



Northern Treatment
Advisory Group

Lurasidone for the treatment of schizophrenia

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Summary

- Lurasidone is a second generation (atypical) antipsychotic agent that inhibits the effects of dopamine and 5-hydroxytryptamine.
- Lurasidone (Latuda®, Sunovion Pharmaceuticals Europe Ltd) is licensed for the treatment of schizophrenia in adults aged 18 years and over. It was launched in the UK in August 2014.
- The recommended starting dose is 37mg daily with food; the maximum dose is 148mg daily. Doses marketed in the UK are expressed as the amount of active moiety, as opposed to lurasidone hydrochloride. Licensed doses therefore appear to differ slightly from those cited in clinical trials.
- Lurasidone has a side-effect profile that is similar to that seen with other second-generation antipsychotics.
- Lurasidone adds to the currently available atypical antipsychotics and may be particularly useful for patients where weight gain or other metabolic-related adverse effects are an issue. Lurasidone appears to be less well tolerated overall than risperidone whilst causing less weight gain and fewer adverse metabolic effects.
- The efficacy of lurasidone compared prolonged release quetiapine was evaluated in a phase III double-blind randomised controlled trial lasting 12 months, whilst its efficacy against placebo has been demonstrated in several 6-week studies.
- There is limited safety and efficacy data beyond the 12 month published trials, and it has not yet been adequately compared to existing alternatives.
- There is no direct comparison in terms of efficacy and safety versus aripiprazole currently available.
- All trials to date included a predominately male population, despite schizophrenia being roughly evenly distributed between the sexes.
- Special patient groups, such as the elderly, those with renal or liver disease, and pregnant or lactating women were excluded from the trials.
- The aims of antipsychotic treatment in schizophrenia are to prevent relapse, maintain long term control, and improve quality of life with as few adverse drug reactions as possible.
- It remains unclear whether the statistically significant improvements in the rating scales used to assess treatment response in the trials are also clinically significant in the management of schizophrenia.
- The annual cost of lurasidone ranges from £1179.36 at a maintenance dose of 37-74mg daily to £2358.72 at a maintenance dose of >74mg to 148mg daily.
- Lurasidone costs fall within the existing price range of licensed antipsychotics and it is currently less expensive than max dose aripiprazole or paliperidone. But it is significantly more expensive than max dose olanzapine or amisulpride.

Introduction and background

Lurasidone (Latuda®▼, Sunovion Pharmaceuticals Europe Ltd) is a second generation antipsychotic drug licensed for the treatment of schizophrenia in adults aged 18 years and over. It binds predominantly to dopaminergic D2 receptors and serotonergic 5-HT_{2A} and 5-HT₇ receptors, as well as possessing antagonistic activity at adrenergic receptors. Lurasidone is administered once daily.¹

The recommended starting dose of lurasidone is 37mg daily with food; the maximum dose is 148mg daily. Dose adjustment is recommended in moderate to severe renal and hepatic impairment.¹

NICE clinical guideline 178 recommends psychological interventions such as cognitive behavioural therapy and family intervention for all patients with psychosis or schizophrenia. An oral antipsychotic medication should be offered in conjunction with these psychological interventions. NICE guidance does not suggest a hierarchy of drug choices, but instead recommends that choice should be guided by the patient, taking into account the possibility of side effects and benefits of each drug.²

NICE does not differentiate between first and second generation antipsychotics, despite differences in side effect profiles. First generation antipsychotics are more commonly associated with extrapyramidal effects compared to second generation agents. The latter are more likely to cause metabolic adverse reactions. However, there is no robust evidence to suggest any benefit in using one group of drugs in preference to the other, providing they are carefully dosed and adjunct anticholinergic use is avoided.³ Aripiprazole is often considered as an alternative antipsychotic for patients troubled with metabolic adverse reactions.³

Clozapine is recommended for people with schizophrenia which has been refractory to treatment with two antipsychotics used sequentially at adequate therapeutic doses.²

This document will review the evidence for the efficacy, safety and place in therapy of Lurasidone for the treatment of schizophrenia.

Clinical evidence

Five pivotal double-blind randomised controlled trials have evaluated the efficacy of lurasidone. Only four of the trials are discussed here as the fifth trial has not been fully published and is only available in abstract form.

Loebel A et al (2013)⁴

The rephase-prevention efficacy of variable doses of lurasidone and extended release version of quetiapine (QXR) were compared in a 12 month extension to a 6 week double-blind randomised controlled trial (PEARL3).

The initial 6 week fixed dose trial enrolled adults (18-75 years) who met DSM-IV-TR criteria for a primary diagnosis of schizophrenia lasting more than one year. Eligible

patients were suffering from an acute exacerbation lasting no longer than two months, and requiring hospitalisation.⁵ Subjects (n=292, 60% of those initially randomised) in the extension period were treatment responders suitable for outpatient treatment, recruited from the initial study pool. Study medication was taken once daily.

