Research Article

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Efficacy and metabolic effects of lurasidone versus brexpiprazole in schizophrenia: a network meta-analysis

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Aim: To assess the relative efficacy and metabolic effects of lurasidone and brexpiprazole in the acute treatment of schizophrenia. **Methods:** Five lurasidone and three brexpiprazole trials were identified. In the absence of head-to-head trials, a Bayesian network meta-analysis comparing lurasidone and brexpiprazole was performed. **Results:** Nonstatistically significant differences in efficacy measures were observed between lurasidone and brexpiprazole. Significant differences favoring lurasidone for weight change (-0.69 kg; 95% CrI: -1.22 to -0.15), total cholesterol (-7.60 mg/dl; 95% CrI: -13.94 to -1.22), and low-density lipoprotein (-6.58 mg/dl; 95% CrI: -12.11 to -1.04) were observed, with a trend indicating half the risk of experiencing ≥7% weight gain. **Conclusion:** This network meta-analysis suggested that lurasidone had similar efficacy and fewer metabolic effects than brexpiprazole in patients with acute schizophrenia.

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Keywords: atypical antipsychotics • brexpiprazole • lurasidone • network meta-analysis • schizophrenia • weight gain

The lifetime prevalence of schizophrenia, one of the most debilitating and expensive chronic psychiatric disorders, is 0.5–1.0% [1,2]. Patients with schizophrenia experience incapacitating symptoms such as hallucinations, delusions and disorganized thinking that can compromise normal daily activities [3]. Antipsychotic medications are the first-line treatment of schizophrenia during acute episodes, when the primary goal is to reduce the severity of psychosis and associated symptoms, as well as during the stable phase, when the goals are to maximize functioning and prevent relapses [4,5].

Adherence often remains sub-optimal in schizophrenia due in part to the difficulty of finding a treatment that is both efficacious and tolerable for a given patient [6–8]. Identifying an antipsychotic that balances efficacy and tolerability could improve treatment adherence, thereby lowering the risk of relapse and hospitalization [9]. A large network meta-analysis that incorporated 212 schizophrenia clinical trials and examined 15 different antipsychotics demonstrated that there are small but consistent differences in efficacy, with clozapine appearing to be the most efficacious [10]. However, treatments clearly differed on tolerability attributes, with extrapyramidal symptoms and weight gain being two primary areas of concern [10].

Atypical antipsychotics are generally preferred over typical antipsychotics because of their lower risk for extrapyramidal symptoms [11]. However, some atypicals are associated with negative metabolic changes such as weight gain and adverse changes in cholesterol and triglyceride levels [12]. Weight gain, as well as other metabolic effects, may increase treatment discontinuations. In a large 3-year observational study of 7728 patients with schizophrenia, only 39.7% stayed on their prescribed antipsychotic for the entire study period, and among patients who discontinued their antipsychotic medications, 38.7% discontinued due to lack of efficacy, and 14.2% discontinued due to tolerability issues [13]. In a clinical effectiveness trial, among 1432 patients who received their randomized antipsychotic, only 25.9% stayed on treatment for the full 18-months, with 23.7% discontinuing due to lack of efficacy and 14.9% due to lack of tolerability [6].

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Both efficacy and tolerability appear to play an important role in the discontinuation rates for antipsychotics. Patients with schizophrenia are at greater risk of developing diabetes and cardiovascular disease and some atypical antipsychotics appear to increase these risks [14,15]. When examining patient concerns about antipsychotics in a patient preference study, treatment-induced weight gain was the third greatest concern for patients with schizophrenia, after improvement in symptoms and elimination of hyperglycemia [16]. Reducing weight gain and the associated cardiometabolic changes may improve treatment adherence [8] and patient outcomes. Even relatively small differences in treatment adherence have been linked to a lower risk of hospitalization [9].

The National Association of State Mental Health Program Directors recognized that antipsychotics are not interchangeable and recommend including at least one weight-neutral treatment on formulary for those patients with potential metabolic issues [17]. Successful treatment for the majority of patients with schizophrenia involves balancing the benefits and risks of antipsychotics, with clozapine being the last resort treatment for refractory patients [17]. Due to the complexity of successfully managing schizophrenia, an individualized treatment for schizophrenia which is based on the patient's needs and preference should be considered [17–19].

