A PROSPECTIVE OBSERVATIONAL STUDY ON COMPARISON OF LURASIDONE VERSUS ARIPIPRAZOLE BASED ON SERUM PROLACTIN LEVELS IN A TERTIARY CARE TEACHING HOSPITAL

R. Venkata Ramudu¹, A. Ramya Sunayana², M. V. Pavan Kumar Reddy³, G. Jyothsna⁴, K. Sree Harinadhi⁵

¹Associate Professor, Department of Psychiatry, Rajiv Gandhi Institute of Medical Sciences, Kadapa, Andhra Pradesh.
²Doctor of Pharmacy, Nirmala College of Pharmacy, Kadapa, Andhra Pradesh.
³Doctor of Pharmacy, Internship, PRRM College of Pharmacy, Kadapa, Andhra Pradesh.
⁴Doctor of Pharmacy, Internship, PRRM College of Pharmacy, Kadapa, Andhra Pradesh.
⁵Doctor of Pharmacy, Internship, PRRM College of Pharmacy, Kadapa, Andhra Pradesh.

ABSTRACT

BACKGROUND
We wanted to determine and compare the serum prolactin levels in lurasidone, and aripiprazole drug administered psychiatric patients.

METHODS
A hospital-based prospective observational study was done in the psychiatric department, RIMS, Kadapa for a period of 06 months (i.e., from Sept. 2018 to Feb. 2019). Patients receiving drugs (Lurasidone/Aripiprazole) were enrolled in our study. Patients in the age group 20-60 years were recruited. Consecutive sampling method was followed during the study procedure. 300 patients were recruited according to study criteria. Ethical approval was obtained from IEC. After taking the informed consent from the patient, data collection form was designed accordingly and given to patients to collect patients’ complete data. Collected data was analysed and interpreted by using the SPSS/Graph Pad Prism/Chi-Square Test.

RESULTS
We have recruited 300 patients with 150 patients in each group. We have analysed the blood samples of the patients for serum prolactin levels. We have reviewed the patients three times and we have found the mean and standard deviation of each drug in every review. We have analysed the serum prolactin levels based on gender and age differences. And we have compared the other ADR's of the two drugs based on gender differences. And we have also compared the serum prolactin levels of each drug from their base line to third review.

CONCLUSIONS
From the data collected after each review, it can be concluded that Aripiprazole is a safe drug compared to lurasidone. After assessing the serum prolactin levels, we noted that lurasidone increased prolactin levels dramatically in females and adult patients with age between 25 to 38.5 years. After the collection of statistical data, it can be concluded that Aripiprazole is the safer antipsychotic drug.

KEYWORDS
Lurasidone, Aripiprazole, Serum Prolactin, Hyperprolactinemia, Bipolar Disorder.

Sites of Synthesis and Secretion of Prolactin

A. Anterior Pituitary Gland

The Cells of the anterior pituitary glands synthesize and secrete prolactin. Although prolactin is largely found and secreted from a distinct cell type in the pituitary gland, the lactotroph, both prolactin and growth hormone can also be secreted from the intermediate cell population called mammosomatotrophs.4

B. Brain

The first observation that prolactin is produced in the brain was by Fuxe et al. who found prolactin immune reactivity in hypothalamic axon terminals. Prolactin immune reactivity was subsequently found in the telencephalon in the cerebral cortex, hippocampus, amygdala, septum, caudate putamen, brain stem, cerebellum, spinal cord, choroid plexus, and the circumventricular organs. Several approaches have been taken to prove that prolactin found in the hypothalamus is synthesized locally, independent of prolactin synthesis in the pituitary gland.5

