PANSS total CGI-S Neurologic, metabolic, and other adverse events assessed throughout the study period	Patients who received fixed-dose LUR 80 mg/day showed significantly greater improvement in the primary efficacy measure compared with the placebo group
[32]	Double-blind, parallel-group study, utilizing a previously randomized study population and a noninferiority design	N = 151, LUR N = 85, quetiapine Extended release N = 56, placebo in the initial trial started on LUR (PBO-LUR group)	Adult outpatients with an acute exacerbation who recently completed 6 weeks of double-blind, placebo-controlled, fixed dose treatment with either LUR (80 mg/d or 160 mg/d) or QXR (600 mg/d, included to confirm assay sensitivity).	Exacerbation	PANSS CGI-S Negative Symptom Assessment Scale Montgomery–Åsberg Depression Rating Scale (MADRS)	Twelve months of treatment with LUR met noninferiority criteria, and was associated with higher rates of remission, and reduced risk of hospitalization compared with QXR. No clinically significant effects on weight or metabolic parameters were observed during maintenance treatment with LUR.
[33]	Pooled data from three randomized, double-blind, placebo-controlled, 6-week studies of LUR	N = 328 patients N = 135, LUR 40 mg/d or 80 mg/d N = 95, LUR 120 mg/d or 160 mg/d N = 98, placebo	Adult patients (aged 18–75 years) with schizophrenia	Stable phase	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression Severity scale (CGI-S)	Change from baseline to week 6 was significantly greater in patients treated with LUR 40–80 mg/d and 120–160 mg/d compared to placebo on both the PANSS total score and the CGI-S score
[34]	Randomized controlled trial, with 2:1 ratio for 12 months	N = 399 LUR (flexibly dosed, 37–111 mg/day) N = 190 risperidone (flexibly dosed, 2–6 mg/day)	Age 18–75 years; primary diagnosis of schizophrenia (DSM-IV criteria) of at least 1-year duration;	Clinically stable for at least 8 weeks before baseline; no change in antipsychotic medications for at least 6 weeks before screening; no hospitalization for psychiatric illness for at least 8 weeks before screening; and <4 severity rating on PANSS items of delusions, conceptual disorganization, hallucinations, and unusual thought content	Treatment-emergent adverse events (TEAEs) – for safety evaluations Relapse rate (DB trial only) PANSS Clinical Global Impression–Severity scale (CGI-S) Montgomery–Åsberg Depression Rating Scale (MADRS)	LUR was generally well tolerated and effective in treating clinically stable patients with schizophrenia over the long term

(Continued)

Table 1. (Continued).

Reference	Study design	Sample size	Inclusion criteria	Phase of the disorder	Outcome measures	Results
[35]	Multicenter, randomized, flexible-dose, double-blind, double-dummy, 6-week non-inferiority study with a 1:1 ratio, to 6 weeks of treatment	N = 194 LUR (40 or 80 mg/day) N = 194 risperidone (2, 4, or 6 mg/day)	Patients 18–65 years of age meeting the DSM-IV-TR criteria for a primary diagnosis of schizophrenia. Both screening and baseline a score ≥ 4 on the CGI-S and PANSS total score of ≥70 and ≤120, with a score ≥4 on 2 or more items of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness	Clinically stable	PANSS subscales (positive, negative) Clinical Global Impression-Severity of Illness (CGI-S) Clinical Global Impression-Improvement scale (CGI-I) Calgary Depression Scale for Schizophrenia (CDSS)	The non-inferiority of LUR relative to risperidone was demonstrated in both the ITT population (primary analysis) and the per-protocol population
[49]	Retrospective cohort study used U.S.-based Truven Health MarketScan Medicaid Multi-State Database and MarketScan Commercial Claims and Encounters Database	Medicaid population N = 122, LUR N = 215, Quetiapine Commercial population N = 116, LUR N = 220, Quetiapine	Adults (at least 18 years of age) and diagnosed with schizophrenia according to ICD-9-CM	Clinically stable	Rates of all-cause, mental-health, and schizophrenia-related hospitalizations	Treatment with LUR was associated with significantly lower rates of all-cause and mental health-related hospital admissions, and similar rates of schizophrenia-related admissions compared with patients switching to quetiapine. Patients switching to LUR had significantly longer treatment duration than those switching to quetiapine, potentially due to differences in efficacy or tolerability.
[28]	Multicenter, 6-month open-label, flexible-dose, extension study	N = 149 patients treated with LUR with flexibly dosed (40–120 mg/day)	Adult patients with either schizophrenia or schizoaffective disorder who had at least a partial response to, and were stable on, a first-line antipsychotic at a dose consistent with product labeling	Clinically stable	Proportion of patients with adverse events (AEs), serious AEs (SAEs), or who discontinued due to AEs	No significant clinically relevant adverse changes in metabolic profile. Treatment failure, defined as any occurrence of discontinuation due to insufficient clinical response, exacerbation of underlying disease, or AE) was observed for 19 patients (12.8% of patients entering) and median time to treatment failure was 58 days. The discontinuation rate due to any cause was 50/148 (33.8%), and median time to discontinuation was 62 days (95% CI 30–75). Patients reported an overall improvement overtime
[46]	Multiregional, prospective, parallel-group study, with randomly assignment to receive 6 weeks of double-blind treatment	N = 125, LUR (80 mg) N = 121, LUR (160 mg) N = 119, Quetiapine XR (600 mg) N = 121, Placebo	Subjects with a primary diagnosis of schizophrenia, who had been recently hospitalized for an acute exacerbation of psychotic symptoms	exacerbation	PANSS total and subscale scores CGI-S Montgomery–Åsberg Depression Rating Scale Negative Symptom Assessment Scale Quality of Well-being Scale (QWB-SA) Medication Satisfaction Questionnaire Epworth Sleepiness Scale	LUR, at fixed dosages of 80 and 160 mg/d, was an effective and well-tolerated treatment for subjects experiencing an acute exacerbation of chronic schizophrenia

(Continued)

Table 1. (Continued).

