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Effect of lurasidone dose on cognition in patients with schizophrenia: Post-hoc analysis of a long-term, double-blind continuation study☆,☆☆

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ABSTRACT

We previously reported that treatment with 160 mg/d of lurasidone improved cognitive performance in a manner superior to placebo, quetiapine XR 600 mg/d, and lurasidone 80 mg/d, based on a 6-week randomized trial of patients with an acute exacerbation of schizophrenia. The objective of this post-hoc analysis was to explore the cognitive and functional performance of patients whose final doses of lurasidone were 40/80 mg/d, 120 mg/d, and 160 mg/d compared to quetiapine XR 200-800 mg/d (QXR) during a 6-month, double-blind continuation study that followed a short-term trial. Subjects who received final doses of lurasidone 120 mg/d (n = 77) and 160 mg/d (n = 49) showed significantly greater improvement in overall cognitive performance compared to QXR (n = 85) at week 32 (month 6 of the extension study), while those on last doses of 40/80 mg/d (n = 25) showed a trend towards significance at week 32. Mean changes in neurocognitive composite z-score from pre-treatment baseline were significant for the 3 lurasidone final dose groups at both weeks 19 and 32, with composite change scores of z = 1.53, z = 1.43, and z = 1.34 for the lurasidone 40/80 mg/d, 120 mg/d, and 160 mg/d, respectively, at week 32. In contrast, the composite change score was not statistically significant in the overall quetiapine group (z = 0.46), with none of the individual quetiapine doses showing any significant improvement. Functional capacity scores improved in all treatment groups. Our findings indicate improved cognitive performance in patients treated with each of the flexible doses of lurasidone 40–160 mg/d, compared to quetiapine XR 200–800 mg/d. All doses of lurasidone were superior to all doses of quetiapine for cognitive performance.

1. Introduction

The focus of mental healthcare has increasingly shifted from the "disease" model of symptom amelioration and relapse prevention to the "rehabilitation" model of functional recovery, patient well-being, and restoration of real-world functioning (Bowie et al., 2006; Leifker et al., 2011). Cognitive deficits are core features of schizophrenia (Harvey and Keefe, 2001; Nuechterlein et al., 2012) and represent a key predictor of poor functional outcomes (Leifker et al., 2011; Harvey et al., 2013). Despite several large-scale trials conducted to investigate novel treatment options, there are, however, no pharmacological interventions approved to date to treat this component of the disorder (Keefe et al., 2013). Previous reports have suggested remission in negative symptoms and long-term functional benefits can be attained in patients who continued treatment with atypical antipsychotics in a double-blind, follow-up study of up to 196 weeks (Potkin et al., 2009; Stahl et al., 2010).

Lurasidone is a novel benzisothiazol derivative with potent binding affinity for D_2, 5-HT_{2A} and $5HT_7$ receptors (antagonist), moderate affinity for $5HT_{1A}$ (partial agonist) and α_{2C} receptors (antagonist), and no appreciable affinity for H_1 and M_1 receptors (Ishibashi et al., 2010). The procognitive effect of lurasidone was supported in preclinical studies (Ishiyama et al., 2007; Enomoto et al., 2008; Horisawa et al., 2011), as well as by a 3-week, double-blind, active-controlled study of lurasidone and ziprasidone (Harvey et al., 2011). In a randomized, double-blind, 6-week, placebo- and active-controlled acute study, lurasidone 160 mg/d demonstrated superiority to both placebo (Cohen's d = 0.37) and quetiapine 600 mg/d (d = 0.41) on a neurocognitive composite score, while lurasidone 80 mg/d, quetiapine XR 600 mg/d, and placebo did not significantly differ (Harvey et al., 2013).

Determining the therapeutic dose range and dose–response relationships is essential to pharmacotherapeutic research and treatment interventions (Davis and Chen, 2004). This may be especially critical for optimizing treatment strategies to maximize the beneficial effects

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of drugs on cognitive impairment associated with schizophrenia (Keefe et al., 2013). The objective of this post-hoc analysis was to explore dose effects of lurasidone on cognitive performance in schizophrenia in a 6-month, double-blind continuation study that followed a short-term trial. Patients receiving 40, 80, 120, or 160 mg/d of lurasidone were compared to patients receiving quetiapine XR at the end of the continuation study. Each lurasidone dose was compared to the entire sample of quetiapine XR patients; due to small sample sizes, individual quetiapine XR doses were examined on an exploratory basis.

