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 serotonin 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., 2007).
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 hypertensive 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 prescriptive 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-
to a 59% reduction in the pre-menopausal group from baseline means (32.0 and 34.2, respectively), an approximately 10% greater reduction in the post-menopausal group. The reduction in MADRS score from baseline to week 6 was similar for both placebo-treated subgroups (39% reduction in presumptive post-menopausal versus 42% in pre-menopausal patients). Post-menopausal women treated with lurasidone also showed approximately 11% greater reduction in the CGI-S, and approximately 22% greater reduction in the HAM-A scores from baseline to Week 6 relative to the younger group, while response on the YMRS was similar between the two groups. The greater reduction for the post-menopausal group on the MADRS, CGI, and HAM-A was also reflected by a larger treatment effect size for these efficacy measures compared to the younger group.

An additional exploratory analysis, which excluded presumptive peri-menopausal patients, included 67 pre-menopausal women (lurasidone n = 39; placebo n = 28) and 42 women (lurasidone n = 17; placebo n = 25) in the post-menopausal population. Prior psychiatric history of hospitalization and number of major depressive episodes were similar between these two groups. Both age groups (≤ 44 year females and ≥ 52 year females) showed significant Baseline to Week 6 endpoint improvement in all efficacy measures comparing lurasidone to placebo. See Table 3 for the results of this exploratory analysis in ≤ 44 year female patients. As in the main analysis, there was also significant separation of lurasidone from placebo for the ≤ 44 female subgroup at Weeks 3–6. The corresponding results for the ≥ 52 year female subgroup are shown in Table 2.

4. Discussion

In this post-hoc analysis, lurasidone significantly improved scores on all efficacy measures (i.e., MADRS, CGI, HAM-A and YMRS) compared to placebo treatment, in both pre- and post-menopausal subgroups, consistent with the results from the larger study from which these data were derived (Suppes et al., 2016). Both the pre- and post-menopausal groups were similar in regard to psychiatric history, number of prior depressive episodes, baseline symptom severity ratings, and mean daily dose of lurasidone during the study.

Based on change in MADRS scores, post-menopausal women showed a 3-point greater reduction, or a 10% greater reduction, in depressive symptoms at study endpoint compared to baseline (effect size = 0.96) relative to younger patients (effect size = 0.64). The magnitude of this reduction for the post-menopausal group was also reflected in the greater effect size compared to the younger group. As seen in Fig. 1, this reduction was most evident in Weeks 5 and 6 of the study. While a 3-point greater reduction in MADRS scores in the post-menopausal group compared to the pre-menopausal group is relatively small, the difference in effect size is 0.32, which better reflects the clinical relevance of the difference between the two groups. These results indicate that in this study the effect of lurasidone on depressive symptoms (assessed by MADRS score change), for both post-menopausal and pre-menopausal subgroups, was in the medium to large effect size range. Depressive symptom improvement among post-menopausal women appears to have been meaningfully larger than among pre-menopausal women in this study. The importance of these findings are underscored by prior reports noting that the patient population studied here has been associated with greater severity of depressive illness, increased frequency of depressive episodes, and poor antidepressant response (Angst et al., 2010; Zimmermann et al., 2009; McIntyre et al., 2015; Nuslock and Frank, 2011; Smith et al., 2009). Improvement in manic symptom severity, assessed by the YMRS, was similar for pre- and post-menopausal subgroups.

Comparing the four prior studies which assessed response to SSRI antidepressant therapy based on menopausal status (Pae et al., 2009; Grigoriadis et al., 2003; Pinto-Meza et al., 2006; Glassman and Roose, 1994), our analysis is the only one to date whose data was derived from a double-blind, randomized, placebo-controlled study design. The
Kornstein et al. (2014) study was also a post-hoc analysis of a large study (Kornstein et al., 2014), which like ours found no difference in response based on menopausal status in females with a history of highly recurrent depressive episodes as defined in DSM-IV. That study, which initially randomized patients to the SNRI venlafaxine ER or the SSRI fluoxetine, employed placebo only during a continuation phase for patients who initially responded to venlafaxine ER, while patients who responded to the fluoxetine continued to receive fluoxetine. The other three studies (Pae et al. (2009) Grigoriadis et al. (2003), and Pinto-Meza et al. (2006)) were naturalistic studies which rated patients who were treated for 6 weeks or longer with SSRIs or, to a lesser extent, SNRIs. These three studies reported that post-menopausal females had significantly poorer response than pre-menopausal females, in spite of apparently adequate dosage and duration of therapy. Another limitation of these naturalistic studies is the lack of clearly defined inclusion and exclusion criteria, including level of depression severity. Although the patients in our study met DSM-IV criteria for MDD, they also had mixed manic features, which makes direct comparison to other studies involving pure MDD patients difficult. Therefore, a significant limitation in generalizing our results is that our analysis involved a mixed MDD population and there are no comparable published studies in this population available for comparison.