C. Mammary Gland and Milk

Prolactin can be detected in epithelial cells of the lactating mammary gland as well as in the milk itself. There is little doubt that a portion of the prolactin found in the milk originates in the pituitary gland and reaches the mammary gland through the circulation. Thus, some of the prolactin found in milk is taken up rather than produced by the mammary epithelial cells. Apparently, prolactin reaches the milk by first crossing the mammary epithelial cell basement membrane, attaches to a specific prolactin-binding protein within the mammary epithelial cell, and is ultimately transported by endocytosis through the apical membrane into the alveolar lumen. The mammary gland may also act as a posttranslational processing site for prolactin.6

D. The Immune System

A great deal of evidence suggests that lymphocytes can be a source of prolactin as well. Indeed, immune-competent cells from thymus and spleen as well as peripheral lymphocytes contain prolactin mRNA and release bioactive prolactin that is similar to pituitary prolactin. Although the control of pituitary prolactin secretion differs from that of lymphocytic origin, there is abundant evidence that lymphocytes contain dopamine receptors that may be involved in the regulation of lymphocytic prolactin production/release. Pharmacological characterization of lymphocytic dopamine receptors suggests that rather than the classical D2 type receptors found on lactotrophs, both the D4 and D5 predominate on lymphocytes.7

Prolactin Receptor: Gene, Splicing Variants and Isoforms

The prolactin-R is a single membrane-bound protein that belongs to class 1 of the cytokine receptor superfamily. Just like their respective ligands, prolactin and growth hormone receptors share several structural and functional features despite their low (30%) sequence homology. Each contains an extracellular, transmembrane, and intracellular domain. The gene encoding the human prolactin-R is located on chromosome 5 and contains at least 10 exons. Transcriptional regulation of the prolactin-R gene is accomplished by three different, tissue-specific promoter regions. Promoter I is specific for the gonads, promoter II for the liver, and promoter III is “generic,” present in both gonadal and non-gonadal tissues. Numerous prolactin-R isoforms have been described in different tissues. These isoforms are results of transcription starting at alternative initiation sites of the different prolactin-R promoters as well as alternative splicing of non-coding and coding exon transcripts. Although the isoforms vary in the length and composition of their cytoplasmic domains, their extracellular domains are identical. The three major prolactin-R isoforms described in rats are the short (291 amino acids), intermediate (393 amino acids), and long (591 amino acids) forms. In mice, one long and three short forms have been described. In addition to the membrane-bound receptors, soluble prolactin-binding proteins were also described in mammary epithelial cells and milk. These soluble forms contain 206 NH2-terminal amino acids of the extracellular domain of the prolactin-R. The soluble prolactin binding proteins are also products of the same prolactin – R gene, but it is still uncertain whether they are results of alternative splicing of primary transcript or products of proteolytic cleavage of the mature receptor (or both).8

Regulation of Pituitary Prolactin Secretion

Prolactin secretion is affected by a large variety of stimuli provided by the environment and the internal milieu. The most important physiological stimuli that elevate pituitary prolactin secretion are suckling, stress and increased levels of ovarian steroids, primarily oestrogen. In humans, prolactin is produced in the anterior pituitary, decidua, myometrium, breast, lymphocytes, leukocytes and prostate.8,9 A key regulator of prolactin production is oestrogens that enhance the growth of prolactin-producing cells and stimulate prolactin production directly, as well as suppressing dopamine.9 Prolactin follows diurnal and ovulatory cycles. Prolactin levels peak during REM sleep and in the early morning.9 During pregnancy, high circulating concentrations of oestrogen and progesterone increase prolactin levels by 10 to 20-fold. Oestrogen and progesterone inhibit the stimulatory effects of prolactin on milk production.9 The sucking activates mechanoreceptors in and around the nipple. These signals are carried by nerve fibers through the spinal cord to the hypothalamus, where changes in the electrical activity of neurons that regulate the pituitary gland increase prolactin secretion. The suckling stimulus also triggers the release of oxytocin.
from the posterior pituitary gland, which triggers milk let-down: Prolactin controls milk production (lactogenesis) but not the milk-ejection reflex; the rise in prolactin fills the breast with milk in preparation for the next feed. Levels can rise after exercise, high – protein meals, minor surgical procedures, following epileptic seizures or due to physical or emotional stress.

