STUDY REPORT

An observational, real-world evidence study to describe clinical experience with lurasidone in the treatment of adult patients with schizophrenia in routine clinical practice in Europe

Confidential

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STUDY GLOSSARY

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
A and E	Accident and emergency
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate transaminase
CGI	Clinical Global Impression
CI	Confidence interval
EDC	Electronic data capture
eDCF	Electronic data collection form
EMA	European Medicines Agency
FDA	Food and Drug Administration
GGT	Gamma glutamyl transpeptidase
HDL	High-density lipoprotein
IQR	Interquartile range
LDL	Low-density lipoprotein
MADRS	Montgomery–Åsberg Depression Rating Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PANSS	Positive and Negative Syndrome Scale
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SD	Standard deviation
SDV	Source data verification
SGA	Second-generation antipsychotic
UK	United Kingdom

STUDY DEFINITIONS

Term	Definition
Index event	Initiation (first prescription) of lurasidone
Index event date	Date of initiation of lurasidone
Baseline	Baseline is defined as the closest measurement taken within 3 months prior to index event
Pre-index observation period	This extends from the date of diagnosis of schizophrenia up to the index event
Post-index observation period	This extends to a maximum of 12 months post index event
Permitted windows for endpoints related to specific time points	Where measurements closest to the 3-, 6-, 9-, and 12-month time points after index event are to be analysed, the closest measurement must fall within 4 weeks of either side of each time point
Schizophrenia relapse	Relapse of schizophrenia was defined according to clinicians' judgement as recorded in patients' medical records

1 INTRODUCTION

1.1 Definition of the disease

Schizophrenia is a psychiatric disorder characterised by positive symptoms including lack of insight, hallucination, delusions, and thought disorders; and negative symptoms including social withdrawal, self-neglect, and loss of motivation (1). The disease course is chronic and disabling, with patients experiencing multiple relapses of acute psychotic exacerbation (2). More than 80% of patients experience a relapse after recovery from their initial psychotic episode (3), and thus prevention of relapse is a key goal of treatment.

1.2 Epidemiology and burden of the disease

An estimated 20 million people are diagnosed with schizophrenia worldwide (4). Disease onset occurs in adolescence and young adulthood, peaking at approximately 40 years of age (5). The incidence of schizophrenia is higher in males than females (6); other known risk

factors include obstetric complications, advanced parental age, childhood trauma, urban environments, and substance use (7).

The economic burden of schizophrenia is substantial and includes direct and indirect healthcare costs. Globally, annual costs range from US$94 million to US$102 billion, with indirect costs such as productivity loss, premature mortality and unemployment comprising 50%-85% of total costs (8). Schizophrenia ranks among the top 20 diseases in years lived with disability globally (4).

1.3 Clinical management

Treatment for schizophrenia includes both pharmacological treatments and psychotherapy. Second-generation antipsychotics (SGAs) are generally the first line of pharmacological treatment for schizophrenia and are preferred over first-generation antipsychotics as they cause fewer extrapyramidal adverse effects like akathisia, dyskinesia and dystonia (9). However, SGAs are associated with several adverse effects (weight gain, metabolic syndrome, akathisia), and their prescription requires careful consideration of patients' previous tolerability, clinical history and comorbidities (9, 10).

Lurasidone is an SGA that has been shown to have a lower risk of weight gain and is associated with a lower incidence of metabolic adverse events (AEs) in comparison with some other drugs of the same therapeutic class (11-14). A recent retrospective analysis of an electronic prescription database in the USA reported that lurasidone treatment for patients with schizophrenia and bipolar disorder was associated with a reduction in body weight during the first year of treatment (15). Long-term treatment with lurasidone has also been associated with lower incidence of disease relapse (16). Lurasidone received a marketing authorisation from the European Medicines Agency (EMA) in 2014 and is indicated for the treatment of schizophrenia in adults and adolescents age 13 years and older (17).

1.4 Rationale of the study objectives

There is currently a paucity of real-world evidence in Europe on the effectiveness of lurasidone treatment and its position in the treatment pathway for schizophrenia. This study aimed to address this knowledge gap by describing the baseline patient demographics, clinical characteristics and adverse drug reactions (ADRs), as well as clinical outcomes such as changes in body weight and metabolic parameters observed during the first 12 months following initiation of lurasidone treatment.

2 STUDY AIMS AND OBJECTIVES

2.1 Aim

The aim of this study was to understand current treatment patterns for lurasidone in adult patients with schizophrenia.

2.2 Objectives

Primary objective:

- To describe the dose titration process, dosing regimens, treatment duration and reasons for discontinuation following initiation of lurasidone in adult patients with schizophrenia.

2.3 Secondary objectives

- To describe baseline demographics and clinical characteristics of adult patients with schizophrenia commencing treatment with lurasidone.
- To describe the treatment history of adult patients with schizophrenia prior to initiation of lurasidone in routine clinical practice.
- To describe the position of lurasidone within the treatment pathway for adult patients with schizophrenia.
- To describe the clinical outcomes of patients over 12 months from the date of initiation of lurasidone.

- To describe the ADRs related to lurasidone treatment observed over the 12 months from date of initiation in adult patients with schizophrenia.
- To describe healthcare resource utilisation for patients over 12 months from the date of first initiation of lurasidone.

2.4 Hypothesis

There was no *a priori* hypothesis tested in this study; this was a descriptive study of current management of schizophrenia using lurasidone in the United Kingdom (UK) and Switzerland.

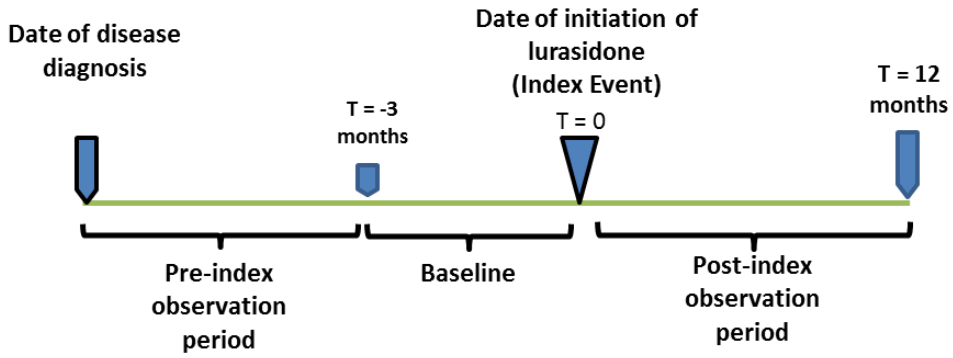
3 METHODOLOGY

3.1 Design

This was an international, multicentre observational study based on both retrospective and prospective collection of data from patients' medical records, conducted in mental health centres in the UK and Switzerland. It is a single-group study without a comparator, to reflect real-world clinical practice. Both retrospective and prospective methods of patient identification and consent were used, as described in section 3.3. There were no changes to patient management for the purposes of any part of the study, and no additional tests, investigations or visits were required. Figure 1 outlines the study design and key data points. The data variables that were collected at various time points of the study are described in section 3.6.