Lurasidone was found to be non-inferior to QXR in the primary outcome of probability of relapse at 12 months (hazard ratio [HR] 0.728, 95% CI 0.410 to 1.295, log-rank p=0.280, pre-specified non-inferiority margin 1.93). Using the Kaplan–Meier estimate of the probability of relapse over 12 months patients in the QXR group had a higher probability of relapse than those in the lurasidone group (QXR 33.6% vs lurasidone 23.7%).

The rate of hospitalization among subjects who met a priori relapse criteria was significantly higher for QXR (61.9%) compared with lurasidone (34.5%; p < 0.05).

In addition, an adhoc analysis demonstrated that lurasidone treatment for 12 months was associated with a 56.7% lower hospitalisation risk compared to QXR (HR 0.433, 95% CI 0.188 to 0.995).

Patients enrolled in the 12 month extension phase of the PEARL3 trial had been previous responders to lurasidone, QXR or placebo. Placebo responders were switched to lurasidone without further randomisation, potentially undermining the original randomisation process. This may limit the applicability of the results to the general population, who may have a varying degree of response to antipsychotic agents.

Meltzer HY et al and Nasarallah HA et al

The efficacy of various fixed doses of lurasidone versus placebo has been demonstrated in short term six-week long trials, three of which were phase III. Each phase III trial used the same inclusion criteria as PEARL3 (hospitalised with an acute exacerbation), and two included an active comparator (QXR or olanzapine) to check assay sensitivity.^{5,6,7} These trials were not designed to compare active agents. All three trials found that lurasidone was superior to placebo at reducing Positive and Negative Syndrome Scale (PANSS) scores (primary endpoint) and Clinical Global Impression of Severity (CGI-S) scores (secondary endpoint).

Meltzer HY et al⁶

Based on the mixed-model repeated-measures (MMRM) analysis, the results of this trial demonstrated a change in the PANSS total score from baseline to week 6 that was statistically significantly greater for the lurasidone 40 mg group (–25.7; adjusted p=0.002) and the lurasidone 120 mg group (–23.6; adjusted p=0.022) compared to placebo (–16.0).

The change in PANSS total score was also statistically significantly greater for the olanzapine group (–28.7, p<0.001) compared to placebo, therefore confirming the assay sensitivity use in the study.

This study showed significant improvement in the CGI-S score from baseline to week 6 for the lurasidone 40mg group (–1.5; adjusted p=0.011) and the lurasidone 120 mg group (–1.4; adjusted p=0.040) when compared to placebo. The change in CGI-S score was also significantly greater for the olanzapine group (–1.5; p<0.001).

Statistically significant separation from placebo on the CGI-S was observed from week 1 onward for the lurasidone 120 mg group, and from week 2 onward for the lurasidone 40 mg group and the olanzapine group compared with the placebo group. There was no significant improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) at week 6 between either of the lurasidone groups and the placebo group, but the olanzapine treatment group showed significantly greater improvement when compared with the placebo group.

Nasrallah HA et al⁷

The primary outcome measure for this study was Positive and Negative Syndrome Scale (PANSS) score. The results showed that patients who received fixed-dose lurasidone 80 mg/day had a significantly greater improvement in PANSS total score from baseline to Week 6 compared to the placebo group (-23.4 versus -17.0; adjusted $p < 0.05$, MMRM). However statistically significant differences in the PANSS score were not observed for patients receiving 40 mg/day or 120 mg/day lurasidone compared with placebo.

One of the secondary outcome measures was change in Clinical Global Impression of Severity (CGI-S) score. This measure saw a statistically significant improvement when compared to the placebo group from baseline to Week 6 for patients receiving lurasidone 80 mg/day (-1.4 versus -1.0; adjusted $p < 0.05$, MMRM) but not for patients receiving lurasidone 40 mg/day or 120 mg/day.

Other results of other secondary outcomes were reported as follows:

- PANSS positive symptoms subscale score: Treatment with 80 mg/day and 120 mg/day of lurasidone saw an improvement in the PANSS positive symptoms subscale score at Week 6 compared with placebo (adjusted $p < 0.001$ and $p < 0.05$, respectively, MMRM).
- PANSS negative symptoms subscale: no significant change compared to placebo seen in any of the lurasidone dose groups.
- PANSS General Psychopathology subscale: no significant change compared to placebo seen in any of the lurasidone dose groups.
- Montgomery-Åsberg Depression Rating Scale (MADRS): change did not achieve statistical significance for any lurasidone dose group versus placebo at the Week 6 study endpoint.

Harvey PD et al (2013)⁸ and Harvey PD et al (2011)⁹

These two studies assessed the effects of lurasidone treatment on cognition. A cohort from the PEARL3 trial, including placebo-responders assigned to lurasidone, were assessed after 6 weeks and 6 months for effects on cognitive dysfunction, using the CogState computerized cognitive battery.⁸ Lurasidone produced a significantly larger improvement in neurocognitive composite scores compared to QXR after 6 months ($p=0.008$)⁸. A short term trial (21 days) among community dwelling patients found no differences in cognition scales between groups randomised to lurasidone 120mg daily or ziprasidone 80mg twice daily ($p=0.73$)⁹. The clinical significance of these cognition results has not been established.