**Functions of Prolactin**
- It stimulates the milk secretion and production after childbirth in females.
- It is also important for both male and female reproductive health.
- Elevated levels of prolactin decrease the levels of sex hormones.
- Prolactin promotes neurogenesis in maternal and fetal brains.
- It has a role in maternal behaviour.
- It counteracts the effect of dopamine.
- In males, it enhances the luteinizing hormone receptors in Leydig cells which causes spermatogenesis.

**The Physiological Importance of Prolactin**
In women, the major action of prolactin is to initiate and sustain lactation. In breastfeeding mothers, tactile stimulation of the nipples and the breast by the suckling infant blocks the secretion of hypothalamic dopamine (which normally inhibits prolactin) into the hypophyseal portal circulation of the pituitary. This results in a sharp rise in serum prolactin concentrations, followed by a prompt fall when feeding stops. High serum prolactin concentrations inhibit secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, thereby decreasing the secretion of gonadotropins (luteinizing hormone and follicle-stimulating hormone), and may also inhibit the action of gonadotropins on the gonads. Thus, high serum prolactin concentrations during lactation reduce fertility, protecting lactating women from a premature pregnancy. Because prolactin acts to maintain the corpus luteum of the ovary, which is the source of the female sex hormone progesterone, it helps to sustain the pregnancy. In addition, prolactin secretion increases progressively during pregnancy. The secretion of prolactin also can be stimulated by high doses of oestrogens, and it is transiently stimulated by stress and exercise. The function of prolactin in males is not known.

<table>
<thead>
<tr>
<th>Serum Prolactin</th>
<th>Normal Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0-20 ng/ml or 3-15 mcg/ml</td>
</tr>
<tr>
<td>Women</td>
<td>0-25 ng/ml or 4-23 mcg/ml</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>34-386 ng/ml</td>
</tr>
<tr>
<td>Children</td>
<td>3.2-20 ng/ml</td>
</tr>
</tbody>
</table>

**Normal Ranges of Serum Prolactin**

**Antipsychotic Medications**
- Risperidone
- Haloperidol
- Fluoxetine
- Sertraline
- Paroxetine
- Serotonin
- Citripipram

**Other Medications**
- Calcium channel blockers
- Methyldopa
- Opiates
- H2 antagonists
- Metoclopramide
- Oestrogen

**Drug-Induced Causes**

**Common Causes**
- Growth/tumour on the pituitary gland.

**Other Causes**
- Idiopathic hyperprolactinemia, oestrogen, Hyperthyroidism, Decreased clearance of prolactin, Chronic renal failure, Chest wall injury.

**Symptoms in Females**
- Cessation of menstrual periods (amenorrhoea), decreased menstrual flow (oligomenorrhoea), abnormal production of breast milk when not breastfeeding (galactorrhoea), excess facial hair (hirsutism), vaginal dryness and pain during intercourse and infertility

**Symptoms in Males**
- Impotence, infertility, decreased libido gynaecomastia, galactorrhoea, decreased muscle mass and reduced body hair, headache, impaired vision may occur as tumour growth exerts pressure within the skull.

**Pathophysiology**
- The primary action of prolactin is the stimulation of breast epithelial cell proliferation and maintaining milk production.
- Oestrogen stimulates proliferation of pituitary lactotroph cells which results in an increased quantity of these cells in premenopausal women, especially during pregnancy.
- Lactation is inhibited by increased levels of oestrogen and progesterone during pregnancy.
- During lactation and breastfeeding ovulation may be suppressed by gonadotrophins by prolactin.
- Dopamine has influence and has inhibitory control over serum prolactin secretion.
- Dopamine acts as a D2 type receptor located on lactotrophs.