Reference	Study design	Sample size	Inclusion criteria	Phase of the disorder	Outcome measures	Results
[39]	6-week open trial of LUR 80 mg/d followed by a randomized, double blind, 24-week trial of LUR, comparing 80- and 240-mg/d doses	N = 133 N = 101 patients in phase 1 N = 67 patients in phase 2 N = 34 LUR 80 mg N = 33 LUR 240 mg	133 outpatients with clinical diagnoses of Treatment-resistant schizophrenia recruited with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder	Treatment resistant schizophrenia	PANSS-Total at 24 weeks Clinical Global Impression (CGI) – Severity Personal and Social Performance Scale (PSP)	Significant non-dose-related improvement in the Positive and Negative Syndrome Scale – Total and subscales were noted. Twenty-eight (41.8%) of 67 patients in the combined sample improved ≥20% in the Positive and Negative Syndrome Scale-Total.
[44]	6-week, multicenter, randomized, fixed-dose, double-blind, parallel-group, placebo-controlled study	N = 149 global sample N = 50, LUR (40 mg/day) N = 49, LUR (120 mg/day) N = 50, Placebo	Adult patients aged 18 and 64 years with a DSM-IV diagnosis of schizophrenia and hospitalized	An acute exacerbation of symptoms evaluated as BPRS score derived from the PANSS of ≥42, a score of ≥4 on two or more items of the positive symptoms subscale on the PANSS, and a CGI-S score of ≥4	BPRS-derived score	LUR provided effective treatment for patients with acute exacerbation of chronic schizophrenia and had minimal effects on weight and metabolic parameters
[62]	Randomized controlled trial	N = 90, LUR (80 mg) N = 90, Placebo	Adult patients hospitalized for an acute exacerbation of DSM-IV-definded schizophrenia	An acute exacerbation	Brief Psychiatric Rating Scale derived from the Positive and Negative Syndrome Scale (BPRSd)	LUR is a safe and effective treatment for patients with an acute exacerbation of schizophrenia.
[65]	12-month, double-blind study	N = 223 N = 136, continued to LUR in open-label study N = 87, switched to LUR in open-label study	Adult patients aged 18–75 years, with a diagnosis of schizophrenia or schizoaffective disorder,	Clinically stable outpatients	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression Severity scale Montgomery–Åsberg Depression Rating Scale (MADRS) Simpson-Angus Scale (SAS) Barnes Akathisia Rating Scale (BARS) Abnormal Involuntary Movement Scale (AIMS) Safety assessments included laboratory tests	Six months of OL treatment with LUR was generally well-tolerated, with a low incidence of parkinsonism and akathisia. Few adverse events were rated as severe. In the LUR continuation versus risperidone switch groups, change from OL baseline to 6-month endpoint was observed in mean body weight, median total cholesterol, triglycerides, glucose and prolactin. Improvement in PANSS total score was maintained, from OL baseline to endpoint in the continuation vs. switch groups.
[29]	Multicenter, randomized, trial, open-label, parallel-group 6-week study	N = 240 N = 74, LUR 40/40 mg N = 88, LUR 40/80 mg N = 82, LUR 80/80 mg	Adult patients with DSM-IV diagnosis of schizophrenia	Clinically stable	Time to treatment failure	Switching to LUR was safe and effective and associated with low rates of treatment discontinuation

Lurasidone: LUR; Brief Psychiatric Rating Scale: BPRS; PANSS: Positive and Negative Symptoms Scale; Clinical Global Impression-Severity of Illness: CGI-S; Clinical Global Impression-Improvement scale: CGI-I; Calgary Depression Scale for Schizophrenia: CDSS; Treatment-emergent adverse events: TEAEs; Montgomery–Åsberg Depression Rating Scale: MADRS; Quality of Well-being Scale: QWB-SA; EuroQOL-5 Dimensions-3 Levels: EQ-5D-3 L

Table 2. Clinical trials on LUR in adolescent population (N = 3).

Reference	Study design	Sample size	Inclusion criteria	Phase of the disorder	Outcome measures	Results
[45]	Double-blind (DB), parallel-group, placebo-controlled, multicenter trial with 1:1:1 randomization to 6 weeks of fixed-dose treatment with LUR (40 or 80 mg/day) or placebo	Treatment-naïve group N = 39, LUR N = 18, Placebo Previously treated N = 175, LUR N = 94, Placebo	Patients aged 13–17 with schizophrenia, and a PANSS global score between 70 and 120	Acute exacerbation (≤2 months in duration) of symptoms defined by a PANSS total score ≥70 and a CGI-S score ≥4	PANSS total score PANSS Positive and Negative subscales CGI-S Clinician-rated Children's Global Assessment Scale (CGAS) Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQLES-Q) Tolerability evaluations	LUR is an effective treatment for both antipsychotic-naive adolescents and those previously treated. It is associated with a significant improvement in the PANSS total score for both the TN and previously treated groups.
[50]	Post-hoc analysis from a 104-week, open-label extension study and an initial 6-week, double-blind, placebo-controlled trial	N = 271, global sample N = 50, treatment-naïve N = 221, previously treated N = 181, LUR (40 mg/d or 80 mg/d) N = 90, Placebo	Patients aged 13–17 with a DSM-IV-TR diagnosis of schizophrenia	Acute exacerbation (≤2 months in duration) evaluated with a PANSS total score ≥ 70, and a CGI-S score ≥ 4	PANSS total score PANSS Positive and Negative subscales CGI-S Clinician-rated Children's Global Assessment Scale (CGAS) Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQLES-Q) Tolerability evaluations	Continued improvement over the course of the 104-week extension phase for both TN and TP patients. On the PANSS total Score, mean improvement was greater in the TN group compared to the TP group at week 6 and through week 104.
[51]	Multiregional, 6-week, randomized, double-blind, placebo controlled parallel-group study, with a 1:1:1 randomization ratio, balanced with stratification criteria for age group (13–15 and 16–17 years) and country	N = 108, LUR (40 mg/day) N = 106, LUR (80 mg/day) N = 112, Placebo	Patients aged 13–17 years with a DSM-IV-TR diagnosis of schizophrenia	Acute exacerbation (>2 months in duration), as indicated by a PANSS total score of 70 and a CGI-S score >4	PANSS total score CGI-S score	LUR at doses of 40 and 80 mg/day demonstrated statistically significant and clinically meaningful symptom improvement in adolescent patients with schizophrenia.

Lurasidone: LUR; Positive and Negative Symptoms Scale: PANSS; Clinical Global Impression-Severity of Illness: CGI-S; Clinical Global Impression-Improvement scale: CGI-I; Calgary Depression Scale for Schizophrenia: CDSS; Treatment-emergent adverse events: TEAEs; Montgomery–Asberg Depression Rating Scale: MADRS; Clinician-rated Children's Global Assessment Scale: CGAS; Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire: PQLES-Q;

Table 3. Summary of findings on efficacy and side-effects of lurasidone.

Efficacy		Side effects	
Adults patients	Adolescent patients	Adults patients	Adolescent patients
• Effective treatment in terms of significant reduction of symptoms' severity in patients with acute exacerbation of the disorder	• In TN patients, the efficacy of LUR was greater on positive symptoms, not on negative symptoms	• In ≥5% of cases, insomnia, akathisia, headache, nausea, and anxiety	• In >5% of cases, nausea, somnolence, akathisia
• Effective treatment in patients with stable schizophrenia in terms of reductions of global symptoms' severity	• In TP, greater improvement than placebo both in positive and negative symptoms	• No significant impact on total cholesterol, triglycerides, glucose, and HbA1c	• Generally, adverse effects of mild or moderate severity
• Effective in the maintenance treatment of patients with schizophrenia, due to the good tolerability and side-effect profile	• Improvement in illness severity in adolescents and young adults with acute exacerbation of schizophrenia	• No clinically relevant changes in ECG parameters	• No clinically relevant changes in ECG parameters
• Greater improvement in overall cognitive performance compared to other antipsychotics			• No alterations in lipids, glycaemic indices, and prolactin during the short term and after two years of treatment
• Effective on negative symptoms dimension of schizophrenia			

TN: treatment-naïve; LUR: lurasidone; TP: treated previously; AE: adverse events

related hospital admission rates, while patients treated with LUR reported similar rates of schizophrenia-related admissions compared to those switching to quetiapine. In patients receiving a switch to LUR, a significantly longer treatment duration compared to switching to quetiapine was found. This could be due to the more favorable tolerability profile of lurasidone compared to quetiapine in terms of low incidence of metabolic side effects, weight gain, and sedation [32].

In a randomized, double-blind, placebo-controlled trial, Loebel et al. [38] assessed the effect of dose increase of LUR (160 mg/day) in adult patients who demonstrated inadequate initial response to standard-dose LUR (80 mg/day). In patients classified as early non-responders, the switch to LUR 160 mg determined the clinical remission, evaluated in terms of reduction of severity score at the PANSS scale. The same study found that low-dose LUR (20 mg/day) is not effective in adult patients with schizophrenia.

