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# Change in daytime sleepiness and cognitive function in a 6-month, double-blind study of lurasidone and quetiapine XR in patients with schizophrenia

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ABSTRACT

Daytime sleepiness is a commonly reported adverse effect associated with psychotropic agents that may impair cognitive performance and functioning. The objective of this post-hoc analysis was to evaluate the long-term effects of lurasidone and quetiapine XR on daytime sleepiness and neurocognitive performance during a 6-month, double-blind continuation study, in subjects who completed an initial 6-week, randomized, placebo-controlled trial comparing these agents. Daytime sleepiness, cognitive performance, and health-related quality of life were assessed with the Epworth Sleepiness Scale (ESS), CogState computerized battery, and the Quality of Well-Being (QWB-SA) Scale, respectively. Treatment with flexible-dose lurasidone 40–160 mg/d, administered once daily in the evening, was associated with significantly reduced daytime sleepiness compared with flexibly dosed quetiapine XR 200–800 mg/d ($p = 0.03$, *effect size* = 0.36) at week 32 (month 6 of the continuation study endpoint). Incidence of markedly high sleepiness (ESS >10) was significantly higher in the quetiapine XR (200–800 mg/d) group compared with the lurasidone (40–160 mg/day) group at both months 3 and 6 visits ($p < 0.05$). Lurasidone (40–160 mg/d) significantly improved neurocognitive performance compared to quetiapine XR (200–800 mg/d) before (*effect size* = 0.49) and after adjustment (*effect size* = 0.45) for sleepiness effect ($p = 0.008$ and 0.010, respectively). Increased daytime sleepiness was significantly associated with reduced neurocognitive performance ($p = 0.019$) and quality of well-being ($p = 0.05$). Our findings suggest that clinicians should actively monitor patients for the presence of daytime sleepiness due in part to its potential impact on neurocognitive performance and well-being.



## 1. Introduction

Daytime sleepiness adversely impacts neurocognitive performance, which is often significantly impaired in patients with schizophrenia (Kane and Sharif, 2008; Leifker et al., 2009; Hawley et al., 2010; Wilson and Argyropoulos, 2012; Loebel et al., 2013a). Daytime sleepiness is a commonly reported adverse effect of pharmacologic agents with significant antihistaminergic and/or antiserotonergic effects, such as certain antipsychotic agents. The propensity to doze while performing daily activities such as driving or working can have serious consequences, including increased motor vehicle and work-related accidents, as well as compromised job performance (National Sleep Foundation, 2007; American Academy of Sleep Medicine 2009). It has been estimated that driving while drowsy contributes to 100,000 police-reported crashes that resulted in 71,000 injuries and 1550 deaths each year in the United States (National Sleep Foundation, 2007). Daytime sleepiness, if persistent, can adversely impact patients' social and daily functioning, quality of life and can compromise treatment adherence (Kane and Sharif, 2008; McWhirter et al. 2007). Despite awareness of the health and economic burden posed by daytime sleepiness, the long-term effects of

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antipsychotic treatments on daytime sleepiness and their clinical consequences have not been adequately studied (Kane and Sharif, 2008; McWhirter et al. 2007).

Lurasidone is a novel benzisothiazol derivative with potent binding affinity for the $D_2$, 5-$HT_{2A}$ and $5HT_7$ receptors (antagonist), and moderate affinity for $5HT_{1A}$ (partial agonist) and $\alpha_{2C}$ receptors (antagonist) (Ishibashi et al., 2010; Horiguchi et al., 2011). Lurasidone has no appreciable affinity for $H_1$ and $M_1$ receptors (Ishibashi et al., 2010). In contrast, quetiapine is associated with a high affinity at the $H_1$ receptor where it acts as an antagonist (Baldwin and Scott, 2009); this mechanism is associated with sedation in both animal models and human studies (Witek et al., 1995). The short-term effects of lurasidone on neurocognitive performance were demonstrated in a 3-week double-blind, active-controlled study of lurasidone and ziprasidone (Harvey et al., 2011), as well as a 6-week, double-blind, placebo- and active-controlled study of lurasidone and quetiapine XR (Harvey et al., 2013). In a 6-month, double-blind, flexible-dose, continuation study, lurasidone (40–160 mg/d) was superior to quetiapine XR (200–800 mg/d) for cognitive performance at both months 3 and 6 of the extension study (Harvey et al., 2013, 2015). The objective of this post-hoc analysis was to evaluate the long-term effects of flexible-dose lurasidone 40–160 mg/d and quetiapine XR 200–800 mg/d on daytime sleepiness, and the impact of daytime sleepiness on neurocognitive performance in a long-term continuation study that followed a 6-week acute trial in patients with schizophrenia.