**Need of The Study**
Aripiprazole and lurasidone are used in the treatment of schizophrenia and bipolar disorder patients. These two drugs have the adverse effects of causing hyperprolactinemia. The purpose of the present study is to identify drug which increases the prolactin hormone levels in the blood and to compare the serum prolactin levels after administration of the drug and to prescribe the drug which has the least effect on prolactin hormone levels and to promote the quality of life of a patient.

**Aim**
To determine and compare the serum prolactin levels in lurasidone and aripiprazole drug administered psychiatric patients.

**Objectives**
- To determine the elevated serum prolactin levels after administration of lurasidone and aripiprazole drugs.
- To assess the drugs which increase prolactin levels and cause hyperprolactinemia.
- To find out the safety and efficacy of two drugs and to improve the patient’s quality of life.
By assessing the prolactin levels, we can finally suggest the drug which is more effective.

**METHODS**

**Study Design**
Prospective observational study.

**Study Site**
Rajiv Gandhi Institute of Medical Sciences, Kadapa.

**Study Duration**
6 months.

**Study Population**
Patients who are having schizophrenia and bipolar disorder.

**Sample Size**
300 Patients.

**Inclusion Criteria:**
- Patients who are having schizophrenia and bipolar disorder.
- Patients who are prescribed with aripiprazole.
- Patients who are prescribed with lurasidone.

**Exclusion Criteria:**
- Pregnancy and lactation.
- Below 20 yrs. and above 65 yrs.
- Multiple disorders.

**Study Materials**
- Informed consent form.
- Patient standard data collection form.

**Statistical Analysis**
Data will be analysed by using the SPSS/Graph Pad prism/chi-square test. Blood samples were collected from the psychiatry patients attending the hospital at regular time intervals.

### Table 1. Distribution of Study Subjects

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>150</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>150</td>
</tr>
</tbody>
</table>

### Table 2. Literacy Rate Among the Recruited Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Literacy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literates</td>
<td>13.4</td>
</tr>
<tr>
<td>Illiterates</td>
<td>86.6</td>
</tr>
</tbody>
</table>

### Table 3. Individual Prolactin Levels of Aripiprazole Subjects (N=150)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline (n=10)</th>
<th>1st Review</th>
<th>2nd Review</th>
<th>3rd Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>9.9</td>
<td>8.2</td>
<td>8.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>13.5</td>
<td>14.5</td>
<td>18.6</td>
<td>19.5</td>
</tr>
<tr>
<td>Total</td>
<td>23.4</td>
<td>22.7</td>
<td>36.1</td>
<td>36.8</td>
</tr>
</tbody>
</table>

### Table 4. Individual Prolactin Levels of Lurasidone Subjects (N=150)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline (n=10)</th>
<th>1st Review</th>
<th>2nd Review</th>
<th>3rd Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>9.9</td>
<td>8.2</td>
<td>8.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>13.5</td>
<td>14.5</td>
<td>18.6</td>
<td>19.5</td>
</tr>
<tr>
<td>Total</td>
<td>23.4</td>
<td>22.7</td>
<td>36.1</td>
<td>36.8</td>
</tr>
</tbody>
</table>

1. The mean value of baseline serum prolactin level for Aripiprazole = 9.82
   Standard deviation value = 99.12

2. The mean value for 1st review = 11.84 Standard deviation value = 96.49
3. The mean value for 2nd review = 13.53 Standard deviation value = 97.69
4. The mean value for 3rd review = 15.65 Standard deviation value = 94.99

Please see the original research article for further details.
1. The mean values of Serum Prolactin level are uniformly higher in Lurasidone than Aripiprazole at each review.
2. There is significant effect of review (F = 47.185, p = 0.000) on the outcome.
3. There is significant effect of drugs (F = 6.219, p = 0.019) on the outcome.
4. There is a joint effect of drugs and review (F = 56.563, p = 0.000) on the outcome. The highest response is at 3rd review with Lurasidone.

Hence it is clear that patients using Lurasidone have higher serum prolactin levels when compared with aripiprazole during the period of study.

From the above graph, it is noticed that serum prolactin is at 3rd review with Lurasidone.