Safety

Citrome et al¹⁰

The long-term safety and tolerability of lurasidone was assessed in a 12 month long double blind study of 629 adult patients, who had remained clinically stable for at least 8 weeks prior to baseline assessments. More patients withdrew from treatment due to adverse events (AEs) in the lurasidone group (17%) than the risperidone comparator group (11%). Similar proportions of the remaining trial participants in both groups suffered overall AEs, serious AEs, and extrapyramidal AEs. The three most frequent AEs reported in the trial were nausea, insomnia, and sedation. Nausea, akathisia and vomiting were seen more frequently in the lurasidone group than in those taking risperidone (NNH 18, 16, and 26 respectively). Conversely, constipation was significantly less common with lurasidone than with risperidone (NNH -20).

Lurasidone appeared to produce fewer metabolic-related AEs (including lipid profile, glucose, HbA1c, insulin and prolactin) compared to risperidone (11.7% vs 20.8%, NNH -11).

Contrary to other atypical antipsychotics, (and the risperidone comparator), lurasidone was associated with a decrease in mean weight, BMI, and waist circumference of the included patients ($p < 0.001$). In the lurasidone group, a mean body weight decrease of 0.97kg (+/-5.06kg) and BMI decrease of -0.33 (+/- 1.71 kg/m²) were observed, whereas an increase of 1.47kg (+/- 5.03kg) and a BMI increase of 0.53 (+/-1.76 kg/m²) were seen with risperidone.

No clinically meaningful changes in ECG, HR, BP, or body temperature occurred in either group.

Loebel et al⁴

In a 12 month double-blind, active comparator, non-inferiority, extension study in 292 adults with a diagnosis of schizophrenia the percentage of patients reporting one or more adverse event was 62.5% in the group originally randomised to placebo then switched to lurasidone, 64.2% in the group originally randomised to lurasidone and 71.8% in the group originally randomised to quetiapine.

The majority of adverse events in all treatment groups in this study were reported as being mild to moderate.

The three most frequent adverse events in the lurasidone group were akathisia (12.6%), headache (10.6%), and insomnia (7.9%); and the three most frequent events in the quetiapine XL group were worsening of schizophrenia (15.3%), insomnia (9.4%), and headache (9.4%).

Extrapyramidal symptom-related adverse events occurred more frequently with lurasidone (21.4% in the group originally randomised to placebo then switched to lurasidone, 11.9% in the group originally randomised to lurasidone, and 3.5% in the group originally randomised to quetiapine prolonged release).

Akathisia was also more common with lurasidone (10.7% in the group originally randomised to placebo then switched to lurasidone, 12.6% in the group originally randomised to lurasidone, and 2.4% in the group originally randomised to quetiapine). This is consistent with results seen in other trials.

A minimal effect on weight, body mass index and waist circumference on was seen in this study for both lurasidone and quetiapine XL, and there were no clinically significant treatment-emergent ECG abnormalities seen with lurasidone or quetiapine XL.

Other studies

Pooled results of the short term placebo controlled studies found headache, akathisia, nausea, insomnia, somnolence, sedation, vomiting, schizophrenia, dyspepsia, agitation, anxiety and constipation to be the most commonly reported AE. Other published trials followed a similar pattern.

In the 6 week study by Meltzer et al⁶ the incidence of akathisia was higher with 120mg of lurasidone (22.9%) than with 40mg of lurasidone (11.8%), olanzapine (7.4%), or placebo (0.9%). In the same study the proportion of patients experiencing $\geq 7\%$ weight gain was 5.9% for the lurasidone groups combined, compare to 34.4% for the olanzapine group, and 7.0% for the placebo group.

Indirect comparison of treatment discontinuation: lurasidone vs other atypical antipsychotics

Data available in poster format from an indirect treatment comparison indicated that the estimated all-cause discontinuation rates, discontinuations due to lack of efficacy, and hospitalizations were lowest for lurasidone and olanzapine compared to aripiprazole, quetiapine XL, risperidone, and ziprasidone.

The indirect comparison was conducted using data from three separate parallel-group studies. Two of the studies were 12 months in duration and one was of 18 months.

Olanzapine and lurasidone were found to have the lowest all-cause discontinuation rates (49.1% and 53.4% respectively), with quetiapine XL and aripiprazole having the highest (67.8% and 66.2% respectively).

Olanzapine and lurasidone were also found to have the lowest discontinuation rates due to lack of efficacy (9.9% and 14.3% respectively) compared to quetiapine XL (19.6%) and risperidone (19.2%).

The products with lowest total annual all-cause hospitalization rates were lurasidone (5.7%) and olanzapine (7.8%). Those with the highest total annual all-cause hospitalization rates were aripiprazole (14.4%) and quetiapine XL (14%).

Cost analysis

The recommended starting dose is 37mg daily with food; the maximum dose is 148mg daily.