## 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 (Loebel et al., 2013b), followed by a double-blind continuation study that continued up to 1 year (Loebel et al., 2013c). The design of these studies will therefore only be 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. Patients

Patients 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 fixed doses of lurasidone (80 mg or 160 mg), quetiapine XR (600 mg), or placebo. Upon completion of the initial 6-week study, eligible patients were enrolled in the 1-year, double-blind, flexible-dose, continuation study, where patients continued treatment with either lurasidone 40–160 mg/d (lurasidone-to-lurasidone) or quetiapine XR 200–800 mg/d (quetiapine XR-to-quetiapine XR). Cognitive and functional capacity assessments were obtained at baseline and up to 6 months in the continuation study.

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

### 2.2. Assessments

Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), a validated self-reported measure of daytime sleepiness at baseline, 6 weeks, and 3 and 6 months in the continuation treatment phase (Johns, 1991, 2008). The total ESS score is the sum of all 8 items (each refers to level of anticipated sleepiness in various routine life situations) and ranges from 0 to 24. Each individual item ranges from 0 = 'would never doze or sleep' to 3 = 'high chance of dozing or sleeping'. Higher ESS scores are associated with a greater severity of daytime sleepiness. If one or more items were missing at a visit, the total score was set to missing. The ESS has been validated in both case-controlled studies of normal patients and in a number of populations with various sleep disorders (Johns, 1991, 2008; Chervin, 2000).

Cognition was assessed by the CogState composite score (Pietrzak et al., 2009) at baseline, week 6 (end of acute treatment phase), week 19 (month 3 of the continuation study), and week 32 (month 6 of the continuation study). The composite measure of overall cognitive performance was calculated as an average of the 7 standardized domain scores over the tasks of: Detection Task, Identification Task, One Back Task, International Shopping List Task, One Card Learning Task, Groton Maze Learning Task, and the Social Emotional Cognition Task. These standardized domain scores were computed using the age stratified CogState normative mean and standard deviation according to the following equation: (raw domain score – norm mean)/norm SD. The sign of the standardized domain score was adjusted so that negative scores indicated performance worse than average, and positive scores indicated performance better than average. If three or more components were missing at a visit, the CogState composite score was set to missing. Health-related quality of life was measured using the Quality of Well-Being (QWB-SA) Scale (Anderson et al., 1989).

### 2.3. Statistical methods

The primary treatment group comparison was between patients continuing on flexibly dosed lurasidone 40–160 mg/d (lurasidone-to-lurasidone) or quetiapine XR 200–800 mg/d (quetiapine XR-to-quetiapine XR) at week 19 and week 32 (month 3 and 6 of the continuation study period). The change in neurocognitive composite score from pretreatment baseline (week 0) to week 19 and week 32 (primary endpoint) was analyzed using a mixed-effects longitudinal data analysis model (Fitzmaurice et al., 2004), with fixed effects for treatment, visit, baseline score, treatment-by-visit interaction, and study sites. In addition, we evaluated the change from the pretreatment baseline in the neurocognitive composite score after controlling for change in ESS total score from baseline (week 0) over time. Cohen's d between-group effect size was calculated as least squares mean difference between LUR-to-LUR and QXR-to-QXR divided by the model estimate of the pooled SD (across treatment groups), adjusting for site effects and baseline at randomization. A Generalized Estimating Equation (GEE) model was applied to evaluate the incidence of markedly high sleepiness.

## 3. Results

A total of 292 patients completed the 6-week acute phase and were enrolled in the double-blind continuation study (Fig. 1). Figure 1 depicts the disposition of patients. The analyses reported herein were based on full analysis sample, with 207 patients had cognitive assessment data at week 19 or week 32 or both visits (month 3 or 6 of the continuation study period). The median doses at the 6-month study endpoint in the continuation study for lurasidone (lurasidone-to-lurasidone, $n = 151$) and quetiapine XR (quetiapine XR-to-quetiapine XR, $n = 85$) were 120 mg/d and 600 mg/d, respectively. There were no significant differences between the treatment