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Lurasidone Effects on Cognition and Functional Capacity in Schizophrenia

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ABSTRACT

Lurasidone is a novel atypical antipsychotic approved in the US and elsewhere for the treatment of schizophrenia and bipolar depression. The effect of lurasidone on cognition in patients with schizophrenia has been examined in several different studies, including short and long term studies. Lurasidone has been shown to improve measures of functional capacity as well as cognition and its cognitive enhancing potential has been compared to placebo and to active antipsychotic comparators. In specific, lurasidone has been reported to be superior to placebo and to quetiapine XR for cognitive functioning in a 6-week acute study along with a 6-month blinded extension, conducted in patients with schizophrenia. All doses of lurasidone assessed at study endpoint were superior to quetiapine during the extension study. When analyses of the effect of sleepiness and sedation were performed, only part of the cognitive benefit of lurasidone was attributable to its less sedating properties compared to quetiapine. Later research will need to replicate and expand these results, including examining cognitive benefits in other conditions.

Keywords: schizophrenia, cognition, functional capacity, lurasidone

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INTRODUCTION

Lurasidone is a second-generation antipsychotic agent that initially received regulatory approval for the treatment of adults with schizophrenia in the US in 2010 [1,2]. Lurasidone received marketing authorization for this indication by the European Medicines Agency in March 2014, and has also been approved in Switzerland, Canada, the UK, and Australia. Additionally, lurasidone recently received US and Canadian regulatory approval for the treatment of adults with major depressive episodes associated with bipolar I disorder (bipolar depression), as either a monotherapy or as adjunctive therapy with lithium or valproate. Detailed systematic reviews of the overall efficacy, tolerability, safety and place in therapy of lurasidone can be found elsewhere [3,4], including analyses of number needed to treat (NNT) and number needed to harm (NNH) [5,6].

BASIC SCIENCE RATIONALE FOR COGNITIVE BENEFITS

Compounds that interact with the 5-HT_7 receptor as their primary binding profile have been shown to have pro-cognitive effects in animal models [7]. Further, partial agonists at the 5-HT_{1A} receptor have also been postulated to have potential benefits for the reduction of flat affect or cognitive impairments [8]. Lurasidone exhibits potent binding affinity (as an antagonist) to

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5-HT_7 receptors and moderate affinity to 5-HT_{1A} receptors [1,2]. Despite the challenges based on extrapolation from animal models, we briefly review the evidence that 5-HT_7 blockade has potential cognitive benefit.

Some research conducted with lurasidone by its developer has shown some preclinical evidence of potential cognitive benefit. MK-801 is a glutamate receptor antagonist that is used to induce cognitive impairments quite similar to those seen in schizophrenia. Like other NMDA antagonists, deficits in memory and problem solving develop after administration of this compound. As NMDA antagonists like ketamine and phencyclidine induce a reliable analogue of schizophrenia in healthy people (and exacerbate psychosis in people with schizophrenia) such manipulations have more intrinsic validity than cholinergic manipulations such as scopolamine challenge. Lurasidone has shown the potential to reverse memory deficits in rats induced by MK-801, including both passive avoidance [9] and learning and memory in the Morris water maze [10]. The Morris water maze has multiple memory parameters relevant to schizophrenia, including learning new information, utilization of working memory, and short-term retention of previously acquired information.

Animal models have notoriously failed to translate in terms of treatment effects to performance on the part of humans with schizophrenia, particularly in terms of reliably predicting beneficial cognitive effects associated with antipsychotic drug treatment [11]. This failure may be in part due to the fact that human cognition may be adversely affected by dopamine D_2 receptor antagonism associated with antipsychotic treatments [12]. Thus, the potential benefits of the "secondary" receptor profile associated with antipsychotic agents have typically failed to be realized. For instance, ziprasidone is a partial agonist at the 5-HT_{1A} receptor. It has never demonstrated cognitive superiority to antipsychotics such as olanzapine that do not interact with that receptor [e.g., 13]. Thus, clear evidence of cognitive enhancement in people with schizophrenia, treated with the medication of interest, compared to other agents is the "bottom line" for meaningful cognitive benefits.