On average, 4 per 1000 people will have a diagnosis of schizophrenia, with 12 new diagnoses per 100,000 population each year.

NICE estimates that number of people taking antipsychotics in England and Wales is 365,394; 39% of whom (142,504) are taking drugs for schizophrenia.¹¹

The manufacturer estimates that the uptake of lurasidone in England Wales will be 0.39% (566 people) in year 1, increasing to 2.59% (3,742 people) by year 3.¹¹

The cost impact of schizophrenia can be wide ranging, with affects on social disability, long term health, and substance misuse. Relapses associated with hospitalisation may also prove costly.

Lurasidone is available in following strengths: 18.5mg, 36mg and 74mg. All strengths cost £90.72 per 28 tablets. Therefore the cost of 28 days treatment with lurasidone at a dose of 37-148mg daily is £90.72 to £181.14.

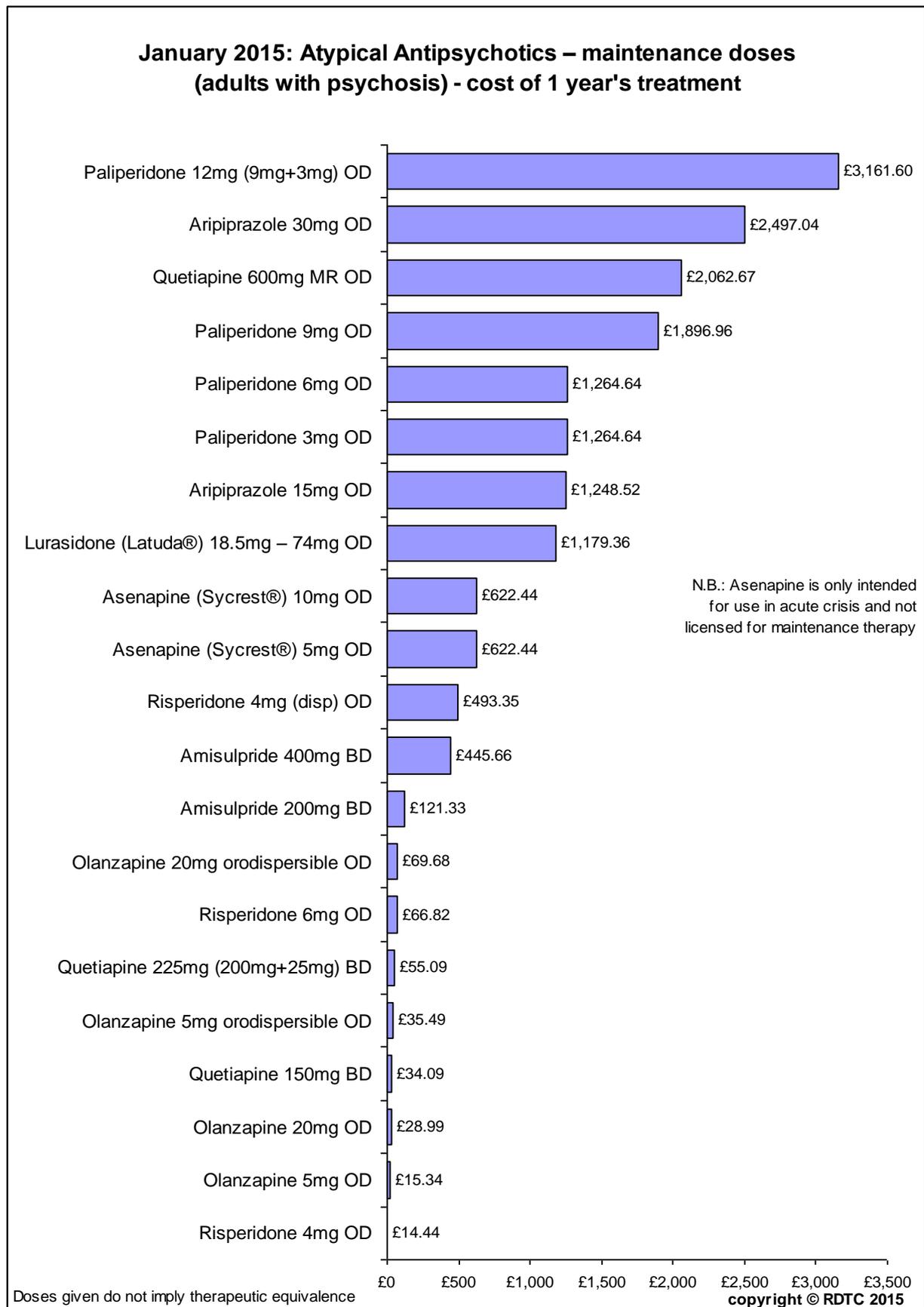
Lurasidone costs fall within the existing price range of licensed antipsychotics and it is currently less expensive than aripiprazole or paliperidone.

The annual cost of lurasidone ranges from £1179.36 at a maintenance dose of 37-74mg daily to £2358.72 at a maintenance dose of >74mg to 148mg daily.