Efficacy of lurasidone has also been assessed on cognitive functioning. Five studies [39–45] including patients with schizophrenia or treatment-resistant schizophrenia have been included in the present review, with a specific focus on the impact of LUR on cognitive functioning. In particular, the first study aiming to assess the efficacy of lurasidone on cognitive functioning has been promoted by Harvey et al [36], and they found that lurasidone was superior to an active comparator on cognitive assessments at 6 weeks and at six months of follow-up. In 2015, Harvey et al. [46] found that patients receiving 120 mg/day and 160 mg/day of lurasidone reported a significantly greater improvement in overall cognitive performance compared to those treated with quetiapine extended release.

Moreover, lurasidone has been found to be effective also on negative symptom dimension in patients with schizophrenia. In the pooled analysis by Calisti et al [40], treatment with lurasidone was associated with a small effect size (0.38) in patients treated with the 40–80 mg/day dose. However, this finding is in line with recent meta-analysis showing that both first- and second-generation antipsychotics have a lower efficacy in treating negative symptoms compared to other symptom domains.

A recent network meta-analysis by Schneider-Thoma et al [43] focusing on the comparative efficacy and tolerability of antipsychotics for the maintenance treatment of adults with schizophrenia found that all antipsychotics had RRs less than 1.00 when compared with placebo for relapse prevention. In particular, lurasidone was associated with a RR of 0.63 (CrI = 0.25 to 1.02), with a 38% rate of adverse events.

The main findings on the efficacy of lurasidone in adult and adolescent patients with schizophrenia have been summarized in Table 3.

3.1.1. Tolerability in adult patients with schizophrenia

According to the results of the network meta-analysis by Huhn et al. [30] focusing on studies for the acute treatment of adults with multi-episode schizophrenia, lurasidone was the most benign drug in terms of QTc prolongation, with a SMD of −2.21 (95% CI = −4.54 to 0.15). Other side effects evaluated in patients treated in acute phase with lurasidone include weight gain, akathisia, increase in prolactin level, sedation, and anticholinergic effects. The quality of evidence was low regarding the presence of the above-mentioned side effects.

Several trials [35,37,44,47,48] confirmed the good safety profile of LUR, with no significant clinically relevant adverse changes in metabolic profile during treatment.

In the study by Patel et al. [34], LUR was generally well tolerated over the first 12 months (LUR versus risperidone: LUR treatment was associated with significantly fewer rates of metabolic syndrome) and remained effective with minimal changes in metabolic variables and prolactin over six additional months of LUR, confirming over 18 months a good tolerability profile. Patients switching from risperidone to LUR (12 months with risperidone + additional 6 months with LUR) experienced a reduction in weight and prolactin levels.

In a study assessing the effect of dose increase in adult patients with schizophrenia with inadequate initial response to standard-dose LUR and evaluating the efficacy of low-dose LUR in adult patients with schizophrenia, Loebel et al. [49] found that the most common adverse effects (AEs) (incidence ≥5%) associated with LUR 18.5 mg/day were insomnia, headache, anxiety, agitation, somnolence, and akathisia; while with a dosage of LUR between 74 mg/day and 148 mg/day also abdominal discomfort was reported.

Higuchi et al. [47] found that increased levels of serum prolactin levels (five times upper limit of normal) were reported both in patients treated with LUR 40 mg (1.6%) and with LUR 80 mg (0.8%) as well as those in the placebo group (2.3%). However, the increase of serum prolactin level was higher in patients treated with risperidone (29.7%). No clinically relevant differences in levels of total cholesterol, triglycerides, glucose, and HbA1c were found comparing lurasidone to placebo. However, in risperidone group, levels of total cholesterol, triglycerides, glucose, and HbA1c were higher than lurasidone group. Regarding changes in body weight (measured as 7% endpoint increase in body weight), 2.4% and 1.5% of patients in LUR 40 mg and 80 mg groups, respectively, reported an increased body weight, compared to 6.2% of patients in risperidone group and 2.3% in placebo group.

These data confirm that LUR is an effective and safe treatment for adult patients with schizophrenia, being one of the antipsychotics with a favorable metabolic side effect profile. This means that it may be used as a first choice for drug-naïve patients to prevent the development of metabolic damage and reduce cardiovascular risk over the long-term, but also as a possible alternative to other treatments that had been associated with the development of metabolic disturbances (harm reduction – switch to LUR).

In particular, the network meta-analysis by Schneider-Thoma et al [43] confirmed that significant differences between antipsychotics in the tolerability outcomes are relevant in the treatment of patients with stable schizophrenia. In particular, lurasidone was associated with good safety profile.

3.2. Efficacy in adolescent and young adult patients with schizophrenia

Lurasidone has been found to be the most effective oral antipsychotic medication for young patients with schizophrenia, as confirmed by the network meta-analysis by Yee et al. [43]. In particular, in long-term studies overall clinical efficacy of lurasidone treatment was associated with a −2.44 SMD (95% CI=−3.55 to −1.34) compared to placebo, while in short-term studies was of −0.31 SMD (95%CI=−0.54 to −0.08).

LUR was an effective treatment option for both antipsychotic-naïve (TN) adolescents and those previously treated with antipsychotics, with a flexible dosage of 40–80 mg/day of LUR. The efficacy of LUR was greater in TN adolescents, both in the acute phase and after 104 weeks of treatment [44,45,50].

In TN patients, the efficacy of LUR was greater at the PANSS Positive Symptom score, but not on the PANSS Negative Symptom score, compared to placebo. Within the previously treated (TP) group, treatment with LUR was associated with greater improvement than placebo in the reduction of

symptoms severity evaluated at PANSS Positive Symptom score and Negative Symptoms score.

Patients treated with LUR treatment (vs. placebo) reported a slightly larger endpoint effect sizes in the TN group compared to the TP group. The improvement was confirmed over the course of the 104-week extension phase both in TN and TP patients. Regarding the global severity of symptoms, measured with PANSS total score, TN patients reported a higher improvement compared to the TP group, both at week six and through week 104. The same improvement was found also when considering other outcome measures, including PANSS Positive Symptom subscale, PANSS General Psychopathology subscale, and PANSS Excitability subscale.

A recently published pooled analysis – from five similarly designed, 6-week, placebo-controlled trials in adult patients and one similarly designed, 6-week, placebo-controlled trial in adolescent patients – found lurasidone effective in improving symptom severity (as assessed by PANSS scale) and illness severity (as assessed by CGI-S scale) in adolescents and young adults (aged 13 to 25 years) with acute exacerbation of schizophrenia [51] (Table 3).

3.2.1. Tolerability in adolescent (and young adult) patients with schizophrenia
Adverse events with incidence >5% included nausea, vomiting, somnolence, anxiety. Yee et al. [43] demonstrated that lurasidone showed good tolerability, in particular in terms of lower risk of weightgain compared to other atypical antipsychotics, including olanzapine, quetiapine, risperidone and paliperidone.

Adverse events were more frequently of mild or moderate severity, while severe events occurred in 5.5% of patients in the LUR 40 mg/day group, in 5.4% of patients in the placebo group, while none was reported in the LUR 80 mg/day patient group [44]. During long-term prescription with LUR, no clinically relevant changes were observed in ECG parameters. Weight gain did not differ from age and developmentally appropriate levels during the 2-year follow-up. LUR has also a good side effect profile in terms of alterations in lipids, glycemic indices, and prolactin during the short term and after two years of treatment.