The purpose of this overview is to summarize lurasidone's efficacy and safety for the treatment of cognitive and functional deficits in schizophrenia, and to examine whether lurasidone has any special benefits that separate it from other atypical medications based on results from both short-term and longer-term controlled clinical trials. Relevant information regarding switching, randomized parallel, and extension studies is reported, focusing on functional and cognitive outcomes. Lurasidone has been studied for its efficacy on cognition and everyday functioning since the earliest stages of its US development program. These studies have examined both performance on neuropsychological tests and on measures of functional capacity. Cognitive assessments have included the MATRICS Consensus Cognitive Battery [MCCB; 14] and the CogState computerized battery [15]. The functional capacity assessments have included both performance-based measures of everyday functional skills, the USCD Performance-Based Skills assessment –Brief Version [UPSA-B, 16] and interview based assessments of cognitive performance.

These studies have included very short term (3-weeks), as well as longer term (6 weeks, 3 months, 6 months) trial durations. Each of the studies has included both cognition and functional capacity measures. In addition, these studies have included active comparator medications. In one study the comparator was ziprasidone and in the other the extended-release version of quetiapine (quetiapine extended release (XR): QXR). In the QXR study, there were a number of other important aspects of symptomatology considered which were associated with the cognitive benefits, including the effects of awareness of illness on cognitive test performance and the effects of sleepiness/sedation on performance on cognitive and functional capacity tests.

The first published study in people with schizophrenia that addressed the issue of cognitive benefit with lurasidone compared to other antipsychotics was a short-term, double-blind, randomized, head to head comparison of lurasidone with ziprasidone in generally clinically stable outpatients with schizophrenia, conducted during the early development phases of lurasidone [17]. At this time no American patients had ever been exposed to the drug. Patients were selected for being naïve to treatment with ziprasidone as well. A three-week randomized trial examined changes in performance on a neuropsychological assessment that contained the majority of the tests in the widely used MATRICS Consensus Cognitive Battery and an interview-based assessment of cognitive functioning. The interview-based assessment was developed in response to the US FDA's requirement that any study that examined the cognitive benefit of a pharmacological treatment also have concurrent evidence of meaningfulness of benefit. The assessment employed, the Schizophrenia Cognition Rating Scale [SCoRS; 18], involved a detailed assessment of both patient reported and

informant reported cognitive functioning. The SCoRS was developed to assess cognition in a functionally meaningful manner, involving questions about the ability to manage cognitively demanding, functionally relevant, everyday tasks such as conversations, watching television, and using electronic devices.

There were no between-group treatment differences in performance on the MCCB or the SCoRS ratings. However, lurasidone patients demonstrated significant within-group improvement from baseline on the MCCB composite score (p=0.026, ES=.16) and on the SCoRS (p<0.001; ES=.43), but ziprasidone patients did not improve on either the MCCB composite (p=0.25; ES=.09) or the SCoRS (p=0.19; ES=.20). At endpoint there was a statistical trend (p=0.058) for lurasidone to demonstrate greater improvement from baseline in SCoRS ratings. Further, improvements on the SCoRS were double the size of the improvements on the neuropsychological assessments. These results cannot be due to practice effects, as the SCoRS is an interview and not a performance-based measure. The fact that the differential effects of lurasidone and ziprasidone were nearly significant (p<.06) argues against a generalized bias effect, because the lurasidone effects were clearly larger and the trial was blinded.

These results suggest that any cognitive benefits of lurasidone are not due to 5-HT_{1A} receptor partial agonist effects, because those effects are common between the two compounds. At the same time, interview-based reports of functionally relevant cognitive processes and their treatment-related improvements clearly address a different element of cognitive functioning than performance-based neurocognitive tests. A particularly important issue to understand is that self-reports in studies utilizing interview-based assessments of cognition have been found to be quite inaccurate on the part of people with schizophrenia. The overlap between the reports of informants and patient self-reports are minimal and the correlation between patient self-report and performance on neuropsychological assessments has been close to zero in several different studies using different self-report rating scales [18-20]. Utilization of these assessments requires contact with informants who are aware of the patient's performance. When using these informant reports, ratings can be obtained that are meaningfully convergent with performance on cognitive tests. Further, in a recent study [21] it was found that SCoRS ratings that were obtained using informant reports were sensitive to the cognitive enhancing effects of encenicline, an alpha-7 nicotinic agonist, while self reports were not. Thus, the results of this initial study demonstrated the sensitivity of informant reports to cognitively beneficial effects.