In the financial year 2013/14 total spend in primary care in the North East & Cumbria on drugs for psychosis was £8,077,568, of this £7,313,023 was spent on oral antipsychotic drugs.

A generic version of aripiprazole has recently been launched in the UK but the Drug Tariff is currently the same as the branded product as of January 2015 (this is reflected in the cost comparison chart below). Annual costs based on NHS List Price for the two available generics at 30mg once daily of aripiprazole range from £1997.58 to £2497.08 per annum.

All costs quoted are NHS List price and exclude VAT.



Points to consider

Lurasidone is a new addition to the list of antipsychotics already available for the treatment of patients with schizophrenia. Data on longer term efficacy and safety are limited and it has not yet been adequately compared to existing alternatives. The limited available data suggest that it may have some advantages over other antipsychotics for patients where weight gain or other metabolic disturbances are likely to have significant adverse consequences, although other adverse effects- including akathisia- may be more troublesome with lurasidone

There is limited safety and efficacy data beyond the 12 month published trials.

Non-inferiority to risperidone was not demonstrated in the Citrome et al study.

Patients enrolled in the 12 month extension phase of the PEARL3 trial had been previous responders to lurasidone, QXR or placebo. Placebo responders were switched to lurasidone without further randomisation (and constituted >25% of the lurasidone group), potentially undermining the original randomisation process. This may substantially limit the applicability of the results to the general population, who may have a varying degree of response to antipsychotic agents.

All trials included a predominantly male population, despite schizophrenia being roughly evenly distributed between the sexes (ratio 1.4:1 male:female)¹². Special patient groups, such as the elderly, those with renal or liver disease, and pregnant or lactating women were excluded.

Effects reported in clinical trials may systematically over-estimate real-life effects, especially in illnesses such as schizophrenia where compliance issues are commonplace.

The aims of antipsychotic treatment in schizophrenia are to prevent relapse, maintain long term control, and improve quality of life with as few adverse drug reactions as possible. Rating scales such as PANSS (as used in the clinical studies) are considered suitable surrogate markers for improvement in symptoms, but patient-orientated outcomes such as relapse rates may be a more desirable method of assessing efficacy.¹³ It remains unclear whether the statistically significant improvements in the rating scales used to assess treatment response in the trials are also clinically significant in the management of schizophrenia.

The PEARL-3 trial was designed only to detect non-inferiority of lurasidone to the comparator. Active comparators in the other trials were included only to confirm assay sensitivity.

There was a high dropout rate seen in the studies. In Citrome et al 66% patients discontinued lurasidone compared to 56% with risperidone, and in the PEARL-3 extension study the study discontinuation rate was 48% with lurasidone and 61% with quetiapine XL.

Lurasidone costs fall within the existing price range of licensed antipsychotics and it is currently less expensive than aripiprazole and paliperidone. But it is significantly more expensive than max dose olanzapine or amisulpride.

A generic version of aripiprazole has recently been launched in the UK but the Drug Tariff is currently the same as the branded product as of January 2015 (this is reflected in the cost comparison chart below). Annual costs based on NHS List Price for the two available generics at 30mg once daily of aripiprazole range from £1997.58 to £2497.08 per annum.

The SMC has accepted lurasidone for restricted use within NHS Scotland for the treatment of schizophrenia in adults aged 18 years and over. It is restricted to an alternative treatment option in patients in whom it is important to avoid weight gain and metabolic adverse effects.

Author's declaration: The author has no relevant interests to declare.

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Evidence Tables – lurasidone for treatment of schizophrenia

Bibliographic reference	Study type	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
[1] Meltzer et al 2011, Lurasidone in the treatment of schizophrenia	[2] Phase III Randomised controlled trial Double blind	[3] Inclusion:18-75 years DSM-IV criteria for primary diagnosis of schizophrenia of duration at least 1 year Hospitalised for ≤2 weeks for an acute exacerbation of psychotic symptoms. CGI-S Score ≥4 PANSS total score ≥80 inc ≥4 on two or more of delusions, conceptual disorganization, hallucinations, unusual thoughts content and suspiciousness.	[4] ITT 78% male Mean age 37 years. Other characteristics similar	[5] Daily doses of either: Lurasidone 40mg Lurasidone 120mg Olanzapine 15mg Placebo	[6] 6 weeks	[7] Primary outcome: changes from baseline in PANSS total score at week 6 Lurasidone 40mg (-25.7; adjusted p=0.002) Lurasidone 120mg (-23.6 p=0.011) Olanzapine 15mg -28.7 (p<0.001) Secondary outcome: change from baseline in CGI-S score at week 6 Lurasidone 40mg -1.5 (p=0.006) Lurasidone 120mg -1.2 (p=0.005) Olanzapine 15mg -1.5 (p<0.001)	[8] Not specified in publication. Possibly sponsored by Sunovion.	[9] Trial not designed to compare lurasidone and olanzapine-only designed to detect differences between lurasidone and placebo.
Loebel et al, 2013 Efficacy and safety of lurasidone 80mg/day and 160mg/day in the treatment of schizophrenia (PEARL 3)	Phase III Randomized , controlled trial Double-Blind	18-75 years DSM-IV-TR criteria for primary diagnosis of schizophrenia of duration at least 1 year. Hospitalised. Acute axacerbation of no more than 2 months. CGI-S Score ≥4 PANSS total score ≥80 inc ≥4 on two or more of delusions, conceptual disorganization, hallucinations, unusual thoughts content and	ITT Predominantly male. 77% male in the lurasidone 80mg group. Slightly lower than this in the other groups. Other characteristics similar.	Daily doses of either: Lurasidone 80mg Lurasidone 160mg Quetiapine 600mg od XR Placebo	6 weeks.	Primary outcome: changes from baseline in PANSS total score at week 6 Lurasidone 80mg -22.2 (p<0.001) Lurasidone 160mg -26.5 (p<0.001) Quetiapine XR 600mg: -27.8 (p<0.001) Placebo -10.3 Secondary endpoint: Lurasidone 80mg: -1.5 (p<0.001) Lurasidone 160mg -1.7 (p<0.001) QXR: -1.7 (p<0.001)	Sunovion	Trial not designed to compare lurasidone and quetiapine XR-only designed to detect differences between lurasidone and placebo.