2. Methods

The analysis reported here is based on data from a previously reported randomized, double-blind, 6-week, placebo- and active-controlled acute study (Harvey et al., 2013; Loebel et al., 2013a), followed by a double-blind continuation study that continued up to 1 year (Loebel et al., 2013b); the design of these studies will therefore be only briefly summarized here. The study was approved by an institutional review board at each investigational site and was conducted in accordance with the International Conference on Harmonisation of Good Clinical Practices guidelines, and with the ethical principles of the Declaration of Helsinki. All patients signed an informed consent document explaining study procedures and potential risks before study entry.

2.1. Subjects

Subjects with a primary diagnosis of schizophrenia, who had recently been hospitalized for an acute exacerbation of psychotic symptoms, were randomly assigned to receive 6 weeks of double-blind treatment with once-daily doses of lurasidone (80 mg or 160 mg), quetiapine XR (600 mg), or placebo. Upon completion of the initial 6-week study, eligible subjects were enrolled in the 1-year, double-blind continuation study, where subjects continued treatment with either flexible-dose lurasidone 40–160 mg/d or quetiapine XR 200–800 mg/d. Cognitive and functional capacity assessments were obtained at months 3 and 6 of the 1-year continuation study. For the purposes of this analysis, lurasidone or quetiapine XR dose was defined as the last dose received by subjects during the initial 6 months of the continuation study. Lurasidone doses assessed were 40/80 mg/d, 120 mg/d, and 160 mg/d; quetiapine XR doses assessed were 200/400 mg/d, 600 mg/d, and 800 mg/d. The 40 and 80 mg/d lurasidone doses and the 200 and 400 mg/d quetiapine XR doses were combined due to the small number of subjects using these doses during the continuation study. All study medications were taken once daily, in the evening, with food.

Subjects who had been treated with placebo in the initial 6 week study were switched in blinded fashion to flexible dose lurasidone treatment, but the present analyses focused primarily on those patients receiving lurasidone during both the acute and continuation study phases (LUR-to-LUR). Entry into the continuation study required subjects to have completed all assessments on the final week 6 visit of the acute phase, and judged by the investigator as suitable for research-oriented treatment in an outpatient setting.

2.2. Assessments

The CogState Computerized Cognitive Battery (Pietrzak et al., 2009) was administered by trained examiners at pre-treatment baseline, week 6 (end of the acute study) and weeks 19 (month 3 of the continuation study) and 32 (month 6 of the continuation study). The primary cognitive outcome measure was the composite Z-score, which was calculated as an average of the 7 standardized Z-scores over the 7 task domains. If three or more components were missing at a visit, the composite score was set to missing (Pietrzak et al., 2009).

The University of California San Diego (UCSD) Performance-based Skills Assessment-Brief version (UPSA-B; Mausbach et al., 2007) was administered at the acute study baseline (randomization), week 6 (end of the acute study), and after 3 months (week 19) and 6 months (week 32) of double-blind continuation study treatment. The UPSA-B consists of two of the five original UPSA domains, finances and communication, and has been shown to be highly correlated with the long form of the UPSA and to have substantial test–retest reliability. Each subscale contributes 50 points so that total scores range from 0 to 100 points, with higher scores reflecting better performance.

2.3. Statistical methods

The dose effect of lurasidone (based on the last dose received by patients in the continuation study phase) on cognitive functioning at week 32 (month 6 of the continuation study) was evaluated using a mixed-effects longitudinal data analysis (LDA) model (Fitzmaurice et al.,