SHORT AND LONG-TERM COGNITIVE BENEFITS OF LURASIDONE IN A CONTROLLED TRIAL

A large-scale randomized trial [22], starting with clinically unstable patients, compared two doses of lurasidone (80 and 160 mg/day), QXR (600 mg/day), and placebo on effects for cognition and functional capacity. A computerized cognitive battery (CogState) was administered at randomization and repeated at the end of 6 weeks of acute double-blind treatment, and after 3 and 6 months of double-blind extension treatment. After 6 weeks of acute treatment, placebo patients were switched to flexible dosing of lurasidone (40-160 mg/day); patients previously treated with fixed daily doses of lurasidone of 80 or 160 mg were also switched to flexible lurasidone dosing at 40-160 mg/day, and the QXR patients remained on QXR, with flexible doses between 200 and 800 mg/day.

During the acute treatment phase of the study, a large number of patients were unable to validly complete the CogState Assessment (45%) at baseline. The evaluable analysis sample (mean baseline neurocognitive composite Z-score = -2.86, SD =for acute phase cohort) had significantly less cognitive impairment at pre-treatment baseline when compared to the full analysis sample (-4.06, SD P<0.001). Subjects with evaluable scores had significantly lower mean Positive and Negative Syndrome Scale [PANSS; 23] total scores at baseline (96.6), compared to those with non-evaluable scores (101.4) (P<0.001). Based on the prespecified ANCOVA model for the full analysis sample, changes from baseline to week 6 endpoint (LOCF) in neurocognitive composite Z-scores were not significant for the lurasidone 80 mg/d or 160 mg/d groups, when compared with placebo. Similarly, no significant differences were observed for the full analysis sample when comparing the lurasidone 80 mg/d and 160 mg/d groups with the QXR group.

In the evaluable analysis sample (excluding subjects with non-evaluable composite Z-scores), the change from baseline to week 6 endpoint (LOCF) in neurocognitive composite Z-score was significant for the lurasidone 160 mg group compared to the placebo group (p=0.04, Cohen's d=0.37) and the quetiapine XR group (p=0.018, Cohen's d=0.41). Change from baseline in composite Z-scores was not significantly

different for the lurasidone 80 mg group (p=0.72, Cohen's d= 0.06) or the QXR group (p=0.80, Cohen's d= -0.04), when compared with placebo.

In the extension phase of the study for the full analysis sample, the change in neurocognitive composite Z-scores from pre-treatment baseline was significant for the overall lurasidone group (LUR-to-LUR), compared with the QXR 200-800 mg group (QXR-to-QXR) at both week 19 (p=0.05, Cohen's d=0.32), and week 32 (p=0.008, Cohen's d=0.49). Similar results were observed for the evaluable analysis sample: improvement in neurocognitive composite Z-scores from pre-treatment baseline to week 32 was significantly greater in the overall lurasidone group (LUR-to-LUR) compared with the QXR group (QXR-to-QXR, p=0.004, Cohen's d=0.57. Thus, inability of patients to perform the CogState assessment at acute phase baseline did not appear to impact on longer-term testability and the cognitive benefits of lurasidone were detected in both the full sample and the sample with maximally valid scores at acute phase baseline.

See Figure 1 for a graphical depiction of these results.