Bibliographic reference	Study type	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
		suspiciousness.				Placebo: -0.9		
Citrome et al 2012 Long term safety and tolerability of lurasidone in schizophrenia: a 12 month, double blind, active-controlled study.	Phase III Randomised controlled trial Double-blind	18-75 years DSM-IV criteria for primary diagnosis of schizophrenia or schizoaffective disorder of duration at least 1 year. Non-acute phase of illness for at least 4 weeks. CGI-S ≤ 4 No change in meds for at least 8 weeks PANSS ≤ 4 <u>Exclusion criteria:</u> Clinically significant somatic disorders Current or history of alcohol/drug abuse in last 6 months Suicidal ideation, behaviour, or violent behaviour in the last 6 months BMI <18.5 or $>40\text{kg}^2/\text{m}^2$ Treatment with risperidone within 6 weeks of baseline. History of poor/inadequate response/	ITT Predominantly male. Other characteristics similar. N= 621	Daily dose of either: lurasidone 80mg or risperidone 2 mg (then dosed as appropriate) Lurasidone n= 419 Risperidone n = 202	12 months	Primary outcome: monitoring of adverse reactions. Secondary objectives: changes in PANSS scores, CGI-S, and MADRS. The lurasidone and risperidone groups had similar proportions of patients reporting one or more treatment emergent AEs [354/419 (84.5%) vs. 171/202 (84.7%), respectively] or treatment-emergent serious AEs [46/419 (11.0%) vs. 20/202 (9.9%), respectively]. A higher proportion of patients discontinued from the study because of a treatment-emergent AE in the lurasidone group, 90/419 (21.5%), compared with the risperidone group, 29/202 (14.4%), with a NNH of 14 (95% CI 8–113). The PANSS total score decreased from baseline to month 12 (MMRM) in both the lurasidone group (– 4.7; 95% CI – 6.4 to – 3.0) and the risperidone group (– 6.5; 95% CI – 8.8 to – 4.3). On comparing lurasidone with risperidone, there were no significant differences in the PANSS total scores at any time during the 12-month doubleblind treatment period.	Sunovion	

Bibliographic reference	Study type	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
		<p>intolerability to risperidone.</p> <p>Treatment with clozapine or depot antipsychotics</p>				<p>The CGI-S score decreased from baseline to month 12 (MMRM) similarly in both the lurasidone group (– 0.4; 95% CI – 0.5 to – 0.3) and the risperidone group (– 0.4; 95% CI – 0.5 to – 0.2). On comparing lurasidone with risperidone, there were no significant treatment differences in the CGI-S score at any time during the 12-month double-blind treatment period.</p> <p>The MADRS total score decreased from baseline to month 12 (MMRM) in both the lurasidone group (– 0.8; 95% CI – 1.6 to – 0.0) and the risperidone group (– 2.4; 95% CI – 3.4 to – 1.4). On comparing the lurasidone group with the risperidone group, there were no significant treatment differences in the decrease at any time point, except for month 12 (treatment difference= 1.6, P=0.007).</p>		
<p>Loebel at al 2013</p> <p>Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia:</p> <p>A 12-month, double-blind, noninferiority</p>	<p>Phase III</p> <p>Randomised controlled trial</p> <p>Double-blind</p> <p>Parallel group</p> <p>Non-inferiority study</p>	<p>Outpatients with an acute exacerbation of chronic schizophrenia who had recently completed a 6-week placebo-controlled trial of treatment with either lurasidone or Quetiapine XL (PEARL-3 study)</p>	<p>Not specified.</p>	<p>12 months of flexible dose treatment with lurasidone (40–160mg once daily), compared with Quetiapine XL (200–800mg once daily).</p>	<p>12 months</p>	<p>Primary endpoint, time-to-relapse, was analysed using a Cox proportional hazards model in this noninferiority trial.</p> <p>Efficacy was assessed using the PANSS total and subscale scores the Clinical Global Impression, Severity scale (CGI-S), the Negative Symptom Assessment Scale (NSA-16), and the Montgomery–Åsberg Depression</p>	<p>Sunovion</p>	