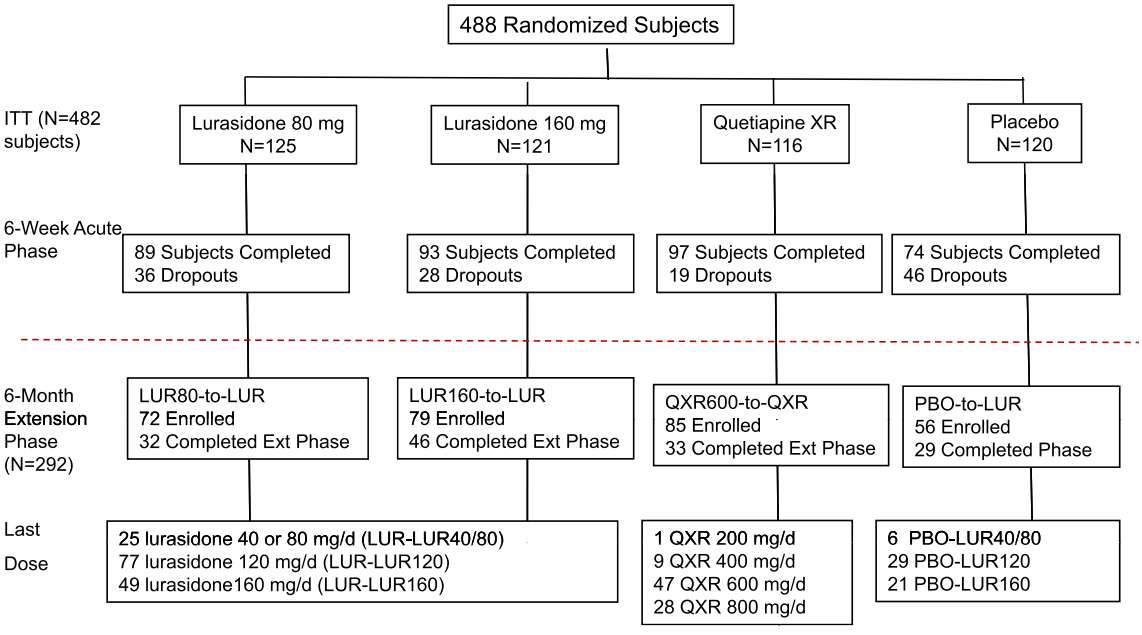

Fig. 1. Disposition of subjects. LUR80: lurasidone 80 mg/d; LUR160: lurasidone 160 mg/d; QXR: quetiapine XR.

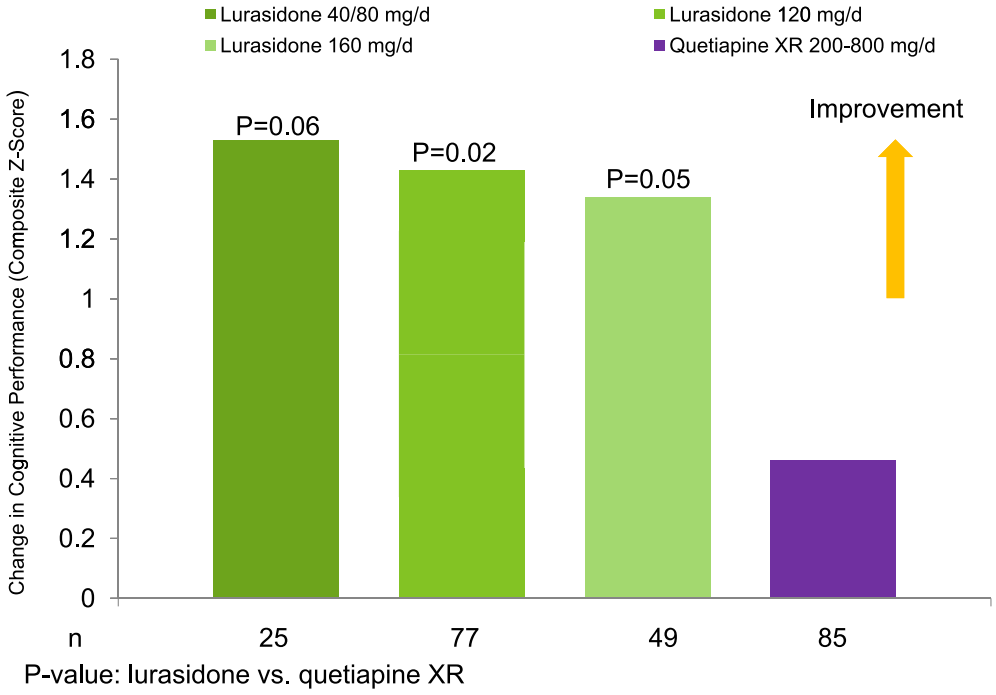

Fig. 2. Cognitive overall performance at week 32: Lurasidone last-dose groups (from lurasidone in acute phase) vs. quetiapine XR (from quetiapine in acute phase).