The pooled analysis of LUR conducted in adolescent and young adult patients (aged 13 to 25 years) with acute schizophrenia, found that short-term treatment with LUR was associated with a favorable safety profile. Nausea (13.5%), somnolence (12.1%) and akathisia (10.1%) were the three adverse events that occurred with a frequency of ≥5% in the LUR combined dose groups. Moreover, no significant differences were found between LUR and placebo, considering that 3.6% of patients in LUR group experienced a weight gain of ≥7% compared to 4.7% in the placebo group. LUR treatment was associated with minimal changes in cholesterol, triglycerides, and glucose plasma levels at 6-week endpoint in this patient group [51] (Table 3).

3.3. Use of lurasidone in pregnancy

In a systematic review on safety of second-generation antipsychotics during pregnancy carried out in 2018, no delivery outcomes following in utero exposure were reported with

lurasidone [52], pointing out that no meaningful risk assessment can be made. Moreover, available studies carried out in adult and adolescent patients have found that lurasidone is weight-neutral and it should be expected a similar finding in pregnant women. However, it should be considered that pregnancy is characterized by several hormonal changes, which could also lead to gestational diabetes but the effects of lurasidone on these hormonal pathways are still unknown. Therefore, further investigation is needed in order to clarify this aspect.

The use of lurasidone during pregnancy has been classified as category B1 by the Australian categorization system for prescribing medicines and as category B by the FDA confirming that no controlled studies in pregnant women have been performed so far. However, this classification system of pregnancy labeling rule for a prescription drug is going to be revised in order to include a summary of risk, a discussion of the data supporting that summary, and relevant information to help health-care providers make prescribing decisions and counsel women about the use of drugs during pregnancy. Actually, according to FDA, lurasidone is not assigned to any FDA pregnancy category due to lack of scientific data.

Lurasidone is more than 99% bound to plasma proteins, so it is unlikely that the drug would be excreted into milk sufficiently to affect a breastfed infant. Data from one mother-infant pair appears to support the poor excretion into milk and lack of effect on the breastfed infant. Until more data are available, an alternate drug may be preferred, especially while nursing a newborn or preterm infant [53].

4. Clinically relevant issues

4.1. Administration

LUR is poorly soluble after oral ingestion and should be administered with a meal of at least 350 calories, regardless of the fat content, which increases its bioavailability, and Cmax and should be administered in a PM dose [54,55].

Peak serum concentration is reached after approximately 1 to 3 hours and a steady-state concentration is reached in 7 days [15] (Box 1).

4.2. Finding the right dose

The recommended LUR starting dose is 37 mg (equivalent to 40 mg of LUR hydrochloride) once daily, according to its labelling. LUR is effective in a dose range of 37 to 148 mg (equivalent to 40 to

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• Administer LUR with a meal of at least 350 calories
• The administration with food increases the Cmax approximately 3-fold and the AUC approximately 2-fold

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160 mg of LUR hydrochloride [US doses]) in adults and 37–74 mg (equivalent to 40–80 mg of LUR hydrochloride [US doses]) in adolescents, once daily. Dose increase and target dose should be based on physician judgement, depending on severity and types of symptoms, tolerability, and clinical response. The maximum recommended daily dose is 148 mg in adults and 74 mg in adolescents.

In adult patients with schizophrenia who did not respond to two weeks of treatment with LUR 74 mg/day, dose increase to 148 mg/day resulted in significant improvement compared with continuing LUR 74 mg/day. The study also demonstrated that LUR 18,5 mg/day was not associated with significant improvement in psychotic symptoms in adult patients with schizophrenia [48].

While a low dose (i.e., 37–74 mg) of LUR may be useful in patients with schizophrenia with predominant negative-affective symptoms and mild positive-productive symptoms, a higher dose (i.e., 111–148 mg) of LUR – which binds to a higher number of dopaminergic receptors – is usually more helpful for patients with acute and/or severe positive symptoms [56].

Higher doses of LUR (120–160 mg) are more effective more effective than lower doses (40–80 mg) on agitation in a posthoc analysis of five 6-week, double-blind, placebo-controlled studies [57]. LUR may be a useful treatment option in patients with agitation associated with acute psychotic symptoms of schizophrenia, with higher doses particularly effective in patients with more severe agitation. Moreover, two recent meta-analyses found that 148 mg/day or more than 160 mg/day are the maximally effective dose of lurasidone for overall psychotic symptoms as measured at the PANSS global score [58,59].

As reported by Meltzer et al [60], in a sample of treatment-resistant schizophrenia (TRS) patients, lurasidone at both 80 and 240 mg/d has been found to be effective to improve cognitive functioning and cognitive symptoms. In particular, executive functioning and speed of processing were improved at both doses, with the lower dose achieving greater improvement in executive function [36].

5. Case examples of complex clinical presentations

The following case examples are virtual patient cases. Although they simulate real-life clinical scenarios based on the authors' clinical experience, they are not referring to any specific patients.

5.1 Sequential treatment with lurasidone and a benzodiazepine in the acute phase of schizophrenia, followed by LUR monotherapy during the maintenance phase

An 18-year-old man presented to the outpatient unit accompanied by his mother because of persecutory delusions and hallucinations that have recently worsened. The parents reported that the symptoms started with anxiety, insomnia, lack of interest, and mildly depressed mood. After three months, he started to show odd behavior such as pacing, constantly writing, walking in circles, withdrawing from family, friends and social activities, and using nonsense words. More recently, he had become increasingly concerned and convinced that someone is poisoning and spying on him and had begun to hear voices that 'totally confirmed' his suspicions and urged him to be as cautious as possible. The

patient was admitted to inpatient treatment and diagnosed with schizophrenia, given that his psychotic symptoms lasted more than six months and his depressive symptoms did not reach the threshold for a depressive episode. He started the treatment on LUR at 37 mg/day (increased to 74 mg after two days), and on lorazepam 2.5 mg at night and 1 mg in the morning. Both the psychotic and subthreshold mood symptoms gradually improved, lorazepam was gradually decreased, and the patient was discharged to outpatient care after seven days, on LUR 74 mg and lorazepam 2,5 mg at night, to be decreased and discontinued as soon as possible. After three weeks of outpatient treatment, the patient was stable and much improved, but continued to experience residual symptoms, such as believing that he was being talked about behind his back and watched by people, that his actions and thoughts were being interfered with by others, and that people are using hints and double meanings to secretly threaten or make him feel bad. These residual symptoms were of moderate intensity and were associated with a moderate functional impairment, therefore, the LUR dose was increased to 148 mg/day and subsequently all symptoms completely clear.

5.2. Treating schizophrenia with negative symptoms and comorbid substance use

A 17-year-old male, diagnosed with schizophrenia and cannabis user, was hospitalized due to social withdrawal, apathy, affective flattening, difficulty concentrating, ideas of reference and brooding rumination, lack of motivation, reduced personal hygiene, inability to feel pleasure and emotional blunting. He seemed unwilling or unable to speak but eventually started speaking with a monotone voice and described his thoughts as 'misty' and 'hazy.' He also reported auditory hallucinations, stating that he could not talk because he needed to hear the music that someone was playing in his head. Presently treated with haloperidol 4 mg/day, he was prescribed LUR 37 mg/day, with a reduction of haloperidol dose to 3 mg/day. After six days, LUR dose was increased to 74 mg/day, haloperidol was reduced to 2 mg/day, and the patient was instructed to discontinue the medication after one more week. LUR led to a clear reduction of negative symptoms, with the improvement of social and work functioning and a reduction of craving for carbohydrates. Positive symptoms improved as well, and no adverse effects were detected.