The study design with a 12-month enrolment period allowed for the identification and recruitment of sufficient numbers of participants who had commenced treatment with lurasidone.

Figure 1: Study design and key data points



Lurasidone received marketing authorisation from the EMA in 2014 (12). Based on feasibility assessments, data required to evaluate the treatment history, baseline demographics and clinical characteristics of patients with schizophrenia initiated with lurasidone treatment were deemed likely to be routinely recorded for all patients. A 12-month post-index observation period was considered a sufficient length of time to capture changes in lurasidone dosage, frequency of schizophrenia relapses and ADRs.

Based on the targetsample size (80 patients), geographic spread (UK and Switzerland) and patient selection criteria, the results of this study should be generalisable to the wider patient population with schizophrenia treated with lurasidone in routine clinical practice.

3.2 Patient eligibility

3.2.1 Inclusion criteria

1. Aged ≥18 years of age at time of initiation of lurasidone.
2. Provided consent for access to medical records for study data collection (applicable to living patients only).
3. Documented diagnosis of schizophrenia before the initiation of lurasidone.
4. Initiated on lurasidone after the 1st January 2016.
5. Judged to have capacity by their clinician to provide valid written informed consent to participate in this study.

3.2.2 Exclusion criteria

1. Patients whose medical records were unavailable for review.
2. Patients who participated in a clinical trial of an investigational medicinal product during the post-index observation period.

3.3 Patient identification, sampling and recruitment

Patients prescribed lurasidone who met the study eligibility criteria were identified by members of their direct care team. Living patients were approached and asked to provide consent for their medical records to be used in the study.

To enable the target sample size to be achieved, two methods of patient identification and consent were used:

1. Retrospective recruitment: All patients who had been previously initiated on lurasidone at least 12 months before the date of enrolment in the participating centres were identified from hospital pharmacy records, hospital databases, electronic prescribing records, and clinic lists or by review of patient medical records. Living patients were approached, given information about the study and asked to complete a consent form either by post or when they attended the clinic for a routine appointment or to return the signed consent form as a scanned copy/picture. Deceased patients were still eligible for participation but could not provide informed consent. To avoid causing distress to the deceased's relatives, consent was not sought for use of data. Instead, data from deceased patients were collected by members of the direct care team who had a right to access medical records.

2. Prospective recruitment: Patients who had been initiated on lurasidone less than 12 months before the date of enrolment (i.e., those for whom the full 12-month post-index period had not yet elapsed) were identified from hospital pharmacy records, hospital databases, electronic prescribing records, clinic lists, and review of patient medical records or at routine appointments. These patients were approached, given information about the study and asked to complete a consent form either by post or when they attended the centre for a routine appointment or to return the signed

consent form as a scanned copy/picture. Consecutive patients were recruited until the required sample size was achieved.

3.4 Observation period

The pre-index observation period of this study extended from the date of diagnosis of schizophrenia up to the date of initiation of lurasidone treatment (the index date). All data to be collected in the pre-index observation period were recorded but only if there was a documented record of the data in the medical records within 10 years prior to the index date.

Baseline patient characteristics and observations were collected within 3 months prior to the index date.

The post-index observation period extended up to 12 months after the index date.
Study enrolment and the entire study duration were dependent on the rate of prescription of lurasidone in normal clinical practice at the participating study centres.

3.5 Data collection

Data were collected from medical records both retrospectively and prospectively using a standardised electronic data collection form (eDCF) designed specifically for the study. Data were collected by members of the direct care team or external researchers via an electronic data capture (EDC) system using eDCFs. Data from deceased patients were collected only by members of the direct care team to preserve confidentiality. Patients were identified in all study records by a unique study code to link multiple study records for each participant (if applicable) and to preserve patient confidentiality.

3.6 Study endpoints and dataset

The study endpoints and dataset required to address the study objectives are summarised in Table 1. Study endpoints were reported using descriptive statistics of distribution, central tendency and dispersion as appropriate for the data collected.

Table 1. Endpoints and dataset required to address the study objectives

Endpoint(s) and variables required to address the primary objective	
Endpoint to address the primary objective	**Variables required to address the primary objective**
To describe the dose titration process, dosing regimens, treatment duration and reasons for discontinuation following initiation of lurasidone in adult patients with schizophrenia	
• Summary measures of lurasidone treatment duration (primary endpoint) • Summary of reasons for initiation of lurasidone • Dose distribution of lurasidone prescribed to patients with schizophrenia during the study observation period • Summary measures of starting and subsequent doses of lurasidone • Summary of reasons for lurasidone dose changes • Summary of lurasidone treatment discontinuations • Summary of reasons for discontinuation of lurasidone • Distribution of patients taking lurasidone in the morning or evening • Distribution of patients taking lurasidone with a meal	• Date of initiation of lurasidone (index date) (DD/MM/YYYY) • Reason for initiation of lurasidone • Total daily dose of lurasidone at initiation • Dosing regimen of lurasidone at initiation (e.g., once daily, twice daily) • Time of day dose of lurasidone is taken (MM:HH) or am/pm • Lurasidone commonly taken with a meal (Yes/No/Not recorded) • Stop date of each dose of lurasidone throughout the observation period (DD/MM/YYYY) • Date of initiation of each subsequent new dose of lurasidone (DD/MM/YYYY) • Total daily dose of each subsequent new dose of lurasidone • Dosing regimen of each subsequent new dose of lurasidone (e.g., once daily, twice daily, etc.) • Reason for dose change/discontinuation of lurasidone

Endpoint(s) and variables required to address the secondary objectives

Endpoint to address the secondary objective	Variables required to address the secondary objective
To describe baseline demographics and clinical characteristics of adult patients with schizophrenia commencing treatment with lurasidone	
• Summary measures of baseline demographics • Summary measures of baseline clinical characteristics and comorbidities	• Month and year of birth (MM/YYYY) • Sex (M/F) • Diagnosis of subtype of schizophrenia (paranoid, disorganized, catatonic, undifferentiated, residual, schizoaffective disorder or other), if recorded • Height (cm), date of measurement (DD/MM/YYYY) • Weight (kg), date of measurement (DD/MM/YYYY) • BMI, date of measurement (DD/MM/YYYY) • Ethnicity (based on but not exclusive to the following categories: White, Mixed / Multiple ethnic groups, Asian, Black / African / Caribbean, Other ethnic group) • A current history of alcohol misuse (Y/N) *(defined as a patient who is known to have a current history of drinking excessively more than the lower-risk limits of alcohol consumption)* • A current history of illicit drug abuse (Y/N) *(defined as a patient who is known to have a current history of taking illicit substances or drugs)* • Smoking status (Y/N) • Positive and Negative Syndrome Scale (PANSS) total score at baseline • Clinical Global Impression (CGI) severity score at baseline • Montgomery–Åsberg Depression Rating Scale (MADRS) total score at baseline • Related comorbidities