2004). The LDA model incorporated pre-treatment baseline score in the acute phase (at week 0) as part of the repeated measures outcome variable, with fixed effects terms for visit, visit-by-treatment, and pooled centers, as well as an unstructured covariance matrix for random effects (Fitzmaurice et al., 2004). The primary treatment group comparison was between patients continuing on flexibly dosed lurasidone (LUR-to-LUR) who received last lurasidone dose of 40/80 mg/d, 120 mg/d, or 160 mg/d in the continuation study phase, and all patients in the quetiapine XR group. No adjustment for multiple treatment comparisons and/or multiple outcomes was applied in this exploratory analysis.

4. Results

Fig. 1 depicts the disposition of subjects in the double-blind, 6-month, continuation study. A total of 292 subjects completed the 6-week acute phase and were enrolled in the double-blind continuation study. The median last dose in the overall lurasidone group (LUR-to-LUR, $n = 151$) was 120 mg/d at the month 6 end point. Of the 151 subjects, 49 (32.5%), 77 (51.0%), and 25 (16.6%) received final doses of lurasidone160 mg/d, 120 mg/d, and 40-80 mg/d, respectively, at month 6. The median last dose in the quetiapine XR group (QXR600-to-QXR, $n = 85$) was 600 mg/d. At month 6, last doses of quetiapine XR 800 mg/d were received by 28 patients (33%), 600 mg/d by 47 patients (55%), and 200–400 mg/d by 10 patients (12%).

Improvement in cognitive performance was significantly greater in patients receiving last doses of lurasidone120 mg/d ($p = 0.02$) and 160 mg/d ($p = 0.05$) in the LUR-to-LUR group, compared to the overall quetiapine XR group (Fig. 2). There was a trend towards significance for the lowest lurasidone dose group (40/80 mg/d) compared to the overall quetiapine XR group ($p = 0.06$) (Fig. 2). The mean change in neurocognitive composite z-score from acute phase baseline was significant for the overall lurasidone group (LUR-to-LUR) at both weeks 19 and 32 (months 3 and 6 of the continuation study) (Table 1), with composite change z-scores of 1.53 ($p < 0.05$), 1.43 ($p < 0.05$), and 1.34 ($p < 0.05$) at month 6 end point for the dose groups of lurasidone 40/80 mg/d, 120 mg/d, and 160 mg/d, respectively. In contrast, the change in neurocognitive composite z-score was not statistically significant in the overall quetiapine XR group ($z = 0.46$) ($p > 0.05$), with none of the individual quetiapine XR doses showing any significant improvement (mean change in z-score: 1.23 for 200/400 mg/d; 1.73 for 600 mg/d; −0.17 for 800 mg/d) from acute phase baseline.

Mean improvement in UPSA-B from acute baseline to week 32 was significant for all dose groups of lurasidone, ranging from 12.2 points (SE 2.6) for the last dose of 40/80 mg/d to 9.2 (SE 2.0) for the 160 mg/d group. These lurasidone dose groups were not significantly different from the overall quetiapine XR group at week 32 (12.1, SE 1.7).

Fig. 3 shows that patients receiving a last lurasidone dose of 40/80 mg/d had significantly better performance in visual learning ($p = 0.03$), working memory ($p = 0.01$), and social cognition ($p = 0.01$) compared to the overall quetiapine XR group. Patients receiving a last lurasidone dose of 120 mg/d had significantly better performance in visual learning ($p = 0.002$), working memory ($p = 0.03$), and reasoning/problem solving ($p = 0.013$) compared to the overall quetiapine XR group. Patients receiving a last lurasidone dose of 160 mg/d had significantly better performance in speed of processing ($p = 0.04$) compared to the overall quetiapine XR group. Superior performance at a trend level of significance ($p = 0.06$) was observed in social cognition for the 120 mg/d lurasidone group, and in attention/vigilance for the 40/80 mg/d and 160 mg/d lurasidone groups compared to the overall quetiapine XR group.