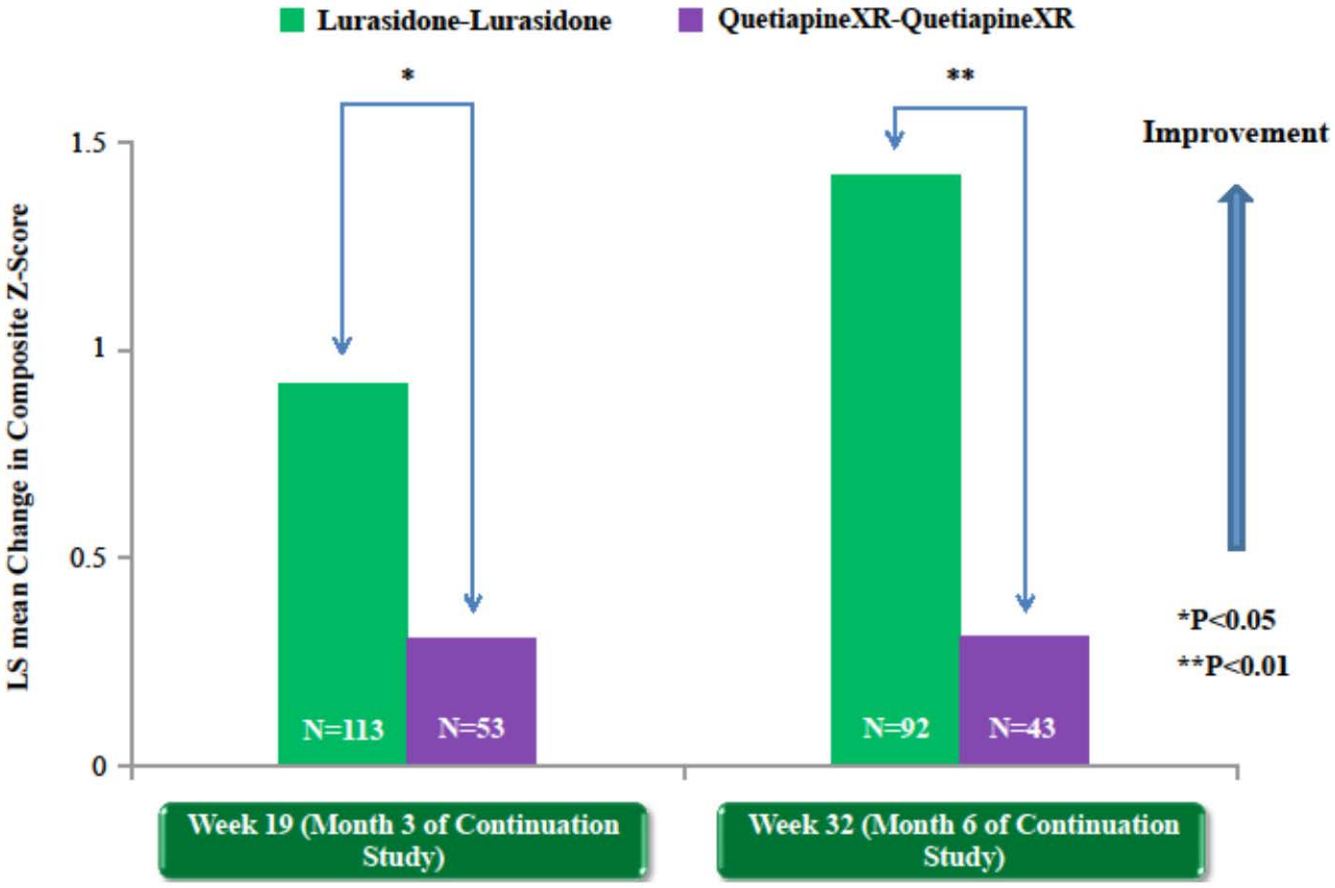

Fig. 1. Cognitive Benefits of Lurasidone Versus Quetiapine XR in Double-Blind, 6-Month Continuation Study

TREATMENT EFFECTS ON FUNCTIONAL CAPACITY MEASURED WITH THE UPSA-B

The LS mean change in UPSA-B total score at week 6 endpoint was significantly better for the lurasidone 80 mg (p=0.036), 160 mg p=0.011), and QXR groups (p<0.001) compared with the placebo group. Improvement in the UPSA-B continued through week 32, with an increase of 10.3 points at week 32 in the lurasidone group, and 12.4 points at week 32 in the quetiapine XR group. There were no significant differences between the lurasidone and quetiapine XR treatment groups at week 32. Treatment-related changes in the cognitive composite score were correlated with improvements on the UPSA-B. The overall longitudinal association between changes in functional capacity and changes in cognitive performance was significant in full (p<0.001) and evaluable analysis (p=0.022) samples, and was similar across the treatment groups (all p >0.206).

In a follow-up analysis, we examined the effects of improvement in depressive symptom on changes in UPSA-B scores (24). While most research suggests that depression in schizophrenia has a smaller effect on everyday functioning than cognition or negative symptoms, longitudinal analyses are not common.

Further, lurasidone is approved for the treatment of bipolar depression, so its impact on depression and its correlates in schizophrenia is of interest.

