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Lurasidone in post-menopausal females with major depressive disorder with mixed features: Post-hoc analysis of a placebo-controlled trial

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ABSTRACT

Background: Several studies have found that depressed, post-menopausal females may respond differently to antidepressants compared to pre-menopausal females. The atypical antipsychotic lurasidone, whose mechanism of action differs from SSRIs and other standard antidepressants, was shown in a 6-week randomized, flexible-dose, placebo-controlled study (n = 209), to be effective in treating major depressive disorder (MDD) with mixed features (subthreshold hypomanic symptoms). This post-hoc analysis assessed the efficacy of lurasidone in this study by menopausal status.

Methods: The main outcome measure for this post-hoc analysis was change in MADRS score from baseline to week 6 endpoint for two lurasidone-treated subgroups: presumptive pre-menopausal (< 52 years) and presumptive post-menopausal (≥ 52 years) patients, compared to placebo treatment, using a mixed-model for repeated-measures analysis, and calculation of the effect size for each subgroup. Additional efficacy assessments included the CGI-S, HAM-A and YMRS. An exploratory analysis was also conducted removing presumptive peri-menopausal women (ages 45–51 years) to allow for clearer definition of pre- and post-menopausal status.

Results: A total of 56 lurasidone-treated and 47 placebo-treated pre-menopausal females, and 17 lurasidone-treated and 25 placebo-treated post-menopausal females were available from the larger study for comparison on key outcome measures. The pre- and post-menopausal subgroups had similar demographic and clinical characteristics at study baseline (other than age), including number of past major depressive episodes as well as depressive and manic symptom severity. Mean daily lurasidone dose was similar for each subgroup during the study. Both the primary and exploratory analyses showed that both lurasidone-treated post-menopausal and pre-menopausal females responded significantly compared to placebo (p = 0.016 or less) on the MADRS, and that post-menopausal patients had a numerically larger response (effect size = 0.96) than pre-menopausal patients (effect size = 0.64). All other secondary outcome measures for lurasidone compared with placebo treatment were significant (p = 0.045 or less) for both subgroups.

Conclusions: In this post-hoc analysis, lurasidone was found to be effective in treating post-menopausal MDD patients with mixed features (subthreshold hypomanic symptoms).

1. Introduction

Compared to males, female gender has been linked to increased incidence of depression and more severe symptom presentation (Weissman et al., 1993; Kornstein et al., 2000a), which has in turn been attributed to sex-related physiological differences such as body fat, altered metabolism, and changing hormonal levels over the female life cycle (Sramek and Cutler, 2011). Both in-vitro and pharmacologic challenge studies suggest that estrogen is linked to both the pathogenesis of depression as well as the effectiveness of antidepressants (Bryant et al., 2006; Halbreich et al., 1995). Further supporting the role of estrogen are a number of clinical studies which report a better response to the selective serotonergic reuptake inhibitor (SSRI) class of antidepressants in females compared to males, (Young et al., 2009; Khan et al., 2005; Haykal and Akiskal, 1999; Kornstein et al., 2000b; Martenyi et al., 2001) although there are also studies that do not confirm these findings (Entsuah et al., 2001; Hildebrandt et al., 2003; Parker et al., 2003; Baca et al., 2004; Thiels et al., 2005; Cuijpers et al.,

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2014).

The literature on antidepressant response in post-menopausal females is sparse, but suggests that menopausal status may be associated with altered treatment response in females (Sramek and Cutler, 2011; Frackiewicz et al., 2000; Yonkers, 2003; Ishibashi et al., 2010). Based on a review of 9 studies, Quitkin et al. reported that elderly females responded better to tricyclic antidepressants (TCAs) than younger females (Quitkin et al., 2002). However, TCAs are rarely used in elderly patients today in large part due to cardiovascular concerns that may lead to arrhythmias or hypotensive episodes with increased risk of falls (Glassman and Roose, 1994). More recently, three naturalistic studies reported poorer response to SSRIs in post-menopausal women when estrogen levels decrease (Pae et al., 2009; Grigoriadis et al., 2003; Pinto-Meza et al., 2006), although one study, which employed a SSRI and a serotonin–norepinephrine reuptake inhibitor (SNRI), reported no difference (Kornstein et al., 2014). Despite conflicting findings, which may be the result of methodological differences between the various studies, the literature taken as a whole suggests that menopausal status may be associated with altered response to antidepressant treatment in females (Sramek and Cutler, 2011; Frackiewicz et al., 2000; Yonkers, 2003; Sramek et al., 2016).

Lurasidone is an atypical antipsychotic, approved in several countries for the treatment of schizophrenia and bipolar depression, which acts as an antagonist at D2, 5-HT2A, 5-HT7 receptors (Ishibashi et al., 2010), and has partial agonist activity at 5-HT1A receptors (Huang et al., 2012). It has shown antidepressant properties in animal models that are believed to be mediated by its action at 5-HT7 receptors (Hedlund, 2009). In addition, lurasidone appears to have partial agonist activity at 5-HT1A receptors (Ishibashi et al., 2010), which may be important for antidepressant activity (Savitz et al., 2009). Recently, lurasidone was shown in a 6 week placebo-controlled trial to be effective in treating major depressive disorder (MDD) associated with subthreshold hypomanic symptoms (mixed features) (Suppes et al., 2016). Lurasidone demonstrated significant efficacy for both MDD symptoms as well as for manic features at doses ranging from 20 to 60 mg per day, with overall response showing no qualitative or quantitative treatment interaction based on gender or age. Given the distinct serotonergic mechanism of lurasidone, which differs from selective serotonin reuptake inhibitors (SSRIs) as well as serotonin–norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants, we hypothesized that, unlike standard antidepressants, lurasidone may be comparably effective in both pre- and post-menopausal women.