Two atypical antipsychotics that had a low incidence of weight gain in a large meta-analysis were lurasidone and aripiprazole [10]. Preclinical studies indicate that lurasidone has a high affinity for dopamine receptor D_2 and the serotonin receptor 5-HT_{2A}, and little to no affinity for histaminergic receptors [20]. In contrast, preclinical studies indicate that aripiprazole is a partial D_2 agonist, with high affinity for 5-HT_{2A} and modest H_1 binding [21]. In the meta-analysis, both lurasidone and aripiprazole had a low risk for weight gain, and similar levels of improvement in symptoms, rates of all-cause discontinuation and rates of sedation [10].

Brexpiprazole, approved by the US FDA in 2015, has a similar binding profile to aripiprazole as a partial D_2 agonist with moderate histamine binding, but with a higher affinity for serotonin receptor 5-HT_{2A} [22]. In a clinical trial that directly compared aripiprazole and brexpiprazole, both had similar efficacy, similar rates of weight gain reported as an adverse event (aripiprazole 9.4% and brexpiprazole 9.1%), but aripiprazole-treated patients were more likely to have extrapyramidal symptoms (21.2 vs 9.4%) [23]. As aripiprazole and lurasidone have comparable efficacy and weight gain rates, examining if brexpiprazole has similar results when compared with lurasidone would be of interest for patients that are particularly vulnerable to metabolic changes.

Currently, there are no head-to-head clinical trials comparing the efficacy and metabolic parameters of lurasidone and brexpiprazole. Given that both of these antipsychotics appear to be relatively weight neutral atypical antipsychotics, evidence is needed to assist physicians and formulary decision makers in understanding potential differences between them. This study, using a network meta-analysis, summarized the relative efficacy and metabolic effects of lurasidone and brexpiprazole based on acute randomized clinical trials in adults with schizophrenia.

Methods

Literature search & selection

A systematic literature review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, aligned with the Centre for Reviews and Dissemination guide for conducting systematic reviews [24,25], and informed by the Population, Intervention, Comparison, Outcome and Study (PICOS) type framework [26]. Randomized controlled trials that included lurasidone and brexpiprazole (Phase II, III and IV trials) for adult populations (≥18 years old) with schizophrenia were identified. Searches were conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and PubMed in November 2015. In addition, proceedings from Schizophrenia International Research Society Conference and the proceedings from the American Psychiatric Association conference were searched from 2013 through the third quarter of 2015. Only articles in English were included. Randomized clinical trials were restricted to those using at least one arm with the FDA-approved doses of lurasidone (40–160 mg/day) or brexpiprazole (2–4 mg/day). The review was restricted to clinical trials assessing the efficacy of the medications in reducing symptoms during acute episodes of schizophrenia. See Supplementary Information for further details on the literature search.

Network meta-analysis

A network meta-analysis of lurasidone and brexpiprazole randomized clinical trials for acute treatment of schizophrenia was conducted using a Bayesian framework in WinBUGS1.4. The framework used guidelines from the National Institute for Health and Care Excellence Decision Support Unit Technical Support Guidance [27]. Using placebo as the common comparator, the analysis compared the efficacy and the tolerability of lurasidone and brexpiprazole. For trials with multiple fixed dose arms, the arms with FDA-approved doses were pooled.

The primary efficacy outcome measure was response rate, defined as ≥20% improvement in Positive and Negative Syndrome Scale (PANSS). Secondary efficacy outcome measures included change from baseline in PANSS and change from baseline in Clinical Global Impressions-Severity Scale (CGI-S) scores. Metabolic outcomes included the proportion with clinically significant weight gain (i.e., ≥7% increase in weight) and changes from baseline in the following parameters: weight, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides.