5.3. LUR in an adolescent with positive, negative and cognitive symptoms

The patient was a 16-year-old Caucasian boy receiving ADHD diagnosis at six year of age, oppositional and defiant disorder at 8 years old, worsening school performances, and cannabis use at age of 12. At age of 14, he was diagnosed with schizophrenia. He presented with persecutory delusion, bizarre behaviors, and depressive symptoms, followed by disorganized behavior and confusion. After starting olanzapine at 10 mg/day and lorazepam 3 mg/day, an early apparent remission was followed, in a few months, by a rapid worsening of psychotic symptoms, including moderate positive symptoms and relatively severe negative and cognitive symptoms, which

did not completely respond to an increase of Olanzapine dose up to 15 mg/day. After a few weeks, olanzapine was tapered, and LUR 37 mg/day was started, with slight clinical improvement of speech, thoughts, and anhedonia. LUR dose was increased up to 74 mg/day, with a gradual but clear and stable improvement of psychotic and affective symptoms, along with an improvement of social and cognitive functioning.

5.4. Use of LUR in combination with other medications

LUR is primarily metabolized by the isoenzyme 3A4 of the cytochrome p450 (CYP) and is contraindicated with *strong* CYP3A4 inhibitors, such as boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, and CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifampicin, and St John's wort (Hypericum perforatum).

In combination with *moderate* CYP3A4 inhibitors, such as fluvoxamine it is recommended to start with 18.5 mg and not exceed 74 mg once daily [61]. Higher than usual doses may be necessary when LUR is prescribed in combination with mild and moderate CYP3A4 inducers [61].

With these precautions and recommendations in mind, clinicians may safely combine LUR with other medications when necessary.

Given the pharmacodynamic profile of LUR (mainly low affinity for the histamine H1 and muscarinic receptors), it may be necessary in clinical practice to initially add other compounds for the treatment of symptoms such as anxiety or sleep problems, for example. It has to be kept in mind that the low affinity for a specific receptor (e.g., H1 receptors) is beneficial over the long term (e.g. low or no weight gain, low or no sedation over the long term), but in the acute treatment (especially if the patient is switched to LUR – may be too quickly – from another antipsychotic with high affinity for the same receptor) it may be necessary to combine LUR with other medications to treat specific symptoms (or to counterbalance withdrawal symptoms in the case of a switch).

In most clinical trials, concomitant medications such as benzodiazepines (for agitation, anxiety and insomnia), anticholinergic agents for extrapyramidal symptoms (EPS) or propranolol for akathisia were permitted. For instance, in one of the 6-week, randomized, placebo-controlled studies of LUR for the treatment of acutely psychotic patients with schizophrenia, concomitant administration of benzodiazepines (oral lorazepam up to 6 mg/day, intramuscular lorazepam up to 4 mg/day for agitation and/or temazepam up to 30 mg/day for sleep) was permitted for severe anxiety, agitation, or insomnia. Similarly, treatment with benzotropine (up to 6 mg/day), biperiden (up to 16 mg/day), trihexyphenidyl (up to 15 mg/day), or diphenhydramine (up to 100 mg/day) was permitted on an as-needed basis if EPS-related symptoms emerged during the study. Propranolol (up to 120 mg/day) or amantadine (up to 300 mg/day) was permitted as needed for akathisia.

Similarly, in the 6-week trial of LUR in adolescents with schizophrenia, anticholinergic agents or propranolol were permitted for movement disorders as needed, while lorazepam, temazepam, and eszopiclone (or their equivalents) were

permitted as needed for anxiety or insomnia [50]. We will provide examples of real-world clinical cases focusing on using combination treatment with lurasidone (other cases are available as supplementary material files).

5.4.1. Lurasidone combined with propanolol for akathisia

The patient was a 25-year-old man affected by schizophrenia who started LUR at a dose of 37 mg, which was gradually titrated up to 111 mg/day in about one week, with a good clinical response but also with a subjective inner restlessness and objective motor manifestations, which were diagnosed as akathisia. He had no contraindications for beta blockers (i.e., asthma, bradycardia) and was then prescribed propranolol at 20 mg twice a day, which led to a partial improvement of akathisia over a period of about 5 days. The increase of propranolol to a dose of 40 mg twice/day led to further improvement but did not determine a complete remission of the side effect. The subsequent reduction of LUR to 74 mg/day, maintaining propranolol at 40 mg twice/day obtains complete remission of akathisia without any loss of LUR efficacy on positive and negative symptoms.

5.4.2. Lurasidone combined with an anticholinergic for extrapyramidal symptoms (EPS)

The patient was a 51-year-old man affected by schizophrenia, overweight, heavy smoker and with essential hypertension.

The duration of the illness was of about 28 years, the patient had been treated with different typical antipsychotics (including haloperidol and chlorpromazine), but he reported several side effects including increase in body weight, prolongation EPS extrapyramidal symptoms including inability to sit still, involuntary muscle contraction, tremors, and involuntary facial movements. Furthermore, he had achieved a remission of positive symptomatology, in terms of reduction of severity of delusions and hallucinations, while anhedonia, cognitive deficits including lack of attention and difficulties in recalling memories, still persisted. Therefore, during the hospital admission due to the persisting and disabling cognitive symptoms and EPS, a treatment with LUR was initiated (with a simultaneous reduction of typical antipsychotics) at a dose of 37.5 mg for three days, and then increased at 74 mg for seven days. The patient reported a reduction in tremors and inability to sit still when haloperidol was completely suspended (after 10 days from hospital admission). A remission of clinical symptomatology - both positive and negative symptoms - was observed with the increased dose at 111 mg/day. At day 17, he started to present akathisia and tremors, therefore it was introduced biperiden 1 mg/twice daily. He reported a subjective reduction of inability to sit and of tremor. After 5 days, biperiden was increased at 2 mg/twice daily with a dosage of 111 mg lurasidone once/daily. Therefore, the EPS were significantly reduced, and the clinical status was in remission.

5.5. Switching to LUR

Patients with schizophrenia are at an increased risk for developing physical illness or conditions that may benefit from a switch to LUR, such as metabolic syndrome, sedation, or sexual side effects. For instance, in a 6-month extension study, LUR treatment was well tolerated and associated with minimal effects on metabolic parameters, weight, and prolactin levels. In this study, patients who switched from risperidone to LUR experienced an initial improvement in weight and lipids profile, followed by minimal long-term effects on weight, metabolic parameters, and prolactin over the following 6-months [35,62]. In the study by Mattingly et al [62] several metabolic parameters, including weight, BMI, and waist circumference, were increased in patients who received 12 months of treatment with risperidone.

In another trial, patients who were treated for 6 weeks with olanzapine showed clinically meaningful reductions in weight, waist circumference, and other metabolic parameters after switching to 6 months of treatment with LUR. Similar results were observed in a study [63] involving 240 patients with a diagnosis of schizophrenia treated with a range of typical (haloperidol, perphenazine, chlorpromazine, fluphenazine, thiothixene) and atypical antipsychotics (e.g. quetiapine, olanzapine, risperidone), who were switched to LUR, 37–111 mg/day and who showed an improvement in weight and lipid parameters after 6 weeks of open-label treatment with LUR. In the following 6-month, open-label observation, improvements in efficacy on LUR were maintained, with minimal long-term effects on weight, metabolic parameters, and prolactin levels.

In a study to evaluate the effectiveness and safety of three strategies of switching subjects from other antipsychotics to LUR, whose primary endpoint was time to treatment failure, 82,5% of participants successfully completed the switch. Study participants were randomized to 1 of 3 LUR dosing regimens for the initial 2 weeks of the study: (1) LUR 37 mg/day for 2 weeks; (2) LUR 37 mg/day for 1 week, increased to 74 mg/day on day 8 of week 2 (up-titration group); and (3) 74 mg/day for two weeks. LUR was then flexibly dosed from 37 to 111 mg/day, for the subsequent four weeks of the study. The pre-switch antipsychotic was tapered to 50% of the original dose by day 7 and discontinued by the end of week 2. Subjects were stratified based on whether the pre-switch antipsychotic was classified as 'sedating' (olanzapine or quetiapine) or 'nonsedating' (all other antipsychotics). Time to treatment failure was defined as any occurrence of insufficient clinical response, exacerbation of symptoms, or discontinuation because of an adverse event.