	○ major depressive disorder ○ substance abuse ○ hypertension ○ hyperlipidaemia ○ diabetes ○ chronic obstructive pulmonary disease ○ anxiety • Blood glucose (mg/dl) • Serum lipids (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides) • Liver function test results (albumin, ALT, ALP, AST, GGT)
To describe the treatment history of adult patients with schizophrenia prior to initiation of lurasidone in routine clinical practice	
• Summary measures of treatment history for schizophrenia (from date of diagnosis to index date), including: ○ Duration of disease until index date ○ Prior treatments for schizophrenia • Distribution of reasons for treatment changes	• Date of diagnosis of schizophrenia (DD/MM/YYYY) • Date of initiation of lurasidone (DD/MM/YYYY) • Names of all prior antipsychotic treatments and other therapies (cognitive behavioural therapy, compliance therapy, individual supportive therapy) for schizophrenia (pre-index period) • Dates of initiation of each prior antipsychotic treatment and other therapies for schizophrenia before index date (DD/MM/YYYY) • Reason for initiating each prior antipsychotic treatment or other therapy for schizophrenia before index date
To describe the position of lurasidone within the treatment pathway for adult patients with schizophrenia	

• Summary distribution of concomitant antipsychotic medications • Summary distribution of other therapies for schizophrenia • Number of treatments for schizophrenia prior to initiation of lurasidone • Number of new treatments for schizophrenia after discontinuation of lurasidone (during post-index observation period)	• Date of initiation of lurasidone (DD/MM/YYYY) • Names of all prior antipsychotic treatments and other therapies (cognitive behavioural therapy, compliance therapy, individual supportive therapy) for schizophrenia (pre-index period) • Dates of initiation of each prior antipsychotic treatment and other therapies for schizophrenia before index date (DD/MM/YYYY) • Reason for initiating each prior antipsychotic treatment or other therapy for schizophrenia before index date • Names of antipsychotic treatments and other therapies (cognitive behavioural therapy, compliance therapy, individual supportive therapy) for schizophrenia following initiation of lurasidone (post-index period) • Dates of initiation of each antipsychotic treatment and other therapies for schizophrenia following the initiation of lurasidone (DD/MM/YYYY) • Reason for initiating each antipsychotic treatment or other therapy for schizophrenia following the initiation of lurasidone
To describe the clinical outcomes of patients over 12 months from the initiation of lurasidone	
• Time until first relapse in the 12 months following initiation of lurasidone • Number of relapses in the 12 months following initiation of lurasidone • Changes in weight, blood glucose, lipid levels, and liver function from baseline	• Dates of first relapse of schizophrenia, as documented in the medical records • Dates of subsequent relapses of schizophrenia • Body weight (kg) and date of measurement (DD/MM/YYYY) • Blood glucose (mg/dl) and date of measurement (DD/MM/YYYY)

at approximately 3, 6, 9 and 12 months (±1 month) following the initiation of lurasidone	• Serum lipids (total cholesterol, LDL, HDL, triglycerides) and date of measurement (DD/MM/YYYY) • Liver function test results (albumin, ALT, ALP, AST, GGT) and date of measurement (DD/MM/YYYY)
To describe the ADRs related to lurasidone treatment observed over the 12 months from date of initiation in adult patients with schizophrenia	
• Summary distribution of ADRs following the initiation of lurasidone	• Name and date (DD/MM/YYYY) of ADR judged to be related to the use of lurasidone if recorded in medical notes
To describe healthcare resource utilisation for patients over 12 months from the date of first initiation of lurasidone	
• Summary measures of schizophrenia-related healthcare resource utilisation following initiation of lurasidone to include: o Inpatient admissions per patient, including specialty, elective or non-elective, and reasons o Inpatient bed days per patient o Length of stay per inpatient admission o Outpatient visits per patient o Emergency department visits per patient	• Date of hospital admission for a schizophrenia-related event (DD/MM/YYYY) • Reason for hospital admission • Date of discharge from hospital for a schizophrenia-related event (DD/MM/YYYY) • Speciality department for hospital admission • Elective/non-elective admission to hospital • Date of admission to emergency department for a schizophrenia-related event (DD/MM/YYYY) • Date of discharge from emergency department for a schizophrenia-related event (DD/MM/YYYY) • Date of schizophrenia outpatient visits (DD/MM/YYYY)

3.7 Pharmacovigilance procedures

3.7.1 Definitions

3.7.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition.

An ADR is an AE that is considered related to the medicinal product.

3.7.1.2 Serious Adverse Events

A serious adverse event (SAE) is any AE as defined above that:

- is fatal
- is life-threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another significant medical hazard

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refers to important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, events that necessitate an emergency department visit, outpatient surgery, or other events that require other urgent intervention.

A serious adverse drug reaction (SADR) is an SAE that is considered related to the medicinal product.

3.7.2 Reporting procedures for adverse events

All AEs considered related to lurasidone and therefore classified as ADRs were reported by the Principal Investigator at each centre within 24 hours of discovery or notification. In the UK, ADRs were reported to vigilance@sunovion.eu, and in Switzerland, ADRs were reported to vigilance@medius.ch and safety.eu@sunovion.com. Initial AE information and all follow-up information were on the AE form and emailed to vigilance@sunovion.eu (UK) or vigilance@medius.ch and safety.eu@sunovion.com (Switzerland).

ADRs for non-Study Sponsor products were notified by the Principal Investigator at each centre to the appropriate Marketing Authorisation Holder (MAH) and/or to the relevant Regulatory Authority.

3.8 Data management & quality control

3.8.1 Data management

Data management for eDCFs was carried out using MACRO™, a data management system which has a secure web-based data entry interface and is fully validated and compliant with Food and Drug Administration (FDA) Information Governance standard 21 Code of Federal Regulations (CFR) part 11 (18). The MACRO™ system has restricted access permissions for data entry management and analysis and maintains an audit trail of all changes to data and activity in the system in line with 21 CFR part 11. Entry to MACRO™ was restricted (by password protection) to only those members of staff directly involved with the study.

3.8.2 Data quality checks

All data collectors were provided with Data Collection Guidelines to facilitate consistent completion of the eDCF. The accuracy and quality of data collection via the eDCF was monitored by reference to source data (source data verification [SDV]). SDV was performed by an external researcher from the study management company on the complete dataset of

a random sample of at least 10% of patients at each centre. Any issues identified related to quality, accuracy or consistency of data collection were discussed with the data collector concerned and further training provided if required. If any subsequent issues were identified related to quality, accuracy or consistency of data collection, a random check of a further 10% of data collected by that data collector was undertaken. If any further issues were identified, 100% SDV was undertaken at the centre. It was the Investigator's responsibility to ensure the accuracy of the data entered in the DCFs.

SDV was performed by a researcher who did not collect data for that patient record.

As consent for access to medical records by an external researcher cannot be obtained from deceased patients, SDV for deceased patients was performed using a 'back-to-back' methodology with a member of the direct care team. This involved the direct care team member at the site reciting data from the patient notes to the external researcher so that they could verify the data in the eDCF without the need to look directly at the identifiable source records.