The four earlier studies each defined post-menopausal status somewhat differently, based on self-report by the patient. Three of these studies excluded peri-menopausal females based on self-reports of vasomotor symptoms or change in regularity of menstrual cycles (Pae et al., 2009; Pinto-Meza et al., 2006; Kornstein et al., 2014), while one defined post-menopausal as 51 years or older (Grigoriadis et al., 2003), and excluded presumptive peri-menopausal females between ages 44 and 50 years, or about 5% of their study population. The reliance on self-report in most of these studies may lead to under-reporting of accurate peri-menopausal symptoms, and erroneous classification of women into menopausal categories. Ideally, reproductive hormones should be measured as a supplement to careful staff interviews and a history compatible with post-menopausal status, in order to best confirm the menopausal status. Although the study by Pae et al. collected blood at baseline for measurement of reproductive hormones (Pae et al., 2009), these were not utilized prospectively to categorize menopausal status, but were employed as a covariate, along with depression severity, in the final statistical analysis.

We did not exclude peri-menopausal women from our main data analysis, but included this subgroup in the pre-menopausal patient category. In addition, the onset of peri-menopause is variable, cited as occurring anytime from the early to late 40s (Hoyt and Falconi, 2015; Soares and Cohen, 2001; Speroff, 2002; Robertson and Burger, 2002; Li et al., 1996; Sulak, 1996). Nonetheless, based on the prior exclusion of peri-menopausal females in several earlier studies, we performed an exploratory analysis which excluded females between the ages of 45 and 51 years old from the younger female group using the same perimenopausal definition as Pae et al. (2009), since the argument can be made that excluding peri-menopausal women helps to better define the other two groups. Analysis of the MADRS, CGI-S, HAM-A and YMRS scales was repeated for pre-menopausal (ages 44 years and under) and post-menopausal (ages 52 year and over) status. Our pre-menopausal group continued to show highly significant differences between lurasidone and placebo on all study efficacy rating scales.

Several limitations of this study should be noted. Neither our study nor the Kornstein study (2014), both relying on a post-hoc analysis from larger studies, employed a prospective stratum in the original design to randomize patients based on menopausal status. Prospective stratification should be built into future studies aimed at assessing treatment response, based on reproductive hormonal status, to ensure a balance between pre- and post-menopausal women in each study arm. Post-hoc analyses have potential limitations, which may be minimized if they meet a number of criteria first outlined by Oxman and Guyatt (Oxman and Guyatt, 1993). In this regard, we note that our post-hoc analysis is strengthened in that results are biologically plausible given the postulated mechanism of action of lurasidone; the hypothesis of differential treatment effects based upon menopausal status is tenable based upon observations in previous studies; subgroup findings did not differ qualitatively from those reported within the larger study; (Suppes et al., 2016) and results within the subgroup remained statistically significant, even with variation in criteria for subgroup eligibility in a limited sensitivity analysis (i.e., the exploratory analysis which excluded presumpive peri-menopausal females).

One limitation of the original study design is that menopausal status was not recorded. We chose a cutoff age that was conservative for purposes of the analysis, and therefore one must regard our 52 years and older group as presumptive for post-menopausal status rather than confirmed. Although the number of presumptive post-menopausal females in our study was relatively small, they did not differ from the younger population in key demographic characteristics (other than age) or psychiatric history, historically recognized as prognostically important to treatment outcome. Only one patient who was in the younger female group received estrogen replacement therapy (ERT) during the study. Since ERT has been reported to enhance SSRI response in

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**Table 3**

Placebo adjusted least square (LS) mean changes from baseline to week 6 endpoint in efficacy assessment scores for ≤ 44 year females.

| Females ≤ 44 years (n = 67) | LS mean treatment difference (SE) | p-Value (effect size) |
|----------------------------|----------------------------------|----------------------|
| MADRS                     | −6.2 (2.51)                      | 0.0159 (0.63)        |
| CGI-S                     | −0.6 (0.28)                      | 0.0384 (0.54)        |
| HAM-A                     | −4.4 (1.55)                      | 0.0049 (0.73)        |
| YMRS                      | −2.4 (0.80)                      | 0.0027 (0.78)        |

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**Fig. 1.** Least square (LS) mean MADRS changes comparing lurasidone to placebo from baseline through week 6 for < 52 years and ≥ 52 years female subgroups.
depressed menopausal females, compared to post-menopausal females receiving an SSRI but no ERT, (Schneider et al., 1997) the paucity of ERT use in our study minimized the potential confounding effect of such treatment.

In summary, in this post-hoc analysis we found that the antidepressant response to the atypical antipsychotic lurasidone in MDD patients with mixed features (subthreshold hypomanic symptoms) was not diminished in females with presumptive post-menopausal status. Lurasidone treatment of post-menopausal patients with MDD and mixed features could therefore address the potential problem of poor response previously associated with SSRIs. Whether these results could be confirmed in a prospectively randomized study using appropriate stratification based on confirmed menopausal status warrants further investigation. Likewise, extension of these observations to patients with MDD not accompanied by mixed features remains to be determined.

Note

Informed consent was obtained for original studies. All authors have materially contributed to and approved the final manuscript. Drs Sramek, Murphy and Cutler are employees of Worldwide Clinical Trials. The study from which this post-hoc analysis was derived was funded by Sunovion Pharmaceuticals. Drs Loebel, Mao and Pikalov are employees of Sunovion Pharmaceuticals Inc. which produces and markets lurasidone (Latuda®).

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