This study found that treatment failure and all-cause discontinuation rates did not differ according to the LUR titration regimen (that is, in patients previously on a different antipsychotic the choice of starting with 74 mg/day immediately was not associated with increased side effects or discontinuation rates as compared to a slower titration regimen). However, treatment failure rates in patients who had been receiving a pre-switch sedating drug were 11.6% versus 5.8% in those who had received a nonsedating antipsychotic (the same for all-cause discontinuation rates). This means that subjects receiving a sedating agent (antipsychotics with high affinity for H1 and muscarinic receptors – olanzapine or quetiapine) would probably have benefited from a longer (more than two weeks) period of cross-tapering during the switch, in order to avoid possible withdrawal or rebound symptoms leading to treatment discontinuation. The incidence of akathisia was 12.5% but only one subject (0.4%) discontinued due to akathisia [63]. We will provide examples of real-world clinical

cases focusing on switch to lurasidone due to lack of efficacy or for managing side effects.

5.5.1. Switch from long-acting injectable antipsychotic (LAI) to lurasidone

The patient was a 30-year-old woman affected by schizophrenia. Since the onset of the disorder – five years previously when she was finishing her master's degree in economy – she has been treated with paliperidone palmitate long-acting injection - LAI (75 mg i.m. once/monthly injection) and she obtained a satisfying remission of clinical symptoms.

Three months previously, during a routine clinical visit with her referring psychiatrist, she was concerned by the lack of interest in daily routine and by the lack of attention and concentration. She was applying for a new job as office secretary, but she was frightened by the idea of not being able to fulfil her working obligations due to these cognitive difficulties. Since the onset of the disorder, she had been able to complete the master's degree, but she had never applied for a job. Her parents strongly supported the decision to looking for a job, but she did not trust in her capacities and skills. She was very disappointed by cognitive dysfunctions, which nurtured her low levels of self-esteem. Taking into consideration this condition, the referring clinician proposed to the patient to change the medication. In particular, the psychiatrist proposed starting the therapy with 37.5 mg/day of lurasidone for seven days in augmentation to the long-acting atypical antipsychotic. After 7 days, lurasidone was increased at 75 mg and following another week, it was increased at 111 mg/day. The augmentation with lurasidone was kept for one month, then the paliperidone LAI was suspended. A good clinical status was maintained over time.

5.5.2. Switch to lurasidone due to hyperprolactinemia

The patient was a 26-year-old man affected by paranoid schizophrenia. The onset of the disorder was at the age of 18 years, following a motor bike accident, when the patient started to present persecutory delusions, auditory hallucinations and marked social isolation. Before the onset of the disorder, he worked as waiter in a local restaurant, but due to his clinical condition, he could not keep working. In fact, he was convinced that the head chef was poisoning him considering that every night the patient was invited by the chef to have dinner with the other waiters. A week ago, he had an argument with the chef and other colleagues and screamed at them and verbally threatened them; the family members were alerted and called the emergency physician. The patient had not insight about his condition and did not accept to take medications and, therefore, he was involuntary admitted. At the hospital, he was treated with paliperidone (9 mg/day) and after two weeks of hospitalization he started to accept medications, but he was still frightened by the idea of coming back to the restaurant. At hospital discharge, he decided to take a period off from work. During the following weeks, he had several meetings with the outpatient staff; at follow-up assessment, a significant increase in prolactin levels (62.0 ng/ml) (at hospital discharge – 3 months earlier – the prolactin level was 15.3 ng/ml) was found. Furthermore, the patient was concerned about a reduction in sexual desire, and

he was scared by the high prolactin levels. Therefore, the physician proposed a switch to lurasidone with a starting dose of 37.5 mg and a reduction to 6 mg of paliperidone for seven days. In absence of significant side effects, lurasidone was then increased to 75 mg and paliperidone reduced to 3 mg/day. At day 20, paliperidone was suspended and prolactin levels were reassessed. A slightly reduction in prolactin was found (56.1 ng/ml), in absence of other side effects. Therefore, lurasidone was increased at 111 mg/day and a routine laboratory check was scheduled after one and three months. After three months of treatment with lurasidone, the prolactin levels were further reduced to 42.1 ng/ml.

Please see also supplementary material for further case examples.

6. Conclusions

The use of LUR in patients with schizophrenia is supported by a robust registration program that has shown significant reductions in symptoms measured with the Brief Psychiatric Rating Scale [64,65], across the dose range of 37–148 mg/day.

In short-term trials involving patients diagnosed with schizophrenia, the most frequently observed adverse effects (i.e., adverse effects with an incidence on lurasidone ≥5% and at least twofold greater than placebo) were somnolence (17% vs. 7%; NNH = 10), extrapyramidal symptoms (excluding restlessness and akathisia) (14% vs. 6%; NNH = 13), akathisia (13% vs. 3%; NNH = 10), and nausea (10% vs. 5%; NNH = 20).

Extrapyramidal symptoms and akathisia are usually dose-related and their incidence and severity increase when the dose is increased within the range from 18.5 to 111 mg/day.

In clinical trials, the incidence of akathisia in LUR-treated patients with schizophrenia was 5.6% for 18.5 mg, 10.7% for 37 mg, 12.3% for 74 mg, and 22.0% for 111 mg.

In the present paper, several case reports have been included in order to provide some practical suggestions to the real-world clinical practice. In fact, although case reports represent the lowest evidence level, these can be useful to inform clinical routine practice. Furthermore, the clinical practice suggestions are based on the results of systematic reviews and meta-analyses included in this paper.

7. Expert opinion

Lurasidone has proven effective in treating patients in the acute phase of schizophrenia as well as in reducing the risk of relapse. Lurasidone, has a relatively good tolerability profile, with minimal effects on metabolic parameters, weightgain, and prolactin levels. Lurasidone is efficacious upon a wide range of symptoms, including positive, negative, and cognitive symptoms of schizophrenia, therefore it could represent the optimal choice for the personalization of treatment of patients with schizophrenia [3]. Choosing the right dose for each patient and temporarily combining LUR with other medications, such as benzodiazepines for patients with insomnia or agitation, betablockers for patients with akathisia, antihistamine, or anti-muscarinic drugs for patients rapidly switched from antipsychotics with high antihistamine and/or high

anticholinergic properties, is key to treatment success [66–69]. ***[70,71]

The starting dose of 37 mg/day may be already efficacious. The daily dose is then increased up to 74 mg in adolescents and 148 mg in adults, based on clinician judgement. In our experience, the dosage is increased in increments of 37 mg every 1–5 days, based on tolerability and severity of symptoms. Patients showing a good tolerability and a suboptimal symptom control at lower doses, usually benefit from higher doses of LUR. In our clinical practice, patients with more severe positive symptoms or agitation associated with positive symptoms more frequently need the full dose of 148 mg/day, unless they experience significant and dose-related side effects. However, according to our clinical experience, it could be useful to prescribe at least 74 mg daily in adolescents and up to 148 mg daily in adults, in order to reach a full remission of positive, negative, and cognitive symptoms. LUR is usually started on 37 mg daily, to be taken with a meal of at least 350 calories.