2. Methods

This was a post-hoc analysis based on a larger (n = 209), placebo controlled study of lurasidone in the treatment of MDD with mixed features (Suppes et al., 2016). The underlying study was approved by an institutional review board at each investigational site and was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's Good Clinical Practice guidelines, and with the ethical principles of the Declaration of Helsinki. A detailed report of study methods for the larger study has been published elsewhere and will therefore be briefly summarized here. This randomized, double-blind, placebo-controlled, flexible dose study enrolled patients at 18 sites in the United States and 26 sites in Europe. Patients were required to have a current major depressive episode, with a score ≥ 26 on the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) at both screening and baseline visits. Patients meeting DSM-IV-TR criteria for MDD with two or three manic symptoms were randomly assigned to 6 weeks of double-blind treatment with lurasidone at 20–60 mg/day (n = 109) or placebo (n = 100). Patients were dosed flexibly, in the range of 20–60 mg/day, starting at 20 mg/day from days 1–7. Dose increase was allowed starting on day 8. This post-hoc analysis focused on presumptive post-menopausal female patients who participated in the larger study. Since the average onset of menopause in Western countries is age 51, age 52 years was used as the cutoff for separating pre- from post-menopausal females (Minkin and Wright, 1997; Kato et al., 1998).

The main efficacy endpoint for this post-hoc analysis was least square (LS) mean change in MADRS scores from baseline to Week 6 endpoint for lurasidone compared to placebo-treated patients in the post-menopausal subgroup and, separately, in the pre-menopausal subgroup. Improvements in the post-menopausal and pre-menopausal subgroups were descriptively compared based on the magnitude of the difference in MADRS scores between lurasidone and placebo, as well the treatment effect size, for each subgroup. Additional outcome measures for each subgroup were change from baseline to Week 6 endpoint in the Clinical Global Impressions - Severity of Illness score (CGI-S) (Busner and Targum, 2007), the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), and the Young Mania Rating Scale (YMRS) (Young et al., 1978). The MADRS and CGI-S efficacy endpoints, as well as the YMRS, were assessed using a mixed model for repeated-measures analysis. Changes from baseline in HAM-A were evaluated using an analysis of covariance model of the last observation carried forward data. Effect sizes (Cohen's d) were calculated as the least square mean treatment difference in the change from baseline efficacy measure score divided by the pooled standard deviation. Because of the post-hoc nature of the analysis, no adjustments for multiplicity were applied. As in the larger lurasidone study, efficacy analyses were conducted on the intent-to-treat population, which was defined as randomized patients who received at least one dose of study medication and had at least one MADRS or CGI-S score after baseline.

An exploratory analysis was also conducted on our sample by excluding females presumptive for peri-menopause (period of life when menstrual cycle becomes irregular and vasomotor symptoms may appear, i.e., between the ages of 45–51) from the data analysis of the MADRS, CGI-S, HAM-A and YMRS scores, which was repeated for pre-menopausal (ages 44 and under) and post-menopausal (ages 52 years and over) status (Hoyt and Falconi, 2015; Soares and Cohen, 2001).

3. Results

Based on our criteria for post-menopausal status, there were 103 females in the < 52 year age group, and 42 females in the presumptive post-menopausal ≥ 52 year age group. The average age of women in the < 52 year age group was 38.8 years (SD = 9.05) and the average age of the ≥ 52 year age group was 58.6 years (SD = 4.33). Additional key demographic characteristics and psychiatric history are shown in Table 1. Demographic data and psychiatric history were similar between the two groups. The three most commonly reported manic symptoms at study baseline were “being more talkative than usual” (females < 52 years, 51.5%; females ≥ 52 years, 73.8%), “flight of ideas” (females < 52 years, 64.1%; females ≥ 52 years, 69.0%), and “decreased need for sleep” (females < 52 years, 43.7%; females ≥ 52 years, 38.1%); these manic symptom frequencies were similar except for “being more talkative than usual” which was more common in older (versus younger) women. Baseline severity scores on all efficacy measures were also similar between the two groups.

The mean daily dose of lurasidone was similar in both groups of females: 34.5 mg in those < 52 years (n = 56), and 35.4 mg in those 52 years and older (n = 17). One 46 year old female received transdermal estradiol therapy during the study. The majority of women in the < 52 year age group (95/103 or 92.2%) and ≥ 52 year age group (35/42 or 83.3%) completed all six weeks of the study, including final efficacy ratings. Of the 8 females in the < 52 year age group who did not complete the study, 3 females (2 placebo, 1 lurasidone) were discontinued early due to insufficient clinical response. Of the 7 females in the 52 years or older age group, 2 females (both placebo, 0 lurasidone) were discontinued early for the same reason.

There were 56 lurasidone-treated and 47 placebo-treated presump-