Bibliographic reference	Study type	Inclusion & exclusion	Patient characteristics	Intervention & comparison(s)	Length of follow-up	Outcome measures and effect size	Source of funding	Additional comments
study						<p>Rating Scale (MADRS).</p> <p>The Kaplan–Meier estimate of the probability of relapse over 12 months was 23.7% for subjects receiving lurasidone vs. 33.6% for QXR. The hazard ratio [95% CI] for probability of relapse was 0.728 [0.410, 1.295] (log-rank p = 0.280).</p> <p>The probability of hospitalization at 12 months was lower for the lurasidone group compared with the QXR group (9.8% vs. 23.1%; log-rank p = 0.049). A significantly higher proportion of lurasidone subjects achieved remission at study endpoint compared with the QXR group (61.9% vs. 46.3%; p = 0.043).</p> <p>Discontinuation rates due to AEs were similar for lurasidone and QXR (7% vs. 5%).</p>		
<p>Nasrallah HA et al 2013</p> <p>Lurasidone for the treatment of acutely psychotic patients with schizophrenia: A 6-week, randomized, placebo-controlled study</p>	<p>Randomized, fixed-dose, double-blind, placebo-controlled, Multi-regional, parallel-group</p>	<p>18-75 years DSM-IV criteria for primary diagnosis of schizophrenia or schizoaffective disorder of duration at least 1 year. Currently experiencing an acute exacerbation of psychotic symptoms (lasting >2 months). CGI-S ≥4 PANSS ≥80</p> <p><u>Exclusion criteria:</u> Acute or unstable medical</p>	<p>Predominantly male. Other characteristics similar.</p>	<p>6 weeks of doubleblind treatment with lurasidone 40 mg/day, 80 mg/day, or 120 mg/day, or placebo. N= 125 40mg N = 123 80mg N= 124 120mg N= 128 placebo</p>	6 weeks	<p>Patients who received fixed-dose lurasidone 80 mg/day showed significantly greater improvement in the primary efficacy measure, change from baseline to Week 6 in PANSS total score, compared with the placebo group (-23.4 versus -17.0; adjusted p < 0.05, MMRM). Statistically significant differences were not observed for patients receiving 40 mg/day or 120 mg/day compared with placebo</p> <p>Significantly greater improvement in PANSS total score was observed from Week 2 onward for patients receiving lurasidone 80 mg/day versus placebo</p>	Sunovion	Large placebo effect seen

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		<p>condition</p> <p>Evidence of any other chronic disease of the central nervous system alcohol or other drug abuse/dependence within the past 6 months</p> <p>History of resistance to treatment with neuroleptics (failure to respond to two or more marketed antipsychotic agents from two different classes in the past year),</p> <p>Evidence of a severe chronic movement disorder</p> <p>Treated with clozapine during the 4 months prior to enrolment</p> <p>Received depot neuroleptics, unless the last injection was at least one treatment cycle prior to randomization.</p>				<p>Differences between all lurasidone groups and placebo for changes in laboratory parameters and electrocardiographic measures were minimal. Weight gain $\geq 7\%$ occurred in 8.2% of patients receiving lurasidone and 3.2% receiving placebo. Modest increases in prolactin (median increase, 0.7 ng/mL) and extrapyramidal symptoms were observed following treatment with lurasidone compared with placebo. Akathisia was the most commonly reported adverse event with lurasidone (17.6%, versus 3.1% with placebo).</p>		
<p>Harvey PD at al 2013</p> <p>Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study</p>	<p>Phase III</p> <p>Randomised controlled trial</p> <p>Double-blind</p> <p>Parallel group</p> <p>Non-inferiority study</p>	<p>Outpatients with an acute exacerbation of chronic schizophrenia who had recently completed a 6-week placebo-controlled trial of treatment with either lurasidone or Quetiapine XL (PEARL-3 study)</p>	<p>N= 292 in extension phase</p> <p>Predominantly male.</p> <p>Other characteristics similar.</p>	<p>6 months of flexible dose treatment with lurasidone (40–160mg once daily), compared with Quetiapine XL (200–600mg once daily).</p>	<p>6 months</p>	<p>Cognitive performance and functional capacity were assessed with the CogState computerized cognitive battery and the UPSA-B.</p> <p>Analyses were conducted for all subjects, as well as the subsample whose test scores met prespecified validity criteria. No statistically significant differences were found for change in the composite neurocognitive score for lurasidone(80mg/day and 160mg/day) groups, quetiapine X L and</p>	<p>Sunovion</p>	<p>Results report pPatients in Quetiapine XL group received 200-800mg/day not 200-600mg/day as described in method.</p> <p>45% of patients in acute phase failed to complete</p>