For continuous outcomes, median difference in change from baseline over 6 weeks was estimated along with the 95% credible interval (CrI). CrIs are the Bayesian equivalent of confidence intervals. For dichotomous outcomes, a logit model estimated the odds ratio (OR) and 95% CrI. Results were considered significant if the 95% CrI did not include zero for continuous outcome variables or one for dichotomous outcome variables.

Following the recommendation of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force [28], a vague prior distribution was used where any parameter value was equally likely. Simulation convergence was evaluated from history, trace plots, and Brooks–Gelman–Rubin convergence statistics model diagnostics from 40,000 iterations with additional iterations used when diagnostics suggested sufficient convergence was not achieved [29,30].

The goodness-of-fit for each model was evaluated using the Deviance Information Criterion (DIC) score, with a lower DIC score indicating a better fitting model. The DIC provides an estimate of model fit that is penalized for increased model complexity [31]. All outcome variables were assessed using both fixed and random effects models. The fixed effects models generally had a better fit and were reported here. Results of the random effect models are available upon request.

Results

Study selection

The systematic literature review identified a total of 419 citations. After removing duplicates and abstract screening, 50 publications (full text and conference abstracts) were included. Of these, 14 were primary publications (10 lurasidone and four brexpiprazole). Figure 1 summarizes the selection and review process.

Within the ten lurasidone trials, six trials assessed outcomes for acute schizophrenia [32–37]. Four other lurasidone trials [38–41] were excluded from the review because they included only stable patients. One acute trial for lurasidone, OPTIMIZE [36], was subsequently excluded from the analysis due to its unique study design which involved a nested randomization of patients not having an early response to a higher dose of lurasidone.

Within the brexpiprazole trials, three trials assessing acute episodes of schizophrenia [23,42,43] were included and one trial [44] was excluded from the review as it was in stable patients. Among the 14 primary lurasidone and brexpiprazole publications, eight trials met all the selection criteria: five for lurasidone [32–35,37] and three for brexpiprazole [23,42,43].

Trial heterogeneity

Trial heterogeneity for every treatment arm using an FDA-approved dose was assessed by examining distribution of the trial baseline characteristics. These characteristics were plotted by drug to assess whether suitably comparable patients were included across the trials available for pooling.

Table 1 presents the baseline characteristics across trials, with weighted averages for the fixed-dose trials that had multiple treatment arms. All eight studies had reasonably comparable baseline characteristics and appeared appropriate to include in the network meta-analysis: mean age ranged from 37.0 to 42.2 years, percent of females ranged from 16.0 to 38.7%, mean age of symptom onset ranged from 23.3 to 27.4, mean BMI ranged from 25.7 to 31.2, mean PANSS ranged from 91.2 to 97.2, and mean CGI-S ranged from 4.8 to 5.0. Table 2 gives the outcome measures from each trial at the end of 6 weeks. Not all trials measured all variables. The relative homogeneity of patients and outcomes across the trials, along with the DIC values, appeared consistent with fixed effects model assumptions.

Network meta-analysis results

Forest plots of results for efficacy and metabolic measures are presented in Figures 2 & 3, respectively. For the efficacy variables, there were no significant differences based on the 95% CrIs. Although not statistically significant, lurasidone was associated with a higher likelihood of treatment response (OR: 1.28; 95% CrI: 0.88–1.87) and

Table 1. Patient baseline characteristics across randomized schizophrenia clinical trials included in the network meta-analysis.