In this analysis, lurasidone at 80 and 160 mg/day, as well as QXR at the fixed dose of 600 mg/day improved depressive symptom, rated by the MADRS, to a significant extent at the 6 week acute treatment endpoint compared with placebo treatment. At the 3-month endpoint, lurasidone was superior to QXR for depressive symptoms($p<.05$), with this advantage nearly significant ($p=.069$) at 6 months. Depression was correlated with UPSA-B scores at baseline ($p<.05$). Improvements in MADRS scores, across both treatment groups, was correlated with improvements in UPSA-B scores across the 6-month treatment period. Although requiring replication, this finding suggests that a possible mechanism of lurasidone's beneficial effect on functional capacity may be through reduction of depression. This is an important finding, because major depression is common in people with schizophrenia and may be associated with suicidality as well as impairments in the ability to perform everyday tasks.

LURASIDONE DOSE AND COGNITIVE EFFECTS

An analysis of the effects of dosing of lurasidone and quetiapine on cognition in the extension study [25] was recently published. Recall that in the acute-phase study it appeared that only lurasidone doses of 160 mg/day separated from either placebo or QXR in their cognitive benefits. A total of 292 subjects were enrolled in the double-blind continuation study. Of the 151 subjects, 32.5%, 51.0% and 16.6% received last doses of lurasidone160 mg/d, 120 mg/d, and 40-80 mg/d, respectively. At month 6, last doses of QXR 800 mg/d were received by 33%, 600 by 55%, and 200-400 mg/d by 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. There was a trend towards significance for the lowest lurasidone dose group (40/80 mg/d) compared to the overall QXR group ($p=0.06$). 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), 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 endpoint 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 QXR group ($z=0.46$) ($p>0.05$), with none of the individual QXR 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. See Figure 2 for a graphical depiction of these results.

Thus, the results of this study indicate that lurasidone markedly outperforms QXR for cognition. These effect sizes are too large for practice effects, as the improvements are close to 1.5 SD for all dosage groups. Patients were tested a total of 5 times and previous studies have suggested test-retest practice effects of 0.1 to 0.2 SD for cognitive tests, at most. These effects are twice that large for the lurasidone patients. Interestingly, the QXR patients had change scores that were not as large as would be expected from practice effects. A previous study of QXR in patients with bipolar depression also found that QXR patients had less improvement with retesting on a neuropsychological assessment than patients treated with placebo [26]. Thus, the reasons why QXR appears to be possibly cognitively toxic as well as why lurasidone seems to have a cognitive benefit are worth considering.

In an analysis of the short term (6-week) clinical trial data from the study above, Loebel et al. [27] examined the effects of daytime sleepiness on cognitive and functional capacity performance. Previous studies of quetiapine [28] have suggested adverse cognitive effects directly related to sleepiness. In this trial, the Epworth Sleepiness Scale [ESS; 29] was collected at all assessments and scores on the ESS were related to cognitive test performance. Both doses of lurasidone and placebo treatment were associated with a statistically significant decline from baseline and significantly less impairment compared to QXR. Scores on the Cogstate composite change scores were significantly associated with ESS item 6, falling asleep while talking, in the QXR group. Further, UPSA-B scores were associated with ESS total scores in the QXR group. Thus, sedation was found to be associated with poorer cognitive and functional capacity performance while receiving treatment with QXR. In contrast, increased sedation was associated with improvements in agitation for the quetiapine group compared to placebo. However, lurasidone improved agitation as much as quetiapine overall

across the two lurasidone doses.

The adverse cognitive effects of sedation have typically been measured in shorter term trials. In this study, there was no habituation of sleepiness and no improvement in the sleepiness-induced cognitive impairments seen in QXR patients over the entire 6-week trial. While induction of sleepiness may be the reason that QXR patients failed to improve with treatment over the entire 6-month trial, lack of sleepiness is not the reason that lurasidone improved cognition. Lurasidone and placebo were associated with equivalent reductions in sleepiness while lurasidone treated patients (160 mg/day) improved cognitively. Sleepiness scores did not correlate with cognitive performance in the lurasidone treated patients, suggesting that the benefits of lurasidone and the adverse cognitive effects of quetiapine must derive from different sources.