All clinical data submitted in the eDCF were checked for eligibility, completeness and accuracy and queries were raised by the data management team from the study management company using agreed manual and programmed validation checks. Study centres were required to co-operate with the data management team in the resolution of these queries.

3.8.3 Data analysis

Analyses were performed by OPEN VIE and were descriptive in nature. For continuous variables (such as duration of time with disease), the mean, standard deviation, median, interquartile range and range were calculated. For nominal variables (e.g., number of patients receiving a given past treatment or discontinuing for a specific reason), frequencies and proportions in the form of percentages were calculated for each group. For investigating changes in weight, blood glucose, lipid levels and liver function from baseline at 3, 6, 9 and 12 months following initiation of lurasidone, changes were described using summary measures as described for continuous variables above for each time; they were then compared using a

paired t-test (or Wilcoxon signed rank test if distributions were non-normal), although based upon a previous study of changes in weight (10) as a result of treatment change, it was expected that any change would be too small to detect a significant change with a feasible sample size for the study (for a change in weight of -0.77 kg over a year with a standard deviation of 25.4, there would only be a power of approximately 5% with the current proposed sample size of 80; a sample of 16,000 per group would be needed for 80% power).

Please note, all percentages are reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding.

3.8.3.1 Subgroup analysis

No subgroup analyses were conducted.

3.8.3.2 Missing Data

Where data were missing from the original medical record, the affected analyses were conducted using only the results of those patients with data available, and the number included in each analysis is stated. The percentage of data missing is reported for each study variable. Where dates were ambiguous because of missing days and/or months, standard imputation was applied: where a day was missing, the 15th of the month was assumed; where both day and month were missing, the 1st of July was assumed.

3.8.4 Assumptions

No assumptions were made.

4 RESULTS

4.1 Study sample

A total of 7 centres participated in the study, 6 in the UK and 1 in Switzerland (Table 2).

Table 2: Participating centres

Centre No.	Centre	Name of principal investigator
GB-01	Hywel Dda Health Board, Wales	Dr Matthew Sargeant
GB-02	West London Mental Health NHS Trust	Dr Sofia Pappa
GB-03	Merlyn Vaz Healthcare Hub, Leicestershire Partnership NHS Trust	Dr Debasis Das
GB-04	Southern Health NHS Foundation Trust, Moorgreen Hospital	Prof Shanaya Rathod
GB-05	Coventry and Warwickshire Partnership NHS Trust, The Railings	Dr Pradeep Peddu
GB-06	Sussex Partnership NHS Foundation Trust, Mill View Hospital	Dr Richard Whale
CH-01	Kliniken für Psychiatrie, Psychotherapie und Psychosomatik	Dr Beat Nick

4.2 Patient demographics

The age and gender of patients are shown in Table 3. Sixty-five percent of patients were male, and 35% were female. The median (interquartile range [IQR]) age was 28.0 (23.0 to 37.0) at schizophrenia diagnosis and 33.5 (25.5 to 50.3) years at initiation of lurasidone.

Table 3: Gender and age of patients

	Overall N=48
Age (years) at schizophrenia diagnosis	
n	29
Mean	32.0
SD	12.0
Median	28.0
IQR	23.0 to 37.0
Range	18.0 to 60.0
Age (years) at initiation of lurasidone	
n	48
Mean	37.8
SD	14.7
Median	33.5
IQR	25.5 to 50.3
Range	19.0 to 78.0
Gender, n (%)	
Male	31 (65%)
Female	17 (35%)

The most common patient ethnicity (Table 4) was White (76%), followed by Asian (11%) and Black (8%).

Table 4: Patient ethnicity

	n (patients)	% (n=48)
White	29	76%
Asian	4	11%
Black	3	8%
Chinese	1	3%
Mixed	1	3%
Missing/not recorded	9	19%

The median (IQR) height was 170.0 (166.3 to 178.5) cm, median (IQR) weight was 84.0 (69.0 to 102.5) kg, and median BMI was 27.4 (24.6 to 33.0) kg/m^2.

Table 5: Patient height, weight, and body mass index

	Overall N=48
Height (cm)	
n	19
Mean	171.7
SD	10.2
Median	170.0
IQR	166.3 to 178.5
Range	148.5 to 190.0
Weight (kg)	
n	21
Mean	87.1
SD	22.5
Median	84.0
IQR	69.0 to 102.5
Range	50.9 to 132.4
Body mass index (kg/m^2)	
n	18
Mean	29.5
SD	7.2
Median	27.4
IQR	24.6 to 33.0
Range	4.0 to 46.0

Most patients (77%) had schizophrenia of the paranoid subtype (Table 6).

Table 6: Schizophrenia subtype

	n (patients)	% (n=48)
Paranoid	37	77%
Catatonic	1	2%
Other specified	3	6%
Not Known	7	15%

As reported by study investigators, half of patients (49%) were current smokers, 20% were current illicit drug users, and 18% were currently misusing alcohol (Table 7).

Table 7. Patient use of drugs, alcohol, and tobacco

	n (patients)	% (n=48)
Current alcohol misuse		
n	40	
Yes	7	18%
No	33	83%
Current illicit drug use		
n	41	
Yes	8	20%
No	33	80%
Current smoker		
n	37	
Yes	18	49%
No	19	51%

Baseline PANSS score, CGI severity score, and MADRS score were missing for all 48 patients. Anxiety (25%) and diabetes (15%) were the most common related comorbidities among study patients. More than half of patients (58%) had no related comorbidities (Table 8).

Table 8. Patient comorbidities

	n (patients)	% (n=48)
Anxiety	12	25%
Diabetes	7	15%
Major depressive disorder	3	6%
Hypertension	3	6%
Hyperlipidaemia	2	4%
Cardiac disease	2	4%
Number of related comorbidities		
One	13	27%
Two	4	8%
Three	3	6%
None	28	58%

Few patients had baseline blood glucose, cholesterol, albumin, and liver function test results at the time of lurasidone initiation (Table 9; Table 10). Median values were within normal limits.