Among patients who switched from placebo in the acute phase to lurasidone in the continuation study (PBO-LUR, $n = 56$), those in the highest dose group of lurasidone 160 mg/d (PBO-LUR160, $n = 21$) showed significantly ($p < 0.05$) greater improvement in the neurocognitive composite z-score from acute baseline to month 6 ($z_{change} = 1.21$, SE 0.57, $p = 0.033$), but not the lower dose groups. However, these other dose comparisons were likely underpowered because of the small sample size.

5. Discussion

This post-hoc analysis extends previous findings regarding the effect of lurasidone on neurocognitive performance by exploring the dose effect of lurasidone on reducing neurocognitive impairment, in patients whose final doses of lurasidone were 40/80 mg/d, 120 mg/d, or 160 mg/d (versus final doses of quetiapine XR 200–400 mg/d,

Table 1
Least-squares mean change in cognitive composite score from acute baseline by last dose in the Continuation Study (mixed effects model, full analysis sample).

Visit	Week 19				Week 32			
Treatment (last dose by week 32)	LUR-to-LUR40/80 $n = 25$	LUR-to-LUR120 $n = 77$	LUR-to-LUR160 $n = 49$	QXR600-QXR $n = 85$	LUR-to-LUR40/80 $n = 21$	LUR-to-LUR120 $n = 55$	LUR-to-LUR160 $n = 37$	vs. QXR600-QXR $n = 57$
Z-Score change from baseline 95% CI	1.05* 0.27, 1.83	0.97* 0.45, 1.49,	0.79* 0.20, 1.39	0.31 -0.24, 0.86	1.53* 0.55, 2.51	1.43* 0.84, 2.03	1.34* 0.64, 2.10	0.46 −0.19, 1.10
Treatment Difference (SE) t, p-value (vs. QXR600-QXR)	t = 1.62 ($p = 0.107$)	t = 1.89 ($p = 0.060$)	t = 1.28 ($p = 0.202$)		t = 1.89 ($p = 0.06$)	t = 2.39 ($p = 0.017$)	t = 1.97 ($p = 0.050$)	

600 mg/d, or 800 mg/d) at month 6 of a continuation study. All doses of lurasidone (i.e., 40/80 mg/d,120 mg/d, or 160 mg/d) were superior to all doses of quetiapine (i.e., 200–400 mg/d, 600 mg/d, or 800 mg/d) for cognitive performance in the continuation study, where the dose groups of lurasidone and quetiapine XR were determined from the last dose received in the continuation study. Among subjects who received lurasidone in both acute and continuation study phases (LUR-LUR, $n = 151$), all three dose groups of lurasidone 40/80 mg/d,120 mg/d, or 160 mg/d were associated with significantly improved performance on the neurocognitive composite score from baseline to weeks 19 (month 3 of the continuation study) and 32 (month 6 of the continuation study). At month 6, the 120 mg/d and 160 mg/d groups showed significantly better cognitive performance compared to the quetiapine XR 200–800 mg/d group (QXR600-QXR). The improvement in functional capacity (as assessed by the UPSA-B) also continued through week 32 for the three lurasidone dose groups, and the mean change scores were not significantly different compared to the quetiapine XR group. Our previously published analysis of this study showed the correlation between changes in cognitive and UPSA-B assessments was significant at week 32 (Harvey et al., 2013). We did not repeat those analyses here because of low power for comparing correlations across the different dose groups.

Cognitive deficits are present at all stages of schizophrenia and are related to functional outcomes (Nuechterlein et al., 2012). We conducted an exploratory analysis to evaluate dose effects of lurasidone on neurocognitive performance and a range of cognitive domains known to be disturbed in schizophrenia. Results suggested that lurasidone 40–160 mg/d improved cognition more than quetiapine XR 200–800 mg/d across all cognitive domains (Fig. 3). Greater improvement in the speed of processing domain was found in subjects who received the highest last dose of lurasidone 160 mg/d, while improvement in visual learning, working memory, reasoning/problem solving, and social cognition were greater in subjects who received lower last doses of lurasidone (40/80 mg/d or 120 mg/d). The beneficial effects of lurasidone (versus quetiapine) might be explained, in part, by the differential receptor pharmacology of these agents. Specifically, quetiapine is a strong antagonist at H_1 receptors, which has been linked to daytime sleepiness (Witek et al., 1995; Baldwin and Scott, 2009; Loebel et al., 2013c). Given that quetiapine XR may be associated with higher levels of daytime somnolence compared to lurasidone (Loebel et al., 2013c), it is possible that this effect could mediate a worsening of cognitive functioning associated with quetiapine XR.