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followed by a 6-month double-blind extension						<p>placebo in the full sample at week 6. For the evaluable sample (N=267), lurasidone 60mg was superior to both placebo and quetiapine on the neurocognitive composite, while lurasidone 80mg, quetiapine XL, and placebo did not differ. UPSA-B scores were superior to placebo at 6 weeks for all treatments. In the double-blind extension study, analysis of the full sample showed significantly better cognitive performance in the lurasidone (40–160 mg) group compared to the quetiapine XL (200–800 mg) group at both 3 and 6 months.</p> <p>Cognitive and UPSA-B total scores were significantly correlated at baseline and for change over time.</p>		computerized neurocognitive scores correctly.
Harvey PD et al 2011 Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs. ziprasidone	Randomized, fixed-dose, double-blind, parallel group, Comparator controlled	<p><u>Inclusion</u></p> <p>Adult outpatients 18–70 years old Met DSM-IV criteria for schizophrenia or schizoaffective disorder that was chronic (at least 6 months duration), and stable, with no hospitalization or acute exacerbation of psychosis in the previous 3 months. Never received treatment with ziprasidone or lurasidone.</p> <p><u>Exclusion</u></p>	Predominantly male. Other characteristics similar.	21 days of double-blind treatment with fixed dose of lurasidone 120 mg once daily (start dose, 80 mg for 3 days) or ziprasidone 80 mg BID (start dose, 40 mg BID for 3 days). Lurasidone n= 150 Ziprasidone n= 151	21 days	<p>Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression, and the Calgary Depression Scale.</p> <p>There were no between-group treatment differences in performance on the MCCB or the SCoRS ratings. Lurasidone patients demonstrated significant within group-improvement from baseline on the MCCB composite score (p=0.026) and on the SCoRS (p=0.001), but ziprasidone patients did not improve on either the MCCB composite (p=0.254) or the SCoRS (p=0.185). At endpoint there was a statistical trend</p>	Sunovion, Merck	Centres only in USA.

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		<p>History of head trauma with loss of consciousness.</p> <p>Current substance abuse or a lifetime history of substance dependence.</p> <p>Active suicidal or homicidal ideation.</p> <p>Inability to provide informed consent.</p> <p>Treated with fluoxetine, clonazepam, or clozapine at any time within 1 month prior to enrollment, or had received depot neuroleptics unless the last injection was at least 2 treatment cycles before entry.</p> <p>Received treatment with amantadine, diphenhydramine, or anticholinergics within 3 days of the initial placebo period; lithium, anticonvulsants, or antidepressants within 1 week of the initial placebo period; or monoamine oxidase (MAO) inhibitors within 2 weeks of the initial placebo period.</p> <p>Received electroconvulsive therapy treatment within the last 3 months.</p> <p>History of hypersensitivity to more than 1 class of</p>				<p>($p=0.058$) for lurasidone to demonstrate greater improvement from baseline in SCoRS ratings.</p>		

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		drug, or any history of hypersensitivity to ziprasidone, or had used ziprasidone in the last year and had a very poor response or intolerable side effects.						

[1] Bibliographic reference: author(s), year, article title, journal, volume, pages.

[2] Study type: for example, randomised controlled trial, cohort or case-control studies.

[3] Inclusion & exclusion: list the inclusion and exclusion criteria.

[4] Patient characteristics: characteristics relevant to the area of interest: age, sex, ethnic origin, comorbidity, disease status, community- or hospital-based.

[5] Intervention & comparison(s): state the treatment, procedure or test studied, including dose and schedule. If important for the study, specify duration of treatment. For diagnostic studies the intervention is the diagnostic test plus associated treatment studied. Comparison: state whether placebo or alternative treatment. For diagnostic studies, comparison of the test is with another test and treatment strategy. Record the number of patients in each arm, and the numbers of patients who started and completed the study.

[6] Length of follow-up: the length of time that patients take part in the study for, from first staging treatment until either a pre-specified end-point (for example, death, specified length of disease-free remission) or the end of the data-gathering phase is reached. If the study is stopped earlier than originally planned for any reason, this should be noted here.

[7] Outcome measures: list all outcome measures defined in the review protocol, including associated harms. For studies with a diagnostic component there will be two interventions to consider – the diagnostic test used and the associated treatment. Use a separate line for each outcome.

Effect size: for example, raw data from the study that allow analyses such as absolute risk reduction and relative risk (reduction), number needed to treat, number needed to harm, odds ratios, as required. Give confidence intervals whenever possible.

[8] Source of funding: government funding (for example, NHS), voluntary/charity (for example, Wellcome Trust), pharmaceutical company; and the role of funding organisations.

[9] Additional comments: additional characteristics and/or interpretations of the studies that the reviewer wishes to record. These might include important flaws in the study not identifiable from other data in the table, and additional questions or issues that will need to be considered but do not figure in the results tables in the study.