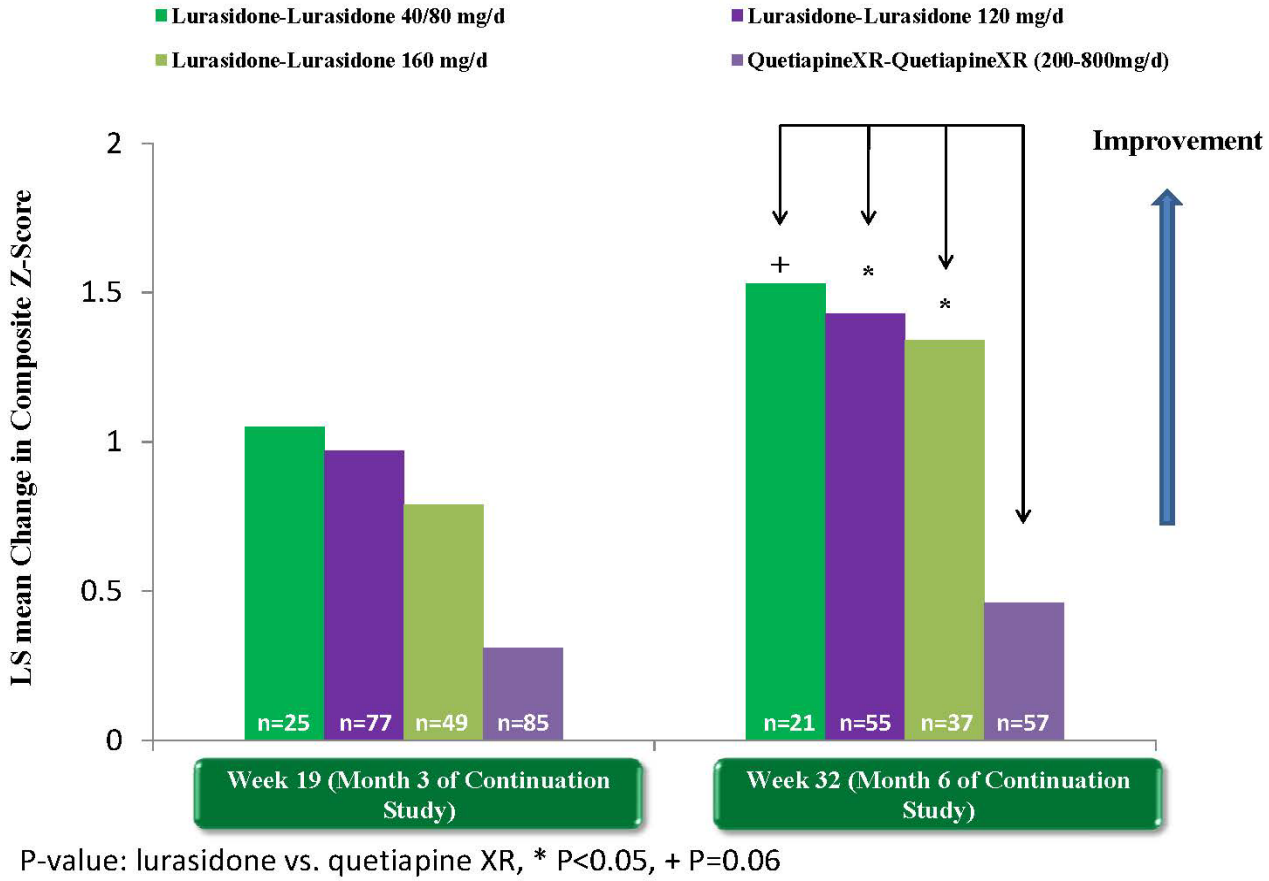

Fig. 2. Cognitive Benefits in Double-Blind, 6-Month Continuation Study: Lurasidone Last Dose Groups versus Quetiapine XR

In a final set of cognitively relevant analyses, awareness of illness was clinically evaluated and its association to subjective quality of well-being, symptoms, cognition, and functional capacity was examined. Impairment of insight was assessed by PANSS item G12 "lack of judgment and insight" at baseline, and at each of the post-randomization visits. The large-scale CATIE study showed that correlation between PANSS item G12 and insight as assessed by Insight and Treatment Attitudes Questionnaire (ITAQ) total score was 0.49: [30];($p<0.001$, N=1099) and that the PANSS G12 had a number of functional correlates in that sample. In these analyses, impairment was defined as a score of 4 or greater on PANSS item 12.