It is of note that data for this analysis were drawn from the first placebo-controlled, acute study to date to find the investigational drug treatment superior to an active comparator, followed by a 6-month, double-blind extension where cognitive performance was also assessed.(Harvey et al., 2013). The study by Harvey et al. was designed to address the methodological limitations of previous studies that

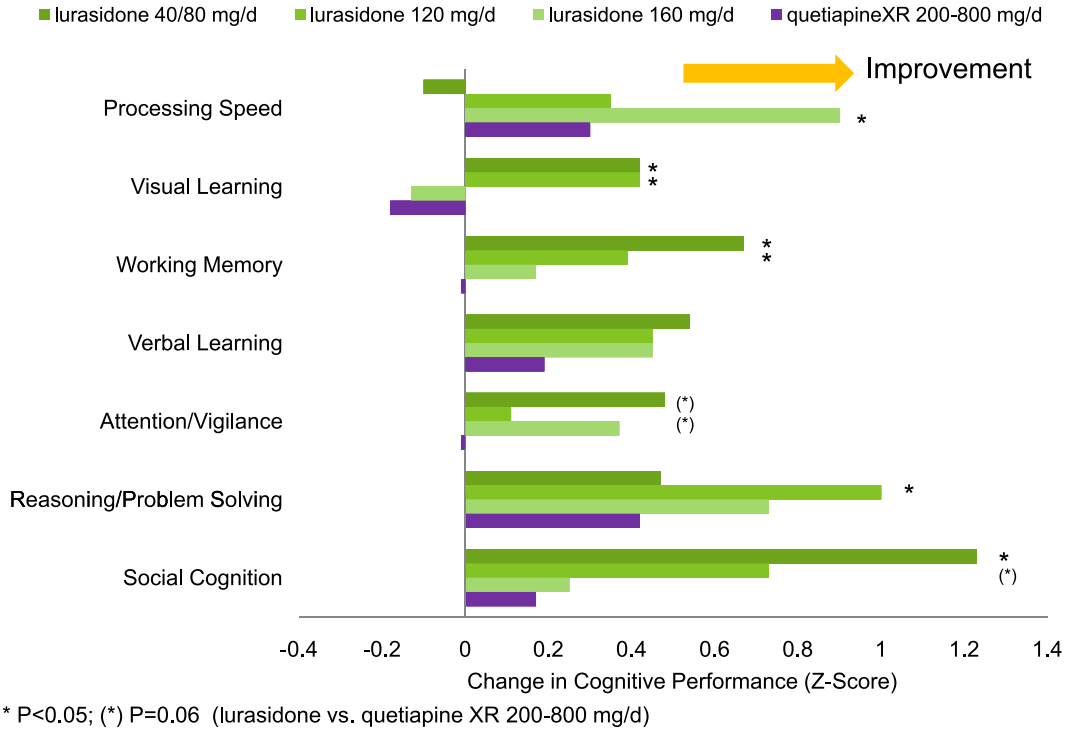

Fig. 3. Cognitive performance for domains at week 32: Lurasidone last dose groups vs. quetiapine XR (mixed effects model).

aimed to assess the effects of pharmacological interventions on improving cognitive performance in schizophrenia. Enhancements included the use of placebo in the acute phase and an active control to examine practice effects and bias due to regression-to-the-mean (Allison et al., 2009), adherence to the consensus research design (Buchanan et al., 2005), and a performance-based, co-primary measure of functional capacity (Mausbach et al, 2007). It also addressed the pseudospecificity issues by adjustment for concurrent symptomatic improvement in PANSS total and subscales (Harvey et al., 2013).