Baseline variables	Lurasidone schizophrenia trials										Brexpiprazole schizophrenia trials				
	Nakamura		*Meltzer*		*Loebel*		*Ogasa*		*Nasrallah*		*Correll*		*Kane*		*Citrome*
	LUR	*PBO*	*LUR*	*PBO*	*LUR*	*PBO*	*LUR*	*PBO*	*LUR*	*PBO*	*BRE*	*PBO*	*BRE*	*PBO*	*BRE*
Age (years)	39.7	41.9	37.8	37.0	37.0	37.4	40.4	38.1	-	-	40.2	39.7	37.7	39.3	42.2
Female gender	24.4	22.2	21.5	23.0	27.4	36.0	27.3	16.0	31.5	27.4	38.7	35.9	36.5	39.7	28.1
BMI (kg/m^2)	30.7	31.2	25.9	25.8	25.7	26.1	29.5	29.4	26.6	26.9	27.2	26.5	26.7	26.6	-
Age at onset (years)	-[†]	-	23.3	23.9	25.1	25.5	-	-	24.6	24.2	27.3	27.4	25.3	25.6	25.6
PANSS	94.4	96.0	97.2	95.8	97.6	96.6	91.2	93.3	96.2	96.8	95.4	95.9	95.7	94.8	94.1
CGI-S	4.8	4.8	5.0	4.9	5.0	4.9	4.8	4.6	4.9	4.9	4.9	4.8	5.0	4.9	5.0

Numbers represent means across trial arms. The Citrome *et al.* trial had patients randomized to either brexpiprazole or aripiprazole. Trials are identified in the table based on the primary authors name. The associated references are as follows: Nakamura [33], Meltzer [35], Loebel [37], Ogasa [32], Nasrallah [34], Correll [42], Kane [43], and Citrome [23].

[†]- indicates no data available.

BRE: Brexpiprazole; CGI-S: Clinical Global Impressions – Severity; LUR: Lurasidone; PANSS: Positive and Negative Syndrome Scale; PBO: Placebo.

Table 2. Observed outcomes: mean changes and percentages at week 6.

Outcome variables	Lurasidone schizophrenia trials										Brexpiprazole schizophrenia trials				
	Nakamura		*Meltzer*		*Loebel*		*Ogasa*		*Nasrallah*		*Correll*		*Kane*		*Citrome*
	LUR	*PBO*	*LUR*	*PBO*	*LUR*	*PBO*	*LUR*	*PBO*	*LUR*	*PBO*	*BRE*	*PBO*	*BRE*	*PBO*	*BRE*
Response rate	44.4	26.7	-†	49.0	-	-	48.0	18.3	63.2	54.0	53.0	34.8	49.2	40.0	39.0
PANSS	-14.1	-5.5	-24.7	-16.0	-24.3	-10.3	-15.5	-6.2	-21.0	-17.0	-20.2	-12.0	-18.3	-13.5	-22.9
CGI-S	-0.6	-0.2	-1.5	-1.1	-1.6	-0.9	-0.8	-0.1	-1.2	-1.0	-1.2	-0.8	-1.1	-0.8	-
Weight change (kg)	0.9	0.5	1.0	0.6	0.6	0.1	0.3	0.0	0.9	0.3	1.4	0.4	1.7	0.4	4.3
Clinically significant weight gain (≥7%)	6.7	7.8	5.9	7.0	4.3	2.6	-	-	8.2	3.2	8.9	4.4	11.8	3.9	-
Total cholesterol (mg/dl)	-10.1	-7.1	-8.0	-6.8	-	-	-	-	-	-	2.4	-3.1	2.8	-3.4	-3.0
LDL (mg/dl)	-5.2	-0.7	-4.8	-1.8	-	-	-	-	-	-	0.9	-2.1	1.8	-1.5	0.8
HDL (mg/dl)	-1.2	-3.0	-0.7	-1.2	-	-	-	-	-	-	0.9	-1.2	1.1	-2.4	-4.6
Triglycerides (mg/dl)	-24.4	-31.7	-6.7	0.1	-	-	-	-	-	-	3.3	-0.8	-3.1	1.5	3.9

Numbers represent averages across trial arms. The Citrome *et al.* trial had patients randomized to either brexpiprazole or aripiprazole. Response was defined as a ≥20% improvement in PANSS. Trials are identified in the table based on the primary authors name. The associated references are as follows: Nakamura [33], Meltzer [35], Loebel [37], Ogasa [32], Nasrallah [34], Correll [42], Kane [43], and Citrome [23].

†- indicates no data available.

BRE: Brexpiprazole; CGI-S: Clinical Global Impressions – Severity; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LUR: Lurasidone; PANSS: Positive and Negative Syndrome Scale; PBO: Placebo.

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