Health-related quality of life was assessed with the quality of well-being scale [QWB-SA; 31], recorded at baseline, week 6 (end of acute study), week 19 (month 3 of the continuation study), and week 32 (month 6 of the continuation study). In that study, the QWB-SA was administered by a qualified interviewer at the site instead of by the subject. QWB-SA scale includes items measuring community mobility, physical activity, social activity, and subjective symptoms, including somatic, cognitive, and emotional symptoms.

In a cross-sectional analysis of the baseline data, lower insight into illness and poorer judgment (as assessed by PANSS G12) was associated with higher cognitive impairment ($p<0.001$), lower UPSA-B scores (p=

0.0023), greater uncooperativeness (as assessed by PANSS G8 item) ($p<0.001$). Better insight and judgment was associated with an increased likelihood for completion of cognitive testing and obtaining valid scores at acute baseline visit ($p <0.002$, chi-square= 9.385). Greater impairments in clinical insight were significantly associated with less depressive symptoms (as assessed by MADRS score) ($p<0.001$, t= -4.59, df=479), but not with the rater-administered quality of well-being score at baseline ($p=0.5638$, t= -0.58, df=416). Thus, lack of insight was associated with reporting less depression, but not with experiencing any reduction in objectively rated illness burden.

LONGITUDINAL ANALYSIS OF OUTCOMES

Insight and judgment (as assessed by PANSS G12) was significantly improved for the lurasidone (80 mg/d or 160 mg/d) and the QXR 600 mg/d groups, compared to the placebo group after the 6-week acute treatment study. Improved insight from baseline during the acute treatment study was significantly correlated with increased neurocognitive performance , better scores for measures of functional capacity ($p<0.05$), and quality of well-being (as assessed by the QWB-SA scale, $p<0.05$) over the 6-week treatment period.

Insight and judgment was significantly more improved from baseline at week 32 (month 6 of the continuation study; $p<0.05$) for lurasidone 40-160 mg/d, compared with QXR 600 mg/d. Treatment-related improvement in insight from baseline to the 6-month endpoint was significantly correlated with better scores for measures of neurocognitive performance ($p<0.05$), functional capacity ($p<0.05$) and quality of well-being ($p<0.05$) across treatment groups and study periods.

Poor insight contributing to deficits in illness awareness and objective measures of cognitive and functional performance is prevalent in schizophrenia [30, 32-35]. Lack of insight was associated with inability to complete neurocognitive testing and provide valid scores at baseline visit in acute study phase. Previous studies have found better insight and greater illness awareness are associated with worse subjective, patient-assessed quality-of-life outcomes [30]. Longitudinal analyses of insight improvement from baseline in treatment studies are therefore crucial to gain further insight into the inter-relationships among these important clinical outcomes over time. Also critical is the temporal ordering of the correlation between insight and cognitive impairments. Most research has found that cognitive impairments in general are not strongly correlated with reduced awareness other than in the domains of executive functioning [30,36]. The modest correlation between cognitive deficits and unawareness of cognitive limitations may be due to the unidirectional nature of the relationship in schizophrenia: most patients have significant limitations and only some are aware of them.

The finding that reduced awareness is also associated with inability to validly complete neuropsychological testing is a new one and potentially important. The finding would suggest that being unaware that one has significant illness features would also lead to limitations in being able to cooperate in their assessment. Very poor performance could be associated with limitations in understanding the reason for the assessment and not in willingness to participate or exert adequate effort. In line with previous research on effort based decision making, patients with schizophrenia fail to increase effort in line with task demands and potential rewards. These results suggest that unawareness of performance limitations may also impact on performance, much the same as our previous results have suggested that unawareness of cognitive limitations is a potent predictor of deficits in everyday functioning.

SUMMARY

Lurasidone has shown promise for improvement of cognitive impairments and functional capacity in acute and stable patients with schizophrenia. Compared to QXR, there are consistent benefits, some of which may be due to the limitations of QXR in domains of sleepiness, sedation, and interference with practice effects. Lurasidone treatment also improves awareness of illness in a manner that may also have beneficial impacts on everyday functioning, through benefits on cognition, the ability to perform tests of functional capacity, and increased awareness of current levels of functioning.

Future directions for lurasidone treatment include considering its cognitive benefits in other conditions where the drug is indicated for the treatment of symptoms, such as bipolar disorder, and as an adjunct and facilitating agent for other cognitive interventions such as cognitive remediation. Finally, lurasidone effects on motivation and awareness may have the potential to improve outcomes indirectly as well as

directly.

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