Limitations inherent in the original and current investigation should also be mentioned. Treatment with the higher dose of lurasidone 160 mg/d demonstrated a superior cognitive enhancement effect over placebo and quetiapine XR in the evaluable analysis sample ($n = 267$) in the acute phase, while lurasidone 80 mg/d and quetiapine XR 600 mg/d did not differ. This may reflect the challenges to obtaining valid computerized neurocognitive testing scores in acutely psychotic patients in the initial 6-week acute study (with a mean PANSS baseline score of 101.4, SD 11.12 in the non-evaluable sample) (Harvey et al., 2013). The observed testing failure rate was, however, consistent with those observed in previous studies using computerized assessments (Harvey et al, 2004; Keefe et al., 2007). The full analysis sample was used in this post-hoc analysis in the 6-month continuation study, which showed a statistically significant treatment difference in neurocognitive performance at month 6 favoring the lurasidone group versus the quetiapine XR group. Findings were derived for specific lurasidone and quetiapine XR doses based on the last dose received in the continuation study (up to 6 months); these results may differ from those obtained had fixed doses of study medication been used throughout the continuation study period. However, improvement of neurocognitive composite z-score was consistent at weeks 19 and 32, suggesting a trend of continued increase in cognitive performance over time. Findings from this analysis based on derived last dose of lurasidone in the continuation study warrant future investigation. The discrepancies in dose response compared to the 6-week study need to be studied more closely, but the benefits of lurasidone compared to quetiapine XR over the 6-month continuation study were all statistically significant, and change scores were too substantial to be attributed to practice effects. Improvement in the UPSA-B was smaller than those seen in the neurocognitive measures and a practice effect for this measure cannot be conclusively ruled out.

In summary, neurocognitive performance associated with all doses of lurasidone (between 40 and 160 mg/d) was superior to quetiapine XR 200–800 mg/d in this long-term, double-blind continuation study that followed a short-term, placebo-controlled trial. Improvement in functional capacity assessment appeared to be similar for both treatment groups. Further study is needed to confirm these findings, given the post-hoc nature of this exploratory analysis.

Role of Funding Source

This study was sponsored by Sunovion Pharmaceuticals Inc. The sponsor was involved in the study design and collection of data.

Contributors

All authors contributed to the design of the study. Drs. Harvey and Siu undertook the statistical analysis. Drs. Harvey and Siu prepared the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Conflict of Interest

Dr. Harvey serves as a consultant/advisory board member for Boeheringer-Ingelheim, Forum Pharma, Genentech, Lundbeck, Otsuka-America, Roche Pharma, Sanofi, Sunovion, and Takeda. Dr. Siu serves as a consultant for Pfizer Inc. and Sunovion Pharmaceuticals. Dr. Ogasa is an employee of Sumitomo Dainippon Pharma Co., Ltd. Dr. Loebel is an employee of Sunovion Pharmaceuticals.