1. The mean values of Serum Prolactin level are higher in Females than Males at each review.
2. There is significant effect of review (F = 14.883, p = 0.001) on the outcome.
3. There is significant effect of drugs (F = 8.161, p = 0.008) on the outcome.
4. There is no joint effect of gender and review on the outcome.

From the above graph, it is noticed that serum prolactin levels in females are higher than in males.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Prolactin Level (ng/ml)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (50)</td>
<td>1st Review</td>
</tr>
<tr>
<td>Male</td>
<td>8.55</td>
<td>8.99</td>
</tr>
<tr>
<td>Female</td>
<td>10.73</td>
<td>12.71</td>
</tr>
</tbody>
</table>

**Table 6. Comparison of Prolactin Levels Between Male and Female**

1. The mean values of Serum Prolactin level are found to be increasing at successive reviews.
2. There is 28.55% increase in Serum Prolactin level during the period of observation.
3. There is a significant difference in serum prolactin levels between pairs of review periods (1st review vs Baseline, 2nd review vs Baseline, 3rd review vs Baseline, 3rd review vs 1st review).

1. There is no significant effect of age on the outcome.
2. There is no joint effect of age and review on the outcome.

Adult Patients with age (in between 25-38.5 years) have higher levels of serum prolactin after using the drugs compared to age below 25 years and above 39 years. Hence the patients with age in between 25-38.5 years may have higher serum prolactin levels after usage of medication.

**Table 8. Overall Comparison of Prolactin Levels**

From the above graph, it is clear that after using the drugs there is a significant change in serum prolactin levels.

<table>
<thead>
<tr>
<th>Pair</th>
<th>Mean Effect*</th>
<th>Std. Error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st review vs Baseline</td>
<td>1.312</td>
<td>0.346</td>
<td>0.001</td>
</tr>
<tr>
<td>2nd review vs Baseline</td>
<td>2.087</td>
<td>0.529</td>
<td>0.000</td>
</tr>
<tr>
<td>2nd review vs 1st review</td>
<td>0.774</td>
<td>0.389</td>
<td>0.056</td>
</tr>
<tr>
<td>3rd review vs Baseline</td>
<td>2.794</td>
<td>0.678</td>
<td>0.000</td>
</tr>
<tr>
<td>3rd review vs 1st review</td>
<td>1.482</td>
<td>0.564</td>
<td>0.014</td>
</tr>
<tr>
<td>3rd review vs 2nd review</td>
<td>0.707</td>
<td>0.425</td>
<td>0.106</td>
</tr>
</tbody>
</table>

**Table 9. Pair-Wise Comparison of Reviews**

* The mean effect is significant at the 0.05 level.

From the above graph, it is clear that prolactin levels are slightly increased in patients administered with lurasidone than in patients with Aripiprazole.

**Table 10. Comparison of Prolactin Levels of Aripiprazole vs. Lurasidone in Males**

**Table 11. Comparing Prolactin Levels of Aripiprazole vs. Lurasidone in Females**
From the above graph, it is clear that there is a significant increase in prolactin levels in patients administered with lurasidone than in patients with aripiprazole and some conclusions can be drawn: female patients using lurasidone are highly prone to the risk of hyperprolactinemia compared to that of males.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>AMN</th>
<th>OLN</th>
<th>GLR</th>
<th>HI</th>
<th>ED</th>
<th>INFERTILITY</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole (N=8)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lurasidone (N=9)</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Review</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>t-value</th>
<th>p-value</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>15</td>
<td>9.82</td>
<td>2.551</td>
<td>9.018</td>
<td>0.000</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Table 17

There is a significant difference between the baseline and 3rd reviews in Lurasidone.