Given the relatively favorable metabolic risk, LUR is often a first-choice antipsychotic for patients at risk of obesity, diabetes, dyslipidemia, or patients who have already developed those metabolic alterations and need an antipsychotic switch. LUR's strong anti-dopaminergic properties usually avoid the risk of a dopaminergic rebound during the switch. However, the lack of significant anti-histamine and anticholinergic properties suggest a slow cross taper (or the temporary combination with an antihistamine and/or anticholinergic agent) when a patient is switched to LUR from a highly anti-histaminergic or anti-muscarinic medication, such as olanzapine, quetiapine, or clozapine.

Our recommendation for patients who experience akathisia include: 1) LUR dose reduction, when possible; 2) LUR combination with a benzodiazepine or a beta blocker; 3) if akathisia is severe and resistant to the interventions above, a switch to a medication that is less likely to give akathisia, such as quetiapine or clozapine. In a study where LUR was administered in the evening [72] akathisia was reported by 7.4% of patients receiving LUR at 148 mg/day. It is likely that evening administration, especially when LUR is combined with a benzodiazepine, is associated with more favorable tolerability profile, compared to morning dosing.

For patients with symptoms such as agitation or insomnia that may temporarily benefit from a drug that induces somnolence or sedation, we often combine LUR with a medication such as a benzodiazepine or an antihistamine, which we attempt to discontinue once those symptoms are controlled. Particular attention is needed in clinical practice when switching to LUR (which is devoid of anti-H1 activity) from antipsychotics with high affinity for H1 receptors (e.g., olanzapine or quetiapine): in that case, in order to prevent the occurrence of histaminergic (and/or anticholinergic) withdrawal/rebound symptoms (with activation, agitation, or insomnia) it may be preferable to prolong the length of the cross-titration (once full LUR dosage is achieved, reduce pre-switch antipsychotic dose very slowly, if possible during a period of at least 1 month or even more).

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. McCutcheon RA, Merritt K, Howes OD. Dopamine and glutamate in individuals at high risk for psychosis: a meta-analysis of in vivo imaging findings and their variability compared to controls. World Psychiatry. 2021; 20:405–416.
2. Carpenter WT. Primary psychosis: more to know, much more to do. World Psychiatry. 2021;20(1):1–2.
3. Maj M, van Os J, De Hert M, et al. The clinical characterization of the patient with primary psychosis aimed at personalization of management. World Psychiatry. 2021;20(1):4–33.
   •• paper of considerable interest reporting the most significant clinical domains to evaluate in patients with schizophrenia.
4. Howes OD, Whitehurst T, Shatalina E, et al. The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. World Psychiatry. 2021;20(1):75–95.
5. Ehring T. Thinking too much: rumination and psychopathology. World Psychiatry. 2021;20(3):441–442.
6. Griswold KS, Del Regno PA, Berger RC. Recognition and differential diagnosis of psychosis in primary care. Am Fam Physician. 2015;91 (12):856–863.
7. Klonsky ED, Dixon-Luinenburg T, May AM. The critical distinction between suicidal ideation and suicide attempts. World Psychiatry. 2021;20(3):439–441.
8. Howes OD, McCutcheon R, Owen MJ, et al. The role of genes, stress, and dopamine in the development of schizophrenia. Biol Psychiatry. 2017;81(1):9–20.
9. Frydecka D, Kotowicz K, Ł G, et al. Effects of interactions between variation in dopaminergic genes, traumatic life events, and anomalous self-experiences on psychosis proneness: results from a cross-sectional study in a nonclinical sample. Eur Psychiatry. 2020;63(1):e104.

10. Drake RE, Xie H, McHugo GJ. A 16-year follow-up of patients with serious mental illness and co-occurring substance use disorder. World Psychiatry. 2020;19(3):397–398.

11. Slade M, Sweeney A. Rethinking the concept of insight. World Psychiatry. 2020;19(3):389–390.

12. Correll CU, Cortese S, Croatto G, et al. Efficacy and acceptability of pharmacological, psychosocial, and brain stimulation interventions in children and adolescents with mental disorders: an umbrella review. World Psychiatry. 2021;20(2):244–275.

13. https://www.ema.europa.eu/en/documents/product-information/latuda-epar-product-information_en.pdf, accessed on November 7, 2022

14. FDA, Food And Drug Administration. LATUDA (LURASIDONE HCL) tablets for oral administration. Initial U.S. Approval; 2010.

15. Jaeschke RR, Sowa-Kućma M, Pańczyszyn-Trzewik P, et al. LUR: the 2016 update on the pharmacology, efficacy and safety profile. Pharmacol Rep. 2016;68(4):748–755.

16. Ishibashi T, Horisawa T, Tokuda K, et al. Pharmacological profile of LUR, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J Pharmacol Exp Ther. 2010;334(1):171–181.

17. Luradisone FDA prescribing information, last accessed on Jul 31 Available at https://www.latuda.com/LatudaPrescribingInformation.pdf

18. Miyake N, Miyamoto S, Jarskog LF. New serotonin/dopamine antagonists for the treatment of schizophrenia: are we making real progress? Clin Schizophr Relat Psychoses. 2012;6(3):122–133.

19. Sadock BJ. 2014. Kaplan & Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry. 11th. Sadock VA, Ruiz P. Philadelphia: Lippincott Williams & Wilkins (LWW). 318

20. Stahl SM, Cucchiaro J, Simonelli D, et al. Effectiveness of LUR for patients with schizophrenia following 6 weeks of acute treatment with LUR, olanzapine, or placebo: a 6-month, open-label, extension study. J Clin Psychiatry. 2013;74:507–515.

21. Egerton A, Ahmad R, Hirani E, et al. Modulation of striatal dopamine release by 5-HT2A and 5-HT2C receptor antagonists: [11C]raclopride PET studies in the rat. Psychopharmacology (Berl). 2008;200(4):487–496.

22. Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry. 2011;168(9):957–967.

23. Nikiforuk A. Targeting the serotonin 5-HT7 receptor in the search for treatments for CNS disorders: rationale and progress to date. CNS Drugs. 2015;29(4):265–275.

24. Citrome L. LUR for schizophrenia: a brief review of a new second-generation antipsychotic. Clin Schizophr Relat Psychoses. 2011;4(4):251–257.

25. Iyo M, Ishigooka J, Nakamura M, et al. Efficacy and safety of lurasidone in acutely psychotic patients with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled study. Psychiatry Clin Neurosci. 2021;75(7):227–235.

26. Potkin SG, Ogasa M, Cucchiaro J, et al. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. Schizophr Res. 2011;132(2–3):101–107.

27. Potkin SG, Kimura T, Guarino J. A 6-week, double-blind, placebo- and haloperidol-controlled, phase II study of lurasidone in patients with acute schizophrenia. Ther Adv Psychopharmacol. 2015 ;5(6):322–331. Erratum in: Ther Adv Psychopharmacol. 2015;5(6):369

28. Citrome L, Weiden PJ, McEvoy JP, et al. Effectiveness of LUR in schizophrenia or schizoaffective patients switched from other antipsychotics: a 6-month, open-label, extension study. CNS Spectr. 2014;19:330–339.

29. McEvoy JP, Citrome L, Hernandez D, et al. Effectiveness of LUR in patients with schizophrenia or schizoaffective disorder switched from other antipsychotics: a randomized, 6-week, open-label study. J Clin Psychiatry. 2013;74:170–179.

30. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394 (10202):939–951.

31. Nasrallah HA, Silva R, Phillips D, et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. J Psychiatr Res. 2013;47 (5):670–677.