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References

Allison, D.B., Loebel, A.D., Lombardo, I., et al., 2009. Understanding the relationship between baseline BMI and subsequent weight change in antipsychotic trials: effect modification or regression to the mean? Psychiatry Res. 170, 172–176.
Baldwin, C.M., Scott, L.J., 2009. Quetiapine extended release: in schizophrenia. CNS Drugs 23, 261–269.
Bowie, C.R., Reichenberg, A., Patterson, T.L., et al., 2006. Determinants of real world functional performance in schizophrenia: correlations with cognition, functional capacity, and symptoms. Am. J. Psychiatry 163, 418–425.
Buchanan, R.W., Davis, M., Goff, D., et al., 2005. A summary of the FDA-NIMH MATRICS Workshop on clinical trial design for neurocognitive drugs for schizophrenia. Schizophr. Bull. 31, 5–19.
Davis, J.M., Chen, N., 2004. Dose response and dose equivalence of antipsychotics. J. Clin. Psychopharmacol. 24, 192–208.
Enomoto, T., Ishibashi, T., Tokuda, K., et al., 2008. Lurasidone reverses MK-801-induced impairment of learning and memory in the Morris water maze and radial-arm maze tests in rats. Behav. Brain Res. 186, 197–207.
Fitzmaurice, G.M., Laird, N.M., Ware, J.H., 2004. Applied longitudinal analysis. John Wiley & Sons, Inc., New Jersey.
Harvey, P.D., Keefe, R.S.E., 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am. J. Psychiatry 158, 176–184.
Harvey, P.D., Siu, C.O., Romano, S., 2004. Randomized, controlled, double-blind, multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill in patients with schizophrenia or schizoaffective disorder. Psychopharmacology 172, 324–332.
Harvey, P.D., Ogasa, M., Cucchiaro, J., et al., 2011. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs. ziprasidone. Schizophr. Res. 127, 188–194.
Harvey, P.D., Siu, C.O., Hsu, J., Cucchiaro, J., Maruff, P., Loebel, A., 2013. Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study followed by a 6-month double-blind extension. Eur. Neuropsychopharmacol. 23, 1373–1382.
Horisawa, T., Ishibashi, T., Nishikawa, H., et al., 2011. The effects of selective antagonists of serotonin 5-HT7 and 5-HT1A receptors on MK-801-induced impairment of learning and memory in the passive avoidance and Morris water maze tests in rats: mechanistic implications for the beneficial effects of the novel atypical antipsychotic lurasidone. Behav. Brain Res. 220, 83–90.
Ishiyama, T., Tokuda, K., Ishibashi, T., et al., 2007. Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test. Eur. J. Pharmacol. 572, 160–170.
Ishibashi, T., Horisawa, T., Tokuda, K., et al., 2010. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-HT7 and 5-HT1A receptor activity. J. Pharmacol. Exp. Ther. 334, 171–181.
Keefe, R.S.E., Bilder, R.M., Davis, S.M., et al., 2007. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. Arch. Gen. Psychiatry 64, 633–647.
Keefe, R.S.E., Buchanan, R.W., Marder, S.R., et al., 2013. Clinical trials of potential cognitive enhancing drugs in schizophrenia: what have we learned so far? Schizophr. Bull. 39, 417–435.
Leifker, F.R., Patterson, T.L., Heaton, R.K., et al., 2011. Validating measures of real world outcome: the results of the VALERO expert survey and RAND panel. Schizophr. Bull. 37, 334–343.
Loebel, A., Cucchiaro, J., Sarma, K., et al., 2013a. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. Schizophr. Res. 145, 101–109.
Loebel, A., Cucchiaro, J., Xu, J., et al., 2013b. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: a 12-month, double-blind, continuation study. Schizophr. Res. 147, 95–102.
Loebel, A., Siu, C.O., Cucchiaro, J., et al., 2013c. Daytime sleepiness associated with lurasidone and quetiapine XR: a randomized, double-blind, placebo-controlled trial in patients with schizophrenia. CNS Spectr. 19, 197–205.
Mausbach, B.T., Harvey, P.D., Goldman, S.R., et al., 2007. Development of a brief scale of everyday functioning in persons with serious mental illness. Schizophr. Bull. 33, 1364–1372.
Nuechterlein, K.H., Subotnik, K.L., Ventura, J., Green, M.F., Gretchen-Doorly, D., Asamow, R.F., 2012. The puzzle of schizophrenia: tracking the core role of cognitive deficits. Dev. Psychopathol. 24, 529–536.
Pietrzak, R.H., Olver, J., Norman, T., et al., 2009. A comparison of the CogState schizophrenia battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. J. Clin. Exp. Neuropsychol. 31, 848–859.
Potkin, S.G., Weiden, P.J., Loebel, A.D., Warrington, L.E., Watsky, E.J., Siu, C.O., 2009. Remission in schizophrenia: 196-week double-blind treatment with ziprasidone versus haloperidol. Int. J. Neuropsychopharmacol. 12, 1233–1248.
Stahl, S.M., Malla, A., Newcomer, J.W., et al., 2010. A post hoc analysis of negative symptoms and psychosocial function in patients with schizophrenia: a 40-week randomized, double-blind study of ziprasidone versus haloperidol followed by a 3-year double-blind extension trial. J. Clin. Psychopharmacol. 12, 319–326.
Witek Jr., T.J., Canestrari, D.A., Miller, R.D., Yang, J.Y., Riker, D.K., 1995. Characterization of daytime sleepiness and psychomotor performance following H1 receptor antagonists. Ann. Allergy Asthma Immunol. 74, 419–426.