DISCUSSION

1. We compared the individual serum prolactin levels of Aripiprazole in 150 subjects and the mean value of baseline serum prolactin level for Aripiprazole = 9.76 standard deviation value = 3.14. The mean value for 1st review =10.36 Standard deviation value=3.37. The mean value for 2nd review=10.21 Standard deviation value=3.05. The mean value for 3rd review=9.52 Standard deviation value=3.07

2. We compared the individual serum prolactin levels of Lurasidone in 150 subjects and the mean value of baseline serum prolactin level for lurasidone = 9.82 Standard deviation value = 99.12. The mean value for 1st review =11.84 Standard deviation value= 97.69. The mean value for 2nd review=13.53 Standard deviation value=96.49. The mean value for 3rd review=15.65 Standard deviation value=94.99

3. We compared the individual serum prolactin levels both the drugs (Aripiprazole & Lurasidone) in 300 subjects and the mean values of Serum Prolactin level are uniformly higher in Lurasidone than Aripiprazole at each review. There is significant effect of review (F = 47.185, p = 0.000) on the outcome. There is significant effect of drugs (F = 6.219, p = 0.019) on the outcome. There is a joint effect of drugs and review (F = 56.563, p = 0.000) on the outcome. The highest response is at 3rd review with Lurasidone.

4. We compared the individual serum prolactin levels in both the genders (Males & Females) in 300 subjects and the mean values of Serum Prolactin level are higher in Females than Males at each review. There is significant effect of review (F = 14.883, p = 0.001) on the outcome. There is significant effect of drugs (F = 8.161, p = 0.008) on the outcome. There is no joint effect of gender and review on the outcome.

5. We compared the individual serum prolactin levels in 300 subjects based on age factor and the Adult Patients with age (in between 25-38.5 years) have higher levels of serum prolactin after using the drugs compared to age below 25years and above 39 years. Hence the patients with age in between 25-38.5 years may have higher serum prolactin levels after usage of medication

6. We also considered pairwise comparison of reviews. The mean values are found to be increasing at successive reviews. There is 28.55% increase in Serum Prolactin level during the period of observation. There is a significant difference in the overall mean Serum Prolactin at baseline, 1st, 2nd, and 3rd reviews. There is a significant difference in means between pairs of
review periods (1st review vs Baseline), (2nd review vs Baseline), (3rd review vs Baseline), (3rd review vs 1st review).
7. We compared the individual serum prolactin levels both the drugs (Aripiprazole & Lurasidone) in female subjects and the It is clear that there is a significant increase in prolactin levels in patients administered with lurasidone than in patients with aripiprazole and some conclusions can be drawn: female patients using lurasidone are highly prone to the risk of hyperprolactinemia compared to that of males.
8. We compared the individual serum prolactin baseline & 3rd review levels in 300 subjects based on body weight. It can be concluded that there is a significant rise in the 3rd review of lurasidone when compared with baseline serum prolactin levels.
9. These are the symptoms we noticed in females during and after the study i.e., Amenorrhea, Oligomenorrhea, Galactorrhoea, Hirsutism, Vaginal dryness, Pain during intercourse. From the above data, we can conclude that Lurasidone caused increased Hyperprolactinemia effects than Aripiprazole in females.
10. These are the symptoms we noticed in males during and after the study i.e., Erectile dysfunction, decreased muscle mass, Reduced body hair, impaired vision. From the above data, we can conclude that Lurasidone is having more effects compared to that of aripiprazole.

CONCLUSIONS
The present study was carried out to determine and compare the serum prolactin levels in lurasidone and aripiprazole drug administered psychiatric patients and to find out as to which drug increases prolactin levels and cause hyperprolactinemia. The study was also carried out to know the safety and efficacy of two drugs and to improve the patient quality of life and compliance. From the data collected after each review, it can be concluded that Aripiprazole is a safe drug compared to that of lurasidone. After assessing the serum prolactin levels, we can finally suggest the lurasidone increased prolactin levels dramatically in females and adult patients with age in between 25 to 38.5 years. After the collection of statistical data, it can be concluded that aripiprazole is the safer antipsychotic drug.

REFERENCES