Table 9: Blood glucose and cholesterol levels at time of lurasidone initiation

	Overall N=48
Blood glucose (mmol/l)	
n	11

	Overall N=48
Mean	14.0
SD	12.3
Median	8.5
IQR	6.2 to 16.9
Range	4.8 to 40.0
Total cholesterol (mmol/l)	
n	8
Mean	5.8
SD	2.4
Median	5.0
IQR	4.2 to 7.0
Range	3.2 to 10.4
Low-density lipoprotein (LDL) cholesterol (mmol/l)	
n	4
Mean	2.9
SD	1.4
Median	2.4
IQR	2.0 to 3.2
Range	1.8 to 4.8
High-density lipoprotein (HDL) cholesterol (mmol/l)	
n	8
Mean	1.4
SD	0.7
Median	1.1
IQR	1.0 to 1.6
Triglycerides (mmol/l)	
n	5
Mean	2.3
SD	1.4
Median	1.9
IQR	1.5 to 2.0

Table 10: Other laboratory values at time of lurasidone initiation

	Overall N=48
Albumin (g/l)	
n	7
Mean	41.7
SD	6.1
Median	43.0
IQR	38.0 to 45.5
Range	32.0 to 50.0
Alanine aminotransferase (u/l)	
n	8
Mean	28.5
SD	21.5
Median	21.0
IQR	14.0 to 36.5
Range	8.0 to 66.0
Aspartate aminotransferase (u/l)	
n	2
Mean	14.5
SD	4.9
Median	14.5
IQR	12.8 to 16.3
Range	11.0 to 18.0
Alkaline phosphatase (u/l)	
n	7
Mean	74.7
SD	31.0
Median	79.0
IQR	64.5 to 93.0
Gamma glutamyl transferase (u/l)	
n	3
Mean	24.4
SD	15.9
Median	20.0
IQR	15.6 to 31.0

Duration of disease prior to initiating lurasidone was available for 15 patients, among whom the median duration (IQR) was 4.5 (0.3 to 8.9) years (Table 11).

Table 11: Duration of disease in patients initiating lurasidone

	Overall N=48
n	15
Mean	5.4
SD	5.7
Median	4.5
IQR	0.3 to 8.9
Range	0.0 to 24.5

4.3 Prior and concomitant therapies

Forty-six of the 48 study patients received at least one typical or atypical antipsychotic prior to initiating lurasidone (Table 12). More than one-third of patients (35%) received clozapine prior to lurasidone, and more than half of patients had previously received aripiprazole (81%) and olanzapine (69%).

Table 12: Antipsychotic medications received prior to lurasidone

	n (regimens)	% (n=48)
Typical antipsychotics	49	
clozapine	17	35%
haloperidol	13	27%
zuclopenthixol	4	8%
flupentixol	3	6%
flupentixol decanoate	3	6%
pipotiazine palmitate	3	6%
fluphenazine decanoate	2	4%
zuclopenthixol decanoate	2	4%
chlorpromazine	1	2%
trifluoperazine	1	2%
Atypical antipsychotics	133	
aripiprazole	39	81%
olanzapine	33	69%
risperidone	23	48%
amisulpride	16	33%
quetiapine	16	33%
paliperidone	5	10%
paliperidone palmitate	1	2%
No prior therapies	2	4%

In addition, 18 patients (38%) had received individual supportive therapy, and none of the patients had received prior cognitive behavioural therapy or compliance therapy (Table 13).

Table 13: Reasons for prior antipsychotic treatment changes

	n (patients)	% (n=48)
Lack of efficacy of previous treatment	43	90%
None, this is the first treatment for schizophrenia	28	58%
Side effect on prior treatment	26	54%
Next line of therapy	9	19%
Patient preference	9	19%
Co-existing conditions	2	4%
Other	31	65%
Unknown	31	65%

* Reasons for treatment changes are not mutually exclusive as patients may have received multiple treatments.

The majority of patients (90%) received one antipsychotic concomitantly with lurasidone (Table 14). Seven patients were receiving concomitant cardiovascular medications, and five patients received diabetes medications.

Table 14: Number of concomitant antipsychotic, cardiovascular and diabetes medications

	n (patients)	% (n=48)
Antipsychotic		
One	43	90%
Two or more	5	10%
Cardiovascular		
One	2	4%
Two or more	5	10%
Diabetes		
One	3	6%
Two or more	2	4%

4.4 Lurasidone utilisation

During the 12-month follow-up period, median duration of lurasidone treatment was 12 months (Table 15). Duration of therapy ranged from 0.1 to 12 months. Thirty-eight out of 48 patients (79%) continued lurasidone for the entire 12-month follow-up period.

Table 15: Duration of treatment with lurasidone during the study observation period

	Overall N=48
n	48
Mean	10.1
SD	3.9
Median	12.0
IQR	12.0 to 12.0
Range	0.1 to 12.0

The median starting dose of lurasidone was 37 mg daily and ranged from 9.3 mg to 148 mg daily (Table 16). Among the 82 subsequent regimens prescribed, the median dose was 74 mg daily and ranged from 37 mg to 148 mg daily.

Table 16: Overview of lurasidone starting and subsequent doses

	Overall	Starting doses	Subsequent doses
n	93	47	82
Mean	98.9	46.8	85.4
SD	40.9	30.5	33.2
Median	111.0	37.0	74.0
IQR	74.0 to 111.0	37.0 to 38.8	74.0 to 111.0
Range	9.3 to 259.0	9.3 to 148.0	37.0 to 148.0

Note: As many subsequent doses were given for one patient, n is higher than the total number of patients for overall and subsequent doses.

Approximately half of patients (53%) initiated lurasidone at 37 mg daily (Table 17). The most common subsequent dose was 74 mg daily (41%), followed by 111 mg daily (20%) and 148 mg daily (13%).

Table 17: Lurasidone starting and subsequent doses prescribed

Dosage (in mg)	Starting Doses		Subsequent Doses	
	n	% (n=47)	n	% (n=82)
9.25	1	2%	0	0%
18.5	7	15%	0	0%
37	25	53%	10	12%
37.5	2	4%	1	1%
40	2	4%	0	0%
55.5	1	2%	6	7%
74	3	6%	34	41%
75	0	0%	1	1%
80	0	0%	1	1%
92.5	0	0%	2	2%
111	5	11%	16	20%
148	1	2%	11	13%
Missing	1		11	

Dose titration was one of the reported reason(s) for dose change for nearly all patients (Table 18). Other common reasons for dose change included patient request (31%) and physician request (19%).

Table 18: Reason for lurasidone dose change

	n	% (n=48)
Dose titration	46	96%
Adverse effect	2	4%
Patient request	15	31%
Psychotic episode	3	6%
Treatment failure	1	2%
Physician request	9	19%
Other	17	35%

Note: Reasons are not mutually exclusive, as one patient may have had multiple reasons to change dose.

Instructions for administration by time of day were available for 25 patients, of whom morning administration was planned for 5 (20%) and afternoon/evening administration was planned for 20 (80%). Timing in relation to meals was recorded for 15 patients, all of which were planned to be administered with meals.

Table 19: Planned administration of lurasidone by time of day and with/without a meal

	Morning (AM)	Afternoon/ evening (PM)	AM/PM not recorded	Overall

	n	% (n=5)	n	% (n=20)	n	% (n=23)	n	% (n=48)
With meal	3	60%	8	40%	4	17%	15	31%
Not recorded	2	40%	12	60%	19	83%	33	69%
Total	5	100%	20	100%	23	100%	48	100%

Three-quarters of patients were treated with lurasidone continuously without temporary or permanent discontinuation (Table 20). Ten patients discontinued or suspended therapy once, and two patients did so twice.

Table 20: Discontinuations (temporary and permanent) of lurasidone

	n	% (n=48)
0	36	75%
1	10	21%
2	2	4%

Ten patients discontinued lurasidone permanently; the reasons included adverse effect, patient request, physician request and treatment failure (Table 21).