32. Loebel A, Cucchiaro J, Xu J, et al. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: a 12-month, double-blind, noninferiority study. Schizophr Res. 2013;147 (1):95–102.

33. Calisti F, Cattaneo A, Calabrese M, et al. Efficacy and safety of lurasidone in schizophrenia: pooled analysis of European results from double-blind, placebo-controlled 6-week studies. Int Clin Psychopharmacol. 2022;37(5):215–222.

34. Patel PJ, Weidenfeller C, Jones AP, et al. Long-term assessment of lurasidone in schizophrenia: post hoc analysis of a 12-month, double blind, active-controlled trial and 6-month open-label extension study. Neurol Ther. 2021;10(1):121–147.

35. Feng Y, Shi J, Wang L, et al. Randomized, double-blind, 6-week non-inferiority study of lurasidone and risperidone for the treatment of schizophrenia. Psychiatry Clin Neurosci. 2020;74 (6):336–343.

36. Loebel A, Citrome L. Lurasidone: a novel antipsychotic agent for the treatment of schizophrenia and bipolar depression. BJPsych Bull. 2015;39(5):237–241.

37. Tandon R, Cucchiaro J, Phillips D, et al. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. J Psychopharmacol. 2016;30(1):69–77.

38. Loebel A, Silva R, Goldman R, et al. LUR dose escalation in early nonresponding patients with schizophrenia: a randomized, placebo-controlled study. J Clin Psychiatry. 2016;77(12):1672–1680.

39. Meltzer HY, Share DB, Jayathilake K, et al. Lurasidone improves psychopathology and cognition in treatment-resistant schizophrenia. J Clin Psychopharmacol. 2020;40(3):240–249.

40. Harvey PD, Siu CO, Ogasa M, et al. Effect of lurasidone dose on cognition in patients with schizophrenia: post-hoc analysis of a long-term, double-blind continuation study. Schizophr Res. 2015;166(1–3):334–338.

41. Harvey PD, Siu CO, Loebel AD. Change in daytime sleepiness and cognitive function in a 6-month, double-blind study of lurasidone and quetiapine XR in patients with schizophrenia. Schizophr Res Cogn. 2016;5:7–12.

42. Harvey PD, Siu CO, Hsu J, et al. Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study followed by a 6-month double-blind extension. Eur Neuropsychopharmacol. 2013;23 (11):1373–1382.

43. Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. Lancet. 2022;399(10327):824–836.

44. Ogasa M, Kimura T, Nakamura M, et al. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. Psychopharmacology (Berl). 2013;225(3):519–530.

45. Yee CS, Bahji A, Lolich M, et al. Comparative efficacy and tolerability of antipsychotics for juvenile psychotic disorders: a systematic review and network meta-analysis. J Clin Psychopharmacol. 2022;42(2):198–208.

46. Loebel A, Cucchiaro J, Sarma K, et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. Schizophr Res. 2013;145(1–3):101–109.

47. Higuchi T, Iyo M, Kwon JS, et al. Randomized, double-blind, placebo, and risperidone-controlled study of lurasidone in the treatment of schizophrenia: results of an inconclusive 6-week trial. Asia Pac Psychiatry. 2019;11(3):e12354. Erratum in: Asia Pac Psychiatry. 2021 Sep;13(3):e12481.

48. Allen MH, Citrome L, Pikalov A, et al. Efficacy of lurasidone in the treatment of agitation: a post hoc analysis of five short-term studies in acutely ill patients with schizophrenia. Gen Hosp Psychiatry. 2017;47:75–82.

49. Newcomer JW, Ng-Mak D, Rajagopalan K, et al. Hospitalization outcomes in patients with schizophrenia after switching to lurasidone or quetiapine: a US claims database analysis. BMC Health Serv Res. 2018;18(1):243.

50. Correll CU, Tocco M, Hsu J, et al. Short-term efficacy and safety of lurasidone versus placebo in antipsychotic-naïve vs. previously treated adolescents with an acute exacerbation of schizophrenia. Eur Psychiatry. 2022;65(1):1–35.

51. Correll CU, Tocco M, Pikalov A, et al. Long-term safety and effectiveness of open-label lurasidone in antipsychotic-Naïve versus previously treated adolescents with Schizophrenia: a post-hoc analysis. Schizophr Res. 2022;240:205–213.

52. Goldman R, Loebel A, Cucchiaro J, et al. Efficacy and safety of LUR in adolescents with schizophrenia: a 6-week, randomized placebo-controlled study. J Child Adolesc Psychopharmacol. 2017;27(6):516–525.

53. Costamagna I, Calisti F, Cattaneo A, et al. Efficacy and safety of lurasidone in adolescents and young adults with schizophrenia: a pooled post hoc analysis of double-blind, placebo-controlled 6-week studies. Eur Psychiatry. 2021;64(1):e35.

54. Damkier P, Videbech P. The safety of second-generation antipsychotics during pregnancy: a clinically focused review. CNS Drugs. 2018;32(4):351–366.

   •paper of interest reporting updated data on using antipsychotic during pregnancy.

55. Drugs and Lactation Database (LactMed) [Internet].

56. Hagi K, Tadashi N, Pikalov, S5 A. Does the time of drug administration alter the adverse event risk of lurasidone? Schizophr Bull. 2020;46(Supplement_1):S31–S32.

57. Higuchi T, Ishigooka J, Iyo M, et al. Lurasidone in the treatment of schizophrenia: results of a double-blind, placebo-controlled trial in Asian patients. Asia Pac Psychiatry. 2019;11(2):e12352.

58. Preskorn S, Ereshefsky L, Chiu YY, et al. Effect of food on the pharmacokinetics of LUR: results of two randomized, open-label, crossover studies. Hum Psychopharmacol. 2013;28(5):495–505.

59. Riva MA, Albert U, de Filippis S, et al. Identification of clinical phenotypes in schizophrenia: the role of lurasidone. Ther Adv Psychopharmacol. 2021;11:20451253211012250.

60. Leucht S, Crippa A, Siafis S, et al. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. Am J Psychiatry. 2020 Apr 1;177(4):342–353.

61. Srisurapanont M, Suttajit S, Likhitsathian S, et al. A network meta-analysis of the dose-response effects of lurasidone on acute schizophrenia. Sci Rep. 2021;11(1):5571.

62. Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(6):829–836.

63. Correll CU, Sikich L, Reeves G, et al. Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the IMPACT trial. World Psychiatry. 2020;19(1):69–80.

64. Taipale H, Tanskanen A, Mehtälä J, et al. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). World Psychiatry. 2020;19(1):61–68.

65. Mattingly GW, Haddad PM, Tocco M, et al. Switching to LUR following 12 months of treatment with Risperidone: results of a 6-month, open-label study. BMC Psychiatry. 2020;20(1):199.

66. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep. 1962;10:799–812.

67. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–276.

68. Menon V. Brain networks and cognitive impairment in psychiatric disorders. World Psychiatry. 2020;19(3):309–310.

69. Citrome L. Lurasidone for the acute treatment of adults with schizophrenia: what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? Clin Schizophr Relat Psychoses. 2012;6:76–85.

70. Heckers S, Kendler KS. The evolution of Kraepelin's nosological principles. World Psychiatry. 2020;19(3):381–388.

71. Chekroud AM, Bondar J, Delgadillo J, et al. The promise of machine learning in predicting treatment outcomes in psychiatry. World Psychiatry. 2021;20(2):154–170.

72. Loebel A, Cucchiaro J, Silva R, et al. Efficacy of lurasidone across five symptom dimensions of schizophrenia: pooled analysis of short-term, placebo-controlled studies. Eur Psychiatry. 2015;30(1):26–31.