Table 21: Reasons for permanent lurasidone discontinuation

	n	% (n=10)
Adverse effect	2	20%
Patient request	2	20%
Physician request	1	10%
Treatment failure	1	10%
Other	4	40%

4.5 Lurasidone outcomes

Fourteen patients experienced a relapse during the 12-month follow-up period. Among those who relapsed, the median (IQR) time to relapse was 3.4 (1.5 to 7.9) months.

Table 22: Time to first relapse (months) in the 12 months following initiation of lurasidone, among those who relapsed

	Overall N=48
n	14
Mean	4.7
SD	4.0
Median	3.4
IQR	1.5 to 7.9
Range	0.0 to 11.7

Median time to relapse could not be estimated using Kaplan–Meier methods due to the small number of patients who relapsed. The proportion of patients who relapsed at each time point is shown in Table 23.

Table 23: Percentage of patients remaining relapse-free, Kaplan–Meier estimates

	Estimate %	95% CI
0 to 3 months	85.4	71.8 to 92.8
3 to 6 months	81.3	67.1 to 89.8
6 to 9 months	75.0	60.2 to 85.0
9 to 12 months	70.8	55.8 to 81.6

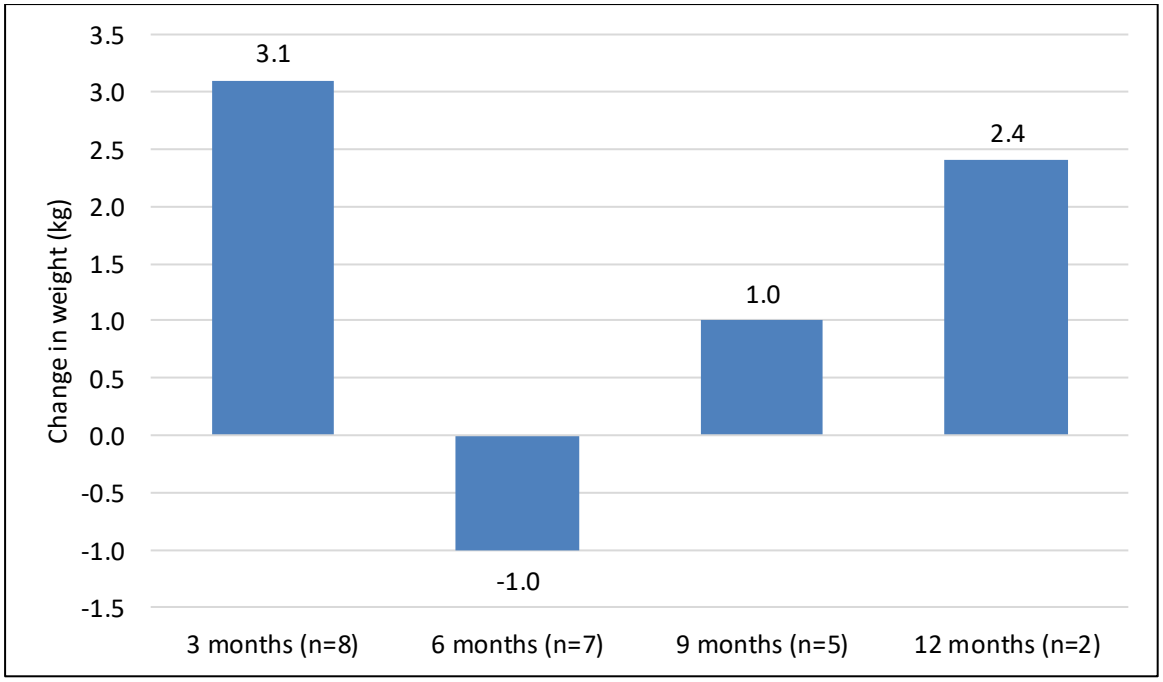
The mean number of relapses per patient among those who relapsed was 1.6 (Table 24). The number of relapses per patient ranged from 1 to 4 during the 12-month follow-up period.

Table 24: Number of relapses in the 12 months following initiation of lurasidone

	Overall N=48
n	14
Mean	1.6
SD	0.9
Median	1.0
IQR	1.0 to 2.0
Range	1.0 to 4.0

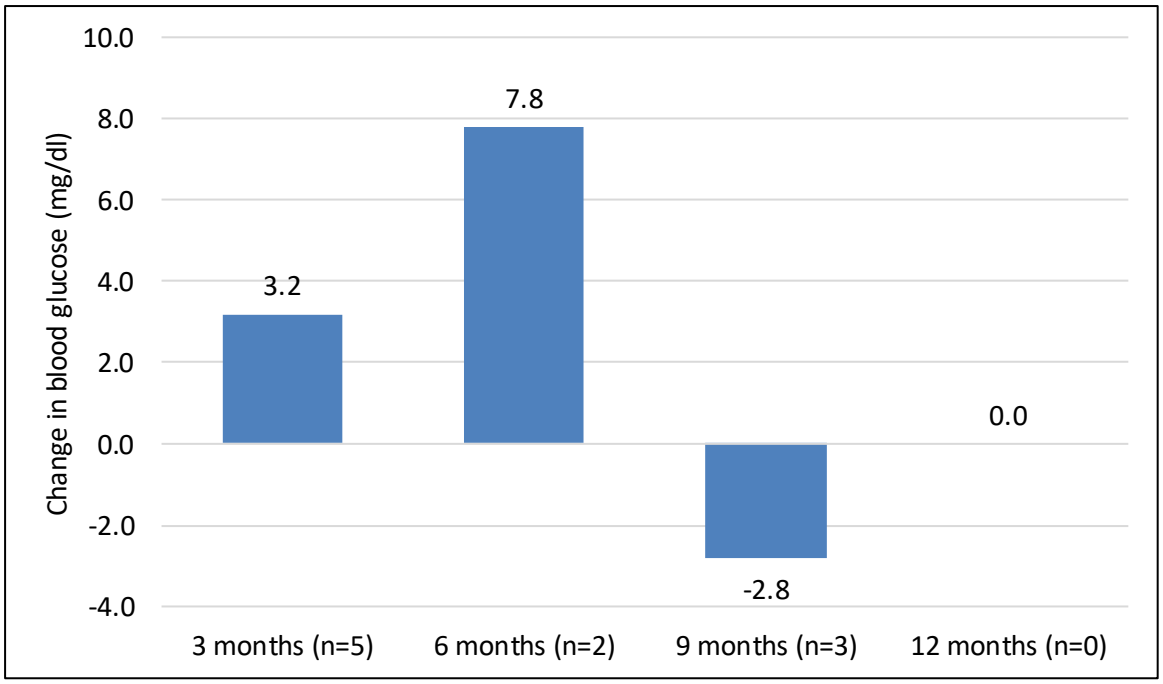
The number of patients with weight recorded during the follow-up period ranged from 8 at 3 months to 2 at 12 months (Figure 2). Mean change in weight varied across the time points, with an increase of up to 3.1 kg at 3 months and a decrease of 1 kg at 6 months. None of these changes were statistically significant.

Figure 2: Change in patient weight (kg) from baseline



Data on blood glucose during the follow-up period were similarly scarce (Figure 3). The largest increase (7.8 mg/dL) was seen at 6 months (n=2), and a decrease of 2.8 mg/dl was seen at 9 months (n=3).

Figure 3: Change in blood glucose (mg/dl) from baseline



Cholesterol, albumin, ALT, AST, ALP and GGT were measured in fewer than 5 patients at any time point; results are summarized in Appendix 1. There were no statistically significant differences at any time point.

Forty-four patients (92%) remained ADR-free during the follow-up period (Table 25). Four patients experienced ADRs, including agitation, nausea, akathisia and somnolence.

Table 25: Adverse drug reactions observed over 12 months following the initiation of lurasidone

	n (patients)	% (n=48)
Agitation	1	2%
Nausea	1	2%
Akathisia	1	2%
Somnolence	1	2%
Vomiting	1	2%
No ADRs	44	92%

Note: One patient recorded two adverse drug reactions.

4.6 Subsequent treatments

Treatments initiated after lurasidone were a mix of typical and atypical antipsychotics, most commonly olanzapine (29% of patients), clozapine (19%) and aripiprazole (17%).

Table 26: Antipsychotic medications received after lurasidone

	n (regimens)	% (n=48)
Typical antipsychotics	26	
clozapine	9	19%
haloperidol	6	13%
zuclopenthixol decanoate	5	10%
flupentixol decanoate	3	6%
haloperidol decanoate	2	4%
zuclopenthixol	1	2%
Atypical antipsychotics	42	
olanzapine	14	29%
aripiprazole	8	17%
amisulpride	6	13%
quetiapine	6	13%
risperidone	3	6%
paliperidone palmitate	3	6%
paliperidone	2	4%
No subsequent treatment	10	21%

Treatments following discontinuation of lurasidone included cognitive behavioural therapy (n=6, 13%), individual supportive therapy (n=3, 6%), and other therapies (n=4, 8%), including group therapy, art therapy, unspecified psychiatric input and physical health intervention.

4.7 Healthcare resource use

Fourteen patients (29%) were admitted to hospital at least once during the follow-up period, with a total of 21 hospitalizations (mean, 1.5 per patient; range, 1 to 3 hospitalizations). Nearly half of admissions were to an acute medical unit (Table 27).

Table 27: Inpatient admissions over the 12 months following the initiation of lurasidone, by specialty

	n	% (n=21)
Acute medical unit	9	43%
General ward	3	14%
Intensive care unit (ICU)	3	5%
None recorded	1	5%
Other	7	33%

Other specialties included recovery ward (n=2), secure mental health unit (n=1), psyche liaison unit (n=1), PICU (n=1), rehab ward (n=1) and psychiatric unit (n=1)

The majority of admission routes were either elective (29%) or via A and E (29%; Table 28).

Table 28: Inpatient admissions over the 12 months following the initiation of lurasidone, by admission route

	n	% (n=21)
Elective	6	29%
Via A and E	6	29%
None recorded	2	10%
Other	7	33%

Other admission routes included admitted to PICU (n=3), via crisis team (n=1), psych liaison unit (n=1), patient preference (n=1), and Section 3 (n=1)

The most common reason for inpatient admission was relapse of symptoms (57%), followed by psychotic episode (10%; Table 29).

Table 29: Inpatient admissions over the 12 months following the initiation of lurasidone, by reason for admission

	n	% (n=21)
Relapse of symptoms	12	57%
Psychotic episode	2	10%
Physical injury secondary to schizophrenia symptom	1	5%
Other	6	29%

Other reasons for admission included ward transfer (n=2), pneumonia (n=1), attempted suicide (n=1), clozapine reaction (n=1) and admitted to reassess (n=1).

Among the 47 patients for whom inpatient bed days could be calculated, the mean (SD) number of bed days was 41.1 (94.7) (Table 30).

Table 30: Inpatient bed days over the 12 months following the initiation of lurasidone, by reason for admission

	Overall N=48
Total inpatient bed days per patient	
n	47
Mean	41.1
SD	94.7
Median	0.0
IQR	0.0 to 8.5
Range	0.0 to 397.0
Length of stay per inpatient admission	
n	20
Mean	98.6
SD	104.1
Median	75.5
IQR	27.0 to 117.3
Range	2.0 to 397.0

Note: Discharge date was not available for one hospitalization.

During the follow-up period, 12 (25%) patients had no outpatient visits, 2 patients (4%) had one visit and 34 patients (71%) had two or more outpatient visits.

Table 31: Number of outpatient visits per patient over the 12 months following initiation of lurasidone

	Overall N=48
n (patients)	48
Mean	6.4
SD	7.5
Median	5.0
IQR	0.8 to 8.0
Range	0.0 to 40.0

A total of 309 outpatient visits occurred over the 12-month follow-up period. Forty-three percent of these were routine visits, and 34% were to a schizophrenia clinic (Table 32).

Table 32: Reasons for outpatient visits over the 12 months following initiation of lurasidone

	n	% (n=48)
Emergency	12	4%
Routine	133	43%
Schizophrenia clinic visit	105	34%
Other	59	19%

During the follow-up period, 3 patients (6%) had one emergency department visit and the remaining 45 patients had no emergency department visits. Two of the 3 emergency department visits ended in inpatient admission.

5 DISCUSSION

5.1 Main findings

In this real-world study of patients with schizophrenia in the UK and Switzerland, 79% of patients continued lurasidone for at least 12 months. Adherence to antipsychotic medication is poor in patients with schizophrenia due to poor insight into disease, negative attitudes toward medications, AEs, suboptimal relationships with prescribers and stigma (19). Previous real-world studies have shown 12-month persistence rates of less than 50% (20-22); however, these studies used prescription refill data to assess persistence rather than physician report. It is possible that this study overestimated persistence if treating physicians were unaware that patients had discontinued therapy.

Few ADRs occurred during the follow-up period. In a 12-month clinical trial comparing lurasidone with risperidone, the most common ADRs included nausea (17%), insomnia (16%) and sedation (15%) (14). ADRs observed in this study are consistent with those observed in the trial, albeit at lower rates (Table 33). Two of these patients had their lurasidone dose reduced due to the ADR, and 2 discontinued lurasidone permanently.

Table 33: Adverse drug reactions in this study compared to a 12-month randomised controlled trial

	This study n (%)	12-month clinical trial n (%)(14)
Agitation	1 (2%)	0 (0%)
Nausea	1 (2%)	70 (17%)
Akathisia	1 (2%)	60 (14%)
Somnolence	1 (2%)	57 (14%)
Vomiting	1 (2%)	42 (10%)

Approximately half of patients initiated therapy at the EMA-approved dose of 37 mg daily, with 7 patients (15%) initiating therapy at 18.5 mg daily. While reasons for dose selection were not collected, it is possible that the 18.5 mg dose was prescribed to account for CYP3A4-related drug interactions, or due to psychiatrist caution. Dose titration occurred in nearly all patients, with the most common subsequent dose being 74 mg daily. Doses of 9.25 mg and 18.5 mg daily were not seen in subsequent regimens, indicating that patients were not titrated down from the recommended starting dose.

Patient weight, blood glucose, cholesterol and liver function data were scarce. In the UK, National Institute of Health and Care Excellence (NICE) guidelines recommend that "GPs and other primary healthcare professionals should monitor the physical health of people with psychosis or schizophrenia when responsibility for monitoring is transferred from secondary care, and then at least annually" (23). Therefore, it is possible that patients were being monitored by providers other than the prescriber of lurasidone, and the results of these tests were not available.

5.2 Limitations

Patient consent was a requirement of this study for living patients; this may have introduced selection bias and resulted in a study sample that may not be representative of the wider patient population of interest.

The interpretation of data collected retrospectively was dependent on the completeness and quality of the medical records and the reliability of the abstraction of data from them. However, SDV was employed to identify and correct abstraction errors.

Participating centres were those identified as high prescribers, so they may not be representative of all centres that prescribe lurasidone in the countries of study.

We evaluated outcomes at 3, 6, 9 and 12 months, but real-world response assessment may differ in terms of the timing of evaluations, with not every patient having data at every time point.

The lack of laboratory data did not allow for an assessment of the impact of lurasidone on weight and metabolic parameters.

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7 APPENDICES

Appendix 1: Other laboratory values during the follow-up period

Change from baseline value	Total cholesterol (mg/dL)			
	Baseline -> 3 months (±1 month)	Baseline -> 6 months (±1 month)	Baseline -> 9 months (±1 month)	Baseline -> 12 months (±1 month)
n (patients)	3	1	2	1
Mean	2.5	0.3	0.6	4.2
SD	4.8	-	1.0	-
Median	0.6	0.3	0.6	4.2
Statistical significance[1]	0.59	0.32	0.65	0.32
IQR	-0.2 to 4.3	0.3 to 0.3	0.2 to 0.9	4.2 to 4.2
Range	-1.0 to 7.9	0.3 to 0.3	-0.1 to 1.3	4.2 to 4.2

Change from baseline value	High-density lipoprotein (HDL) (mg/dL)			
	Baseline -> 3 months (±1 month)	Baseline -> 6 months (±1 month)	Baseline -> 9 months (±1 month)	Baseline -> 12 months (±1 month)
n (patients)	2	1	2	0
Mean	0.7	0.1	0.1	-
SD	1.2	-	0.5	-
Median	0.7	0.1	0.1	-
Statistical significance[1]	0.65	0.32	0.65	-
IQR	0.3 to 1.2	0.1 to 0.1	-0.1 to 0.3	-
Range	-0.1 to 1.6	0.1 to 0.1	-0.3 to 0.5	0.0 to 0.0

Change from baseline value	Triglycerides (mg/dL)			
	Baseline -> 3 months (±1 month)	Baseline -> 6 months (±1 month)	Baseline -> 9 months (±1 month)	Baseline -> 12 months (±1 month)
n (patients)	1	0	1	0
Mean	1.8	-	-3.1	-
SD	-	-	-	-
Median	1.8	-	-3.1	-
Statistical significance[1]	0.32	-	0.32	-
IQR	1.8 to 1.8	-	-3.1 to -3.1	-
Range	1.8 to 1.8	0.0 to 0.0	-3.1 to -3.1	0.0 to 0.0

Change from baseline value	Albumin (mg/dL)			
	Baseline -> 3 months (±1 month)	Baseline -> 6 months (±1 month)	Baseline -> 9 months (±1 month)	Baseline -> 12 months (±1 month)
n (patients)	3	2	3	2
Mean	-7.0	4.0	-3.3	3.5
SD	8.2	4.2	10.2	2.1
Median	-5.0	4.0	1.0	3.5
Statistical significance[1]	0.17	0.18	1	0.18
IQR	-10.5 to -2.5	2.5 to 5.5	-7.0 to 2.5	2.8 to 4.3
Range	-16.0 to 0.0	1.0 to 7.0	-15.0 to 4.0	2.0 to 5.0

Change from baseline value	Alanine aminotransferase (ALT)			
	Baseline -> 3 months (±1 month)	Baseline -> 6 months (±1 month)	Baseline -> 9 months (±1 month)	Baseline -> 12 months (±1 month)
n (patients)	4	1	3	3
Mean	14.0	-4.0	-3.7	1.7
SD	17.6	-	6.7	32.9
Median	12.5	-4.0	-7.0	-4.0
Statistical significance[1]	0.14	0.32	0.29	1
IQR	7.5 to 19.0	-4.0 to -4.0	-7.5 to -1.5	-16.0 to 16.5
Range	-6.0 to 37.0	-4.0 to -4.0	-8.0 to 4.0	-28.0 to 37.0

Change from baseline value	Alkaline phosphatase (ALP)			
	Baseline -> 3 months (±1 month)	Baseline -> 6 months (±1 month)	Baseline -> 9 months (±1 month)	Baseline -> 12 months (±1 month)
n (patients)	3	1	3	1
Mean	-11.3	19.0	-29.7	4.0
SD	16.9	-	47.1	-
Median	-7.0	19.0	-3.0	4.0
Statistical significance1	0.29	0.32	0.11	0.32
IQR	-18.5 to -2.0	19.0 to 19.0	-43.5 to -2.5	4.0 to 4.0
Range	-30.0 to 3.0	19.0 to 19.0	-84.0 to -2.0	4.0 to 4.0

Change from baseline value	Aspartate aminotransferase (AST)			
	Baseline -> 3 months (±1 month)	Baseline -> 6 months (±1 month)	Baseline -> 9 months (±1 month)	Baseline -> 12 months (±1 month)
n (patients)	0	1	1	0
Mean	-	-5.0	-58.0	-
SD	-	-	-	-
Median	-	-5.0	-58.0	-
Statistical significance1	-	0.32	0.32	-
IQR	-	-5.0 to -5.0	-58.0 to -58.0	-
Range	0.0 to 0.0	-5.0 to -5.0	-58.0 to -58.0	0.0 to 0.0

Change from baseline value	Gamma glutamyl transferase (GGT)			
	Baseline -> 3 months (±1 month)	Baseline -> 6 months (±1 month)	Baseline -> 9 months (±1 month)	Baseline -> 12 months (±1 month)
n (patients)	1	0	0	0
Mean	-9.0	-	-	-
SD	-	-	-	-
Median	-9.0	-	-	-
Statistical significance1	0.32	-	-	-
IQR	-9.0 to -9.0	-	-	-
Range	-9.0 to -9.0	0.0 to 0.0	0.0 to 0.0	0.0 to 0.0

- Statistics could not be calculated as there are 1 or no values.

[1] Statistical significance assessed through Wilcoxon signed-